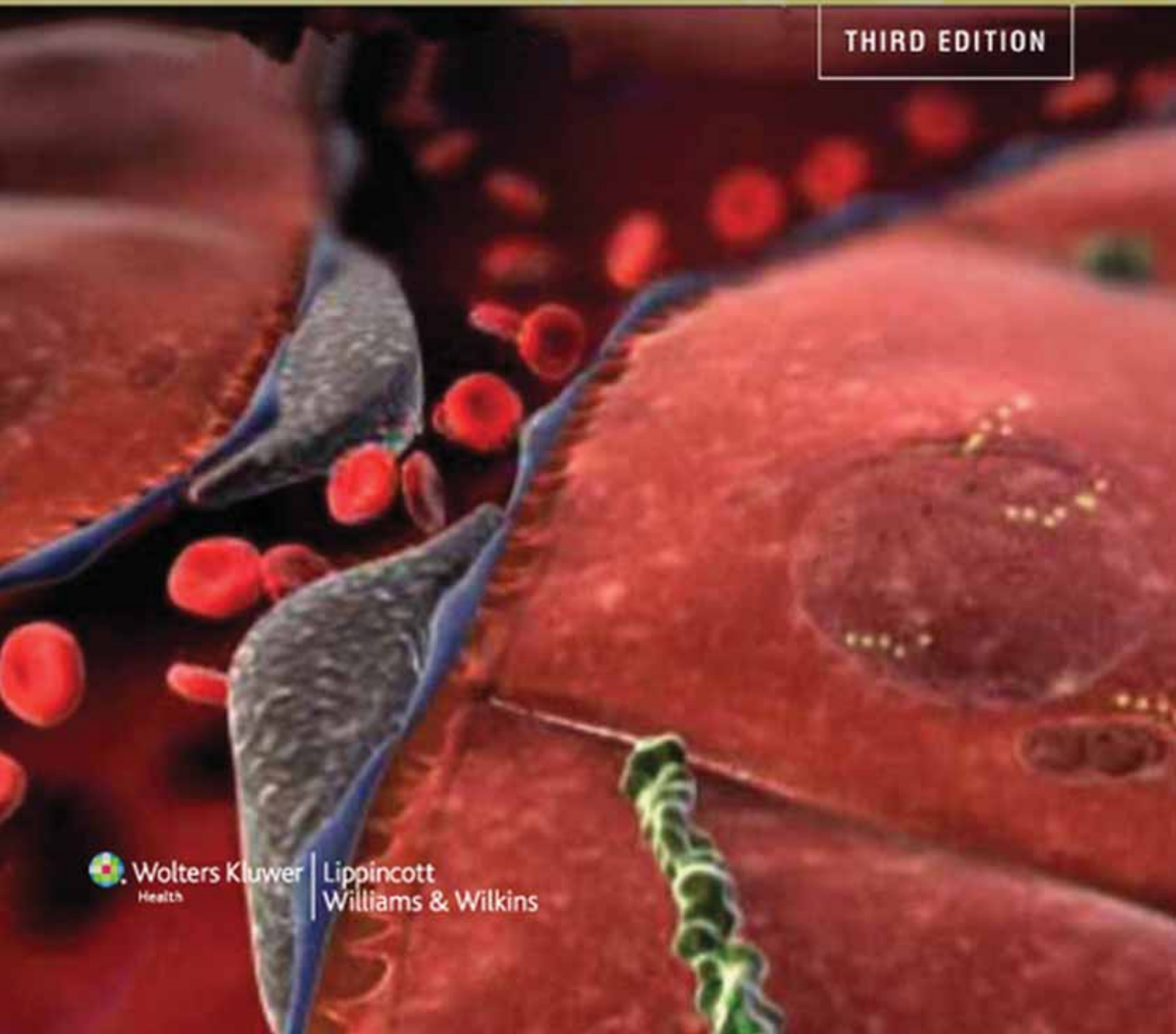
Essentials of Pathophysiology

Carol Mattson **Porth**

THIRD EDITION



Wolters Kluwer Health | Lippincott Williams & Wilkins

Quick Table of Contents

Introduction to Pathophysiology xix

UNIT 1 Cell and Tissue Function 1

Chapter 1 Cell Structure and Function 1
Chapter 2 Cellular Responses to Stress, Injury, and Aging 33
Chapter 3 Inflammation, the Inflammatory Response, and Fever 51
Chapter 4 Cell Proliferation and Tissue Regeneration and Repair 73
Chapter 5 Genetic Control of Cell Function and Inheritance 89
Chapter 6 Genetic and Congenital Disorders 109
Chapter 7 Neoplasia 131

UNIT 2 Integrative Body Functions 159

Chapter 8 Disorders of Fluid, Electrolyte, and Acid-Base Balance 159
Chapter 9 Stress and Adaptation 209
Chapter 10 Disorders of Nutritional Status 224

UNIT 3 Hematopoietic Function 243

Chapter 11 Disorders of White Blood Cells and Lymphoid Tissues 243
Chapter 12 Disorders of Hemostasis 263
Chapter 13 Disorders of Red Blood Cells 279

UNIT 4 Infection and Immunity 299

Chapter 14 Mechanisms of Infectious Disease 299
Chapter 15 Innate and Adaptive Immunity 319
Chapter 16 Disorders of the Immune Response 345

UNIT 5 Circulatory Function 377

Chapter 17 Control of Cardiovascular Function 377
Chapter 18 Disorders of Blood Flow and Blood Pressure 405
Chapter 19 Disorders of Cardiac Function 447
Chapter 20 Heart Failure and Circulatory Shock 486

UNIT 6 Respiratory Function 513

Chapter 21 Control of Respiratory Function 513
Chapter 22 Respiratory Tract Infections, Neoplasms, and Childhood Disorders 540
Chapter 23 Disorders of Ventilation and Gas Exchange 566

UNIT 7 Kidney and Urinary Tract Function 601

Chapter 24 Structure and Function of the Kidney 601
Chapter 25 Disorders of Renal Function 620
Chapter 26 Acute Renal Failure and Chronic Kidney Disease 641
Chapter 27 Disorders of the Bladder and Lower Urinary Tract 659

UNIT 8 Gastrointestinal and Hepatobiliary Function 679

Chapter 28 Structure and Function of the Gastrointestinal System 679
Chapter 29 Disorders of Gastrointestinal Function 700
Chapter 30 Disorders of Hepatobiliary and Exocrine Pancreas Function 729

UNIT 9 Endocrine System 761

Chapter 31 Mechanisms of Endocrine Control 761
Chapter 32 Disorders of Endocrine Control of Growth and Metabolism 774
Chapter 33 Diabetes Mellitus and the Metabolic Syndrome 799

UNIT 10 Nervous System 829

Chapter 34 Organization and Control of Neural Function 829
Chapter 35 Somatosensory Function, Pain, and Headache 863
Chapter 36 Disorders of Neuromuscular Function 891
Chapter 37 Disorders of Brain Function 927
Chapter 38 Disorders of Special Sensory Function: Vision, Hearing, and Vestibular Function 966

UNIT 11 Genitourinary and Reproductive Function 1009

Chapter 39 Disorders of the Male Genitourinary System 1009
Chapter 40 Disorders of the Female Genitourinary System 1033
Chapter 41 Sexually Transmitted Infections 1067

UNIT 12 Musculoskeletal Function 1081

Chapter 42 Structure and Function of the Skeletal System 1081
Chapter 43 Disorders of the Skeletal System: Trauma, Infections, Neoplasms, and Childhood Disorders 1096
Chapter 44 Disorders of the Skeletal System: Metabolic and Rheumatic Disorders 1130

UNIT 13 Integumentary Function 1159

Chapter 45 Structure and Function of the Skin 1159
Chapter 46 Disorders of Skin Integrity and Function 1172

Glossary 1207
Appendix A: Laboratory Values 1217
Index 1219

Essentials of Pathophysiology

CONCEPTS OF ALTERED HEALTH STATES

Carol Mattson Porth, RN, MSN, PhD (Physiology)
Professor Emeritus, College of Nursing
University of Wisconsin—Milwaukee
Milwaukee, Wisconsin

CONSULTANTS

Kathryn J. Gaspard, PhD
Clinical Associate Professor Emerita
University of Wisconsin—Milwaukee
College of Nursing
Milwaukee, Wisconsin

Kim A Noble, PhD, RN, CPAN
Assistant Professor
Temple University
Department of Nursing
Philadelphia, Pennsylvania

EDITION 3

Wolters Kluwer Health | Lippincott Williams & Wilkins
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Hilarie Surrena
Product Manager: Katherine Burland
Editorial Assistant: Shawn Loht
Design Coordinator: Joan Wendt
Illustration Coordinator: Brett MacNaughton
Manufacturing Coordinator: Karin Duffield
Prepress Vendor: Aptara, Inc.

3rd edition

Copyright © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Copyright © 2007, 2004 by Lippincott Williams & Wilkins. All rights reserved. This book is protected by copyright. No part of this book may be reproduced or transmitted in any form or by any means, including as photocopies or scanned-in or other electronic copies, or utilized by any information storage and retrieval system without written permission from the copyright owner, except for brief quotations embodied in critical articles and reviews. Materials appearing in this book prepared by individuals as part of their official duties as U.S. government employees are not covered by the above-mentioned copyright. To request permission, please contact Lippincott Williams & Wilkins at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103 USA, via email at permissions@lww.com, or via our website at lww.com (products and services).

9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data

Porth, Carol.
Essentials of pathophysiology : concepts of altered health states / Carol Mattson Porth ; consultants, Kathryn J. Gaspard, Kim A. Noble. — 3rd ed.
p. ; cm.
Other title: Pathophysiology
Abridgement of: Pathophysiology / Carol Mattson Porth. 8th ed. c2009.
Includes bibliographical references and index.
Summary: "Designed to present students with essential concepts of disease processes and altered health states, this third edition text is ideal for both discrete and integrated pathophysiology courses. The third edition continues to build on the extremely successful art program and the 'Understanding' feature and has an even more robust electronic support ancillary program to make both faculty and student learning easier and more successful"—Provided by publisher.
ISBN 978-1-58255-724-3
1. Physiology, Pathological. 2. Nursing. I. Porth, Carol. Pathophysiology. II. Title. III. Title: Pathophysiology.
[DNLM: 1. Disease—Nurses' Instruction. 2. Pathologic Processes—Nurses' Instruction. 3. Physiological Phenomena—Nurses' Instruction. QZ 4]

RB113.P668 2010
616.07—dc22

2010029202

Care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, the author, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. Application of this information in a particular situation remains the professional responsibility of the practitioner; the clinical treatments described and recommended may not be considered absolute and universal recommendations.

The author, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health care provider to ascertain the FDA status of each drug or device planned for use in his or her clinical practice.

This book is dedicated to
All the Students who use the book, for it is for them that the book was written

Carol Mattson Porth

Contributors

Judith A. Aberg, MD
Principal Investigator, AIDS Clinical Trials Unit
Director of HIV, Bellevue Hospital Center
Associate Professor of Medicine
New York University School of Medicine
(Chapter 16, Acquired Immunodeficiency Syndrome)

Toni Balistrieri, RN, MSN, CCNS
Milwaukee, Wisconsin
(Chapter 19, Disorders of Cardiac Function)

Anna Barkman, RN, BN, MN
Bridge to Canadian Nursing Program
School of Nursing
Faculty of Health & Community Studies
Calgary, Alberta, Canada
(Chapter 20)

Diane S. Book, MD
Assistant Professor of Neurology
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 37)

Edward W. Carroll, MS, PhD
Clinical Assistant Professor
Marquette University
Department of Biomedical Sciences, College of Health Sciences
Milwaukee, Wisconsin
(Chapters 1, 5, 34, 38 Disorders of Special Sensory Function: Vision)

Robin Curtis, PhD
Professor, Retired
Department of Cellular Biology, Neurobiology, and Anatomy
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 34)

W. Michael Dunne Jr., PhD
Professor of Pathology, Immunology, and Molecular Microbiology
Washington University School of Medicine
Medical Director of Microbiology
Barnes-Jewish Hospital
St. Louis, Missouri
(Chapter 14)

Jason Faulhaber, MD, Fellow
Division of Infectious Diseases and Immunology
New York University School of Medicine
New York, New York
(Chapter 16, Acquired Immunodeficiency Syndrome)

Susan A. Fontana, PhD, APRN-BC
Associate Professor and Family Nurse Practitioner
University of Wisconsin—Milwaukee
College of Nursing
Milwaukee, Wisconsin
(Chapter 38, Disorders of Hearing and Vestibular Function)

Kathryn J. Gaspard, PhD
Clinical Associate Professor Emerita
University of Wisconsin—Milwaukee
College of Nursing
Milwaukee, Wisconsin
(Chapters 12, 13)

Kathleen E. Gunta, MSN, RN, OCNS-C
Clinical Nurse Specialist
Aurora St. Luke's Medical Center
Milwaukee, Wisconsin
(Chapters 43, 44 Disorders of the Skeletal System: Metabolic Disorders)

Safak Guven, MD, MBA, FACP
Las Vegas, Nevada
(Chapter 33)

Serena W. Hung, MD
Assistant Professor, Department of Neurology
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 50)

Scott A. Jens, OD, FAAO
Doctor of Optometry
Isthmus Eye Care, SC
Middleton, Wisconsin
(Chapter 38 Disorders of Special Sensory Function: Vision)

Julie A. Kuenzi, RN, MSN, CDE
Manager—Diabetes and Endocrine Center
Froedtert Hospital and Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 33)

Mary Pat Kunert, RN, PhD
Associate Professor
University of Wisconsin—Milwaukee
College of Nursing
Milwaukee, Wisconsin
(Chapter 9)

Nathan A. Ledeboer, PhD
Assistant Professor of Pathology
Medical College of Wisconsin
Director, Clinical Microbiology
DynaCare Laboratories
Milwaukee, Wisconsin
(Chapter 14)

Kim Litwack, RN, PhD, FAAN, APNP
Associate Professor
University of Wisconsin—Milwaukee
College of Nursing
Milwaukee, Wisconsin
(Chapter 35)

Patricia McCowen Mehring, RNC, MSN, WHNP
Nurse Practitioner, Department of OB-GYN
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapters 40, 41)

Glenn Matfin, BSc (Hons), MSc (Oxford), MB ChB, DGM, FFPM, FACE, FACP, FRCP (London)
Senior Physician
Joslin Diabetes Center
Harvard Medical School, Boston
(Chapters 10, 18 Disorders of Blood Flow, 31, 32, 33, 39)

Carrie J. Merkle, RN, PhD, FAAN
Associate Professor
University of Arizona
College of Nursing
Tucson, Arizona
(Chapters 2, 4, 7)

Kathleen Mussatto, RN
Specialty-based Nurse Scientist
Children's Hospital of Wisconsin
Milwaukee, Wisconsin
(Chapter 19, Heart Disease in Infants and Children)

Kim A. Noble, PhD, RN, CPAN
Assistant Professor
Widener University
School of Nursing
Chester, Pennsylvania
(Chapters 8, 35)

Joan Pleuss, RD, MS, CDE, CD
Program Manager/Bionutrition Core
General Clinical Research Center (GCRC)
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 10)

Charlotte Pooler, RN, BScN, MN, PhD (Nursing), CNCC(C), CNC(C)
Grant MacEwan College
Director, Baccalaureate Nursing Program
Faculty of Health and Community Studies
Edmonton, Alberta, Canada
(Chapters 20, 23)

Debra Bancroft Rizzo, RN, MSN, FNP-C
Nurse Practitioner
Rheumatic Disease Center
Glendale, Wisconsin
(Chapter 44, Disorders of the Skeletal System: Rheumatic Disorders)

Gladys Simandl, RN, PhD
Professor
Columbia College of Nursing
Milwaukee, Wisconsin
(Chapters 45, 46)

Cynthia Sommer, PhD, MT (ASCP)
Associate Professor Emerita
University of Wisconsin—Milwaukee
Department of Biological Sciences
Milwaukee, Wisconsin
(Chapter 15)

Reviewers

Nikki Chapple, MS
Delaware State University
Dover, Delaware

Rachel Claggett, RN, BSN
University of Arkansas
Fayetteville, Arizona

Jessica Downing, BN
Memorial University of Newfoundland, School of Nursing
St. John's, Newfoundland

Julie Fisher, BSN
Wesley College
Dover, Delaware

Susan Griffin Garcia, RN, BSN, CEN
Georgia Baptist College of Nursing
Atlanta, Georgia

Sharon Hall, BSN, RN
Clinical Director
Georgia Baptist College of Nursing
Atlanta, Georgia

Betty Hawxhurst, RN, BSN
Grand Canyon University
Phoenix, Arizona

Ronald David Hunziger, FNP
Southwest Baptist University
Bolivar, Missouri

Joan Elizabeth Ozon-Veitch, BN, RN
Memorial University of Newfoundland, School of Nursing
St. John's, Newfoundland

Stephanie Peak, RN
Grand Canyon University
Phoenix, Arizona

Jane Shelby, BSN, MSN
Belmont University
Nashville, Tennessee

Laurie Singel, MSN, RN, BC
University of the Incarnate Word
San Antonio, Texas

Frederick Slone, MD
University of South Florida College of Nursing
Tampa, Florida

Melissa Smith, DNP, RN, FNP-BC
University of Missouri—Kansas City, School of Nursing
Kansas City, Missouri

Mary Stanley, RN, MA
University of Nebraska Medical Center College of Nursing
Omaha, Nebraska

Jill Steuer, PhD, RN
Capital University
Columbus, Ohio

Costellia Talley, PhD, MSN, RN
Michigan State University
East Lansing, Michigan

Dorie Weaver, MSN, FNP, RN, APRN, BC
DeSales University
Center Valley, Pennsylvania

Michelina Eva Weicker, PhD
Alvernia College
Philadelphia, Pennsylvania

Keeta Wilborn, BSN, MSN, PhD, MS
Brenau University
Gainesville, Georgia

K. Mark Wooden, PhD
Grand Canyon University
Phoenix, Arizona

Preface

The text, which is based on the eighth edition of *Pathophysiology: Concepts of Altered Health,* has been prepared specifically for those students who do not need the extensive breadth or detail of content provided in the larger book. To accomplish this task, content deemed to be less essential has been omitted, while essential content has been reorganized, revised, and condensed.

The integration of full color into the design and illustrations from the eighth edition has been carried over into the third edition of the essentials version. Over 200 of the illustrations that appear in this edition are new or have been extensively modified. The illustrations—line drawings of anatomic structures and pathophysiologic processes, flow charts, and photographic illustrations of disease states—have been carefully chosen to support the concepts that are presented in the text. This offers not only visual appeal but also enhances conceptual learning, linking text content to illustration content A new element, the "clinical feature," uses illustration to depict the clinical manifestations of selected disease states.

The third edition also retains the list of suffixes and prefixes, the glossary, and the table of normal laboratory values that were in the previous edition. The table of laboratory values includes conventional and SI units, as well as conversion units and internet addresses for additional information. The key concept boxes have been retained within each chapter. They are intended to help the reader retain and use text information by providing a mechanism to incorporate the information into a larger conceptual unit as opposed to merely memorizing a string of facts. Review exercises appear at the end of each chapter and assist the reader in using the conceptual approach to solving problems related to chapter content.

Along with the extensive changes and revision, every attempt has been made to present content in a manner that is logical, understandable, and that inspires reader interest. The content has been arranged so that concepts build on one another, with concepts from physiology, biochemistry, physics, and other sciences reviewed as deemed appropriate. A conceptual model that integrates the developmental and preventative aspects of health has been used. Selection of content was based on common health problems, including the special needs of children, pregnant women, and elderly persons. Although first and foremost intended as a course textbook, it also serves as a reference book that students can take with them and use in their practice once the course is finished.

And finally, as a nurse–physiologist, my major emphasis with each edition has been to relate normal body functioning to the physiologic changes that participate in disease production and occur as a result of disease, as well as the body's remarkable ability to compensate for these changes. The beauty of physiology is that it integrates all of the aspects of human genetics, molecular and cellular biology, and organ anatomy and physiology into a functional whole that can be used to explain both the physical and psychological aspects of altered health. Indeed, it has been my philosophy to share the beauty of the human body and to emphasize that in disease as in health, there is more "going right" in the body than is "going wrong." This book is an extension of my career and, as such, of my philosophy. It is my hope that readers will learn to appreciate the marvelous potential of the body, incorporating it into their own philosophy and ultimately sharing it with their clients.

Carol Mattson Porth

Student and Instructor Resources

Student Resources

The student resource DVD accompanying this text contains several useful study resources including

- **Animations** of selected pathophysiologic processes
- **Student Review Questions** for every chapter

Resources are also available online at thePoint.lww.com!

Instructor Resources

The instructor resource DVD available to accompany this text is a comprehensive resource including the following:

- **Test Generator** containing over 900 multiple-choice questions
- **PowerPoint** presentations with incorporated images from the book
- **Image Bank** featuring all of the figures from each chapter
- **Lecture Outlines** for presenting key information to your students
- **Assignments** and **Quizzes** for gauging student understanding
- **Discussion Topics** to encourage critical thinking
- **Case Studies** providing real life application of concepts
- **WebCT- and Blackboard-ready materials** for use with your institution's Learning Management System.

Resources are also available online at thePoint.lww.com!

To the Reader

This book was written with the intent of making the subject of pathophysiology an exciting exploration that relates normal body functioning to the physiologic changes that occur as a result of disease, as well as the body's remarkable ability to compensate for these changes. Indeed, it is these changes that represent many of the signs and symptoms of disease.

Using a book such as this can be simplified by taking time out to find what is in the book and how to locate information when it is needed. The *table of contents* at the beginning of the book provides an overall view of the organization and content of the book. The *index,* which appears at the end of the book, can be viewed as a road map for locating content. It can be used to quickly locate related content in different chapters of the book or to answer questions that come up in other courses.

Organization

The book is organized into units and chapters. The *units* identify broad areas of content, such as alterations in the circulatory system. Many of the units have *introductory chapters* that contain information about the normal structure and function of the body systems that are being discussed in the unit. These chapters, which are intended as a review of content from previous courses as well as an update on recent scientific advances in genetic and molecular biology, provide the foundation for understanding the pathophysiology content presented in the subsequent chapters. The *disorder chapters* focus on specific areas of pathophysiology content, such as heart failure and circulatory shock. The *chapter outline* that appears at the beginning of each chapter provides an overall view of the chapter content and organization. *Icons* identify specific content related to infants and children , pregnant women , and older adults .

Reading and Learning Aids

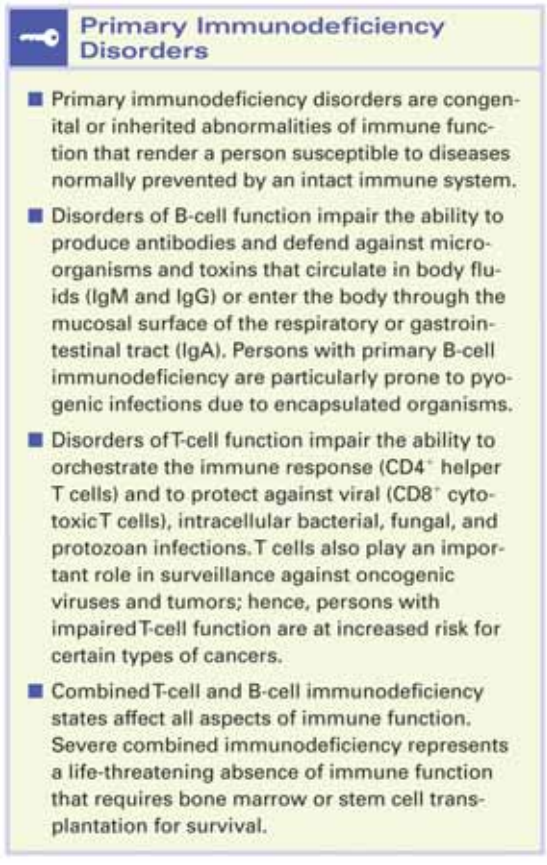
In an ever-expanding world of information you will not be able to read, let alone remember, everything that is in this book, or in any book, for that matter. With this in mind, we have developed a number of special features that will help you focus on and master the essential content for your current as well as future needs.

It is essential for any professional to use and understand the vocabulary of his or her profession. Throughout the text, you will encounter terms in *italics*. This is a signal that a word and the ideas associated with it are important to learn. In addition, in the back of the book are two aids that can be used to help you expand your vocabulary and improve your comprehension of what you are reading: the glossary and the list of prefixes and suffixes.

The *glossary* contains concise definitions of frequently encountered terms. If you are unsure of the meaning of a term you encounter in your reading, check the glossary in the back of the book before proceeding. The *list of prefixes and suffixes,* found in the inside back cover, is a tool to help you derive the meaning of words you may be unfamiliar with and increase your vocabulary. Many disciplines establish a vocabulary by affixing one or more letters to the beginning or end of a word or base to form a derivative word. Prefixes are added to the beginning of a word or base, and suffixes are added to the end. If you know the meanings of common prefixes and suffixes, you can usually derive the meaning of a word, even if you have never encountered it before.

Boxes

Boxes are used throughout the text to summarize and highlight key information. You will frequently encounter two types of boxes: *Key Concept Boxes* and *Summary Boxes*. One of the ways to approach learning is to focus on the major ideas or concepts rather than trying to memorize significant amounts of information. As you have probably already discovered, it is impossible to memorize everything that is in a particular section or chapter of the book. Not only does your brain have a difficult time trying to figure out where to store all the different bits of information, your brain doesn't know how to retrieve the information when you need it. Most important of all, memorized lists of content can seldom, if ever, be applied directly to an actual clinical situation. The *Key Concept Boxes* guide you in identifying the major ideas or concepts that form the foundation for truly understanding the major areas of content. When you understand the concepts in the Key Concept Boxes, you will have a framework for remembering and using the facts given in the text.



The *Summary Boxes* at the end of each section provide a review and a reinforcement of the main content that has been covered. Use the summaries to assure that you have covered and understand what you have read.

In summary, heart failure occurs when the heart fails to pump sufficient blood to meet the metabolic needs of body tissues. The physiology of heart failure reflects the interplay between a decrease in cardiac output that accompanies impaired function of the failing heart and the compensatory mechanisms that preserve the cardiac reserve. Compensatory mechanisms include the Frank-Starling mechanism, sympathetic nervous system activation, the renin-angiotensin-aldosterone mechanism, natriuretic peptides, endothelins, and myocardial hypertrophy and remodeling. In the failing heart, early decreases in cardiac function may go unnoticed because these compensatory mechanisms maintain the cardiac output. Unfortunately, the mechanisms were not intended for long-term use, and in severe and prolonged heart failure the compensatory mechanisms no longer are effective, and instead contribute to the progression of heart failure.

Tables and Charts

Tables and charts are designed to present complex information in a format that makes it more meaningful and easier to remember. Tables have two or more columns, and are often used for the purpose of comparing or contrasting information.

TABLE 8-2 Sources of Body Water Gains and Losses in the Adult

Gains		Losses	
Oral intake		Urine	1500 mL
As water	1000 mL	Insensible losses	
In food	1300 mL	Lungs	300 mL
Water of oxidation	200 mL	Skin	500 mL
		Feces	200 mL
Total	2500 mL	Total	2500 mL

Charts have one column and are used to summarize information.

CHART 18-1 Risk Factors for Atherosclerosis

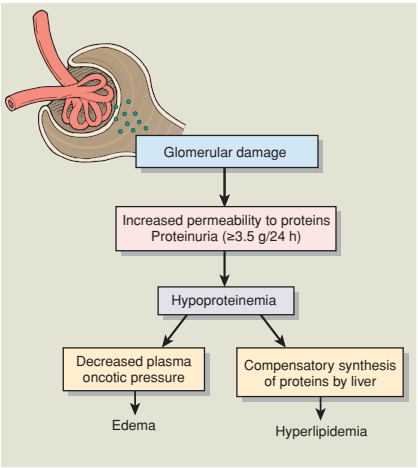
Nonmodifiable
- Increasing age
- Male gender
- Genetic disorders of lipid metabolism
- Family history of premature coronary artery disease

Potentially Modifiable
- Cigarette smoking
- Obesity
- Hypertension
- Hyperlipidemia with elevated low-density lipoprotein and low high-density lipoprotein cholesterol
- Diabetes mellitus

Additional Nontraditional
- Inflammation marked by elevated C-reactive protein levels
- Hyperhomocystinemia
- Increased lipoprotein (a) levels

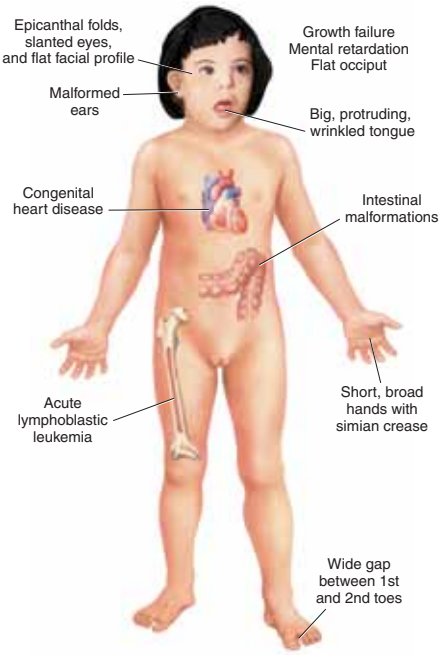
Illustrations and Photos

The full-color illustrations will help you to build your own mental image of the content that is being presented. Each drawing has been developed to fully support and build upon the ideas in the text. Some illustrations are used to help you picture the complex interactions of the multiple phenomena that are involved in the development of a particular disease; others can help you visualize normal function or understand the mechanisms whereby the disease processes exert their effects. In addition, photographs of pathologic processes and lesions provide a realistic view of selected pathologic processes and lesions.



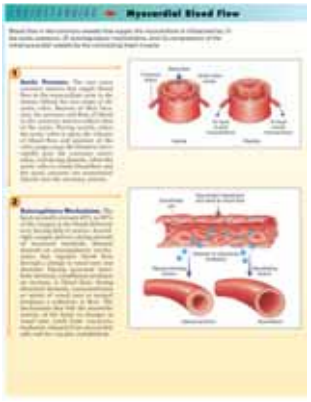
Clinical Features

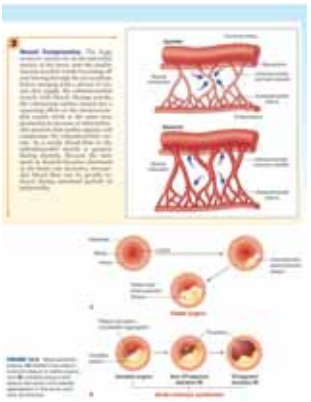
New to this edition is a new type of illustration that depicts the clinical features of persons with selected diseases. This feature is designed to help you visualize the entire spectrum of clinical manifestations that are associated with these disease states.



Understanding Physiologic Processes

Included in a number of chapters is an "*Understanding*" feature that focuses on the physiologic processes and phenomena that form the basis for understanding disorders presented in the text. This feature breaks a process or phenomenon down into its component parts and presents them in a sequential manner, providing an insight into the many opportunities for disease processes to disrupt the sequence.





Material for Review

An important feature has been built into the text to help you verify your understanding of the material presented. After you have finished reading and studying the chapter, work on answering the *review exercises* at the end of the chapter. They are designed to help you integrate, conceptualize, and apply material from the text. If you are unable to answer a question, reread the relevant section in the chapter.

REVIEW EXERCISES

1. A 6-year-old boy is admitted to the emergency department with nausea, vomiting, and abdominal pain. He is very lethargic; his skin is warm, dry, and flushed; his pulse is rapid; and he has a sweet smell to his breath. His parents relate that he has been very thirsty during the past several weeks, his appetite has been poor, and he has been urinating frequently. His initial plasma glucose is 420 mg/dL (23.1 mmol/L), and a urine test for ketones is strongly positive.

A. What is the most likely cause of this boy's elevated blood glucose and ketonuria?
B. Explain his presenting signs and symptoms in terms of the elevated blood glucose and metabolic acidosis.
C. What type of treatment will this boy require?

Appendix

The *Lab Values table* in the appendix of your book provides rapid access to normal values for many laboratory tests in conventional and SI units, as well as a description of the prefixes, symbols, and factors (e.g., micro, μ, 10^{-6}) used for describing these values. Knowledge of normal values can help you put abnormal values in context.

We hope that this guide has given you a clear picture of how to use this book. Good luck and enjoy the journey!

Acknowledgements

As in past editions, many persons participated in the creation of this work. The contributing authors deserve a special mention. Without their long hours of work preparing the eighth edition of *Pathophysiology: Concepts of Altered Health States,* which served as a foundation, the preparation of this essentials version would not have been possible. I would like to expressly share my gratitude to and esteem of Dr. Edward W. Carroll, who expired during the preparation of this edition. He was with the book from its beginning and played an important role in its genesis and continued development.

I would also like to acknowledge Dr. Kathryn Gaspard and Dr. Kim Noble for their consultation and help in making this edition become a reality. Dr. Gaspard, in particular, deserves special thanks. Her genial nature, wide-breadth of knowledge, and skillful assistance were invaluable in preparing the text and developing the illustrations for the book. Several other persons deserve special recognition. Georgianne Heymann assisted in editing the manuscript. As with previous editions, she provided not only excellent editorial assistance but also encouragement and support when the tasks associated with manuscript preparation became most frustrating.

Special thanks also to those at Lippincott Williams & Wilkins who participated in the development of this edition: Hilarie Surrena, Senior Acquisitions Editor; Katherine Burland, Product Manager; and Brett MacNaughton, Art Director. Acknowledgement also goes to Wendy Beth Jackelow, MFA, CMI, for her talent and expertise in creating and modifying the illustrations; and to Jeri Litteral, Managing Editor, Aptara Corporation, for her dedication in managing the production and printing of the book.

The students in the classes I have taught over the years also deserve a special salute, for they are the inspiration upon which this book was founded. They provided the questions, suggestions, and contact with the "real world" of patient care that directed the organization and selection of content for the book.

And last, but certainly not least, I would like to acknowledge my family and my friends for their unlimited patience, understanding, and encouragement throughout the entire process.

Contents

Introduction to Pathophysiology xix

UNIT 1 Cell and Tissue Function 1

Chapter 1 Cell Structure and Function 1
Edward W. Carroll
Functional Components of the Cell 1
Cell Metabolism and Energy Storage 9
Integration of Cell Function 12
Body Tissues 20

Chapter 2 Cellular Responses to Stress, Injury, and Aging 33
Carrie J. Merkle
Cellular Responses to Persistent Stress 33
Cell Injury, Death, and Senescence 38

Chapter 3 Inflammation, the Inflammatory Response, and Fever 51
General Features of Inflammation 51
Acute Inflammation 55
Chronic Inflammation 63
Systemic Manifestations of Inflammation 64

Chapter 4 Cell Proliferation and Tissue Regeneration and Repair 73
Carrie J. Merkle
Cell Proliferation and Tissue Regeneration 73
Healing by Connective Tissue Repair 80

Chapter 5 Genetic Control of Cell Function and Inheritance 89
Edward W. Carroll
Genetic Control of Cell Function 89
Chromosomes 97
Patterns of Inheritance 100
Gene Technology 103

Chapter 6 Genetic and Congenital Disorders 109
Genetic and Congenital Disorders
Genetic and Chromosomal Disorders 109
Disorders Due to Environmental Influences 123
Prenatal Screening and Diagnosis 126

Chapter 7 Neoplasia 131
Carrie J. Merkle
Characteristics of Benign and Malignant Neoplasms 131
Etiology of Cancer 139
Clinical Manifestations 146
Screening, Diagnosis, and Treatment 148
Childhood Cancers 154

UNIT 2 Integrative Body Functions 159

Chapter 8 Disorders of Fluid, Electrolyte, and Acid-Base Balance 159
Carol M. Porth and Kim A. Noble
Composition and Compartmental Distribution of Body Fluids 159
Sodium and Water Balance 167
Potassium Balance 178
Calcium and Magnesium Balance 183
Acid-Base Balance 192

Chapter 9 Stress and Adaptation 209
Mary Pat Kunert
Stress and Adaptation 209
Disorders of the Stress Response 218

Chapter 10 Disorders of Nutritional Status 224
Joan Pleuss and Glenn Matfin
Energy Metabolism and Nutritional Status 224
Overweight and Obesity 231
Undernutrition and Eating Disorders 235

UNIT 3 Hematopoietic Function 243

Chapter 11 Disorders of White Blood Cells and Lymphoid Tissues 243
Hematopoietic and Lymphoid Tissues 243
Nonneoplastic Disorders of White Blood Cells 248
Neoplastic Disorders of Hematopoietic and Lymphoid Origin 251

Chapter 12 Disorders of Hemostasis 263
Kathryn J. Gaspard
Hemostasis and Blood Coagulation 263
Hypercoagulability States 269
Bleeding Disorders 271

Chapter 13 Disorders of Red Blood Cells 279
Kathryn J. Gaspard
The Red Blood Cell 279
Anemia 284
Polycythemia 293
Age-Related Changes in Red Blood Cells 293

UNIT 4 Infection and Immunity 299

Chapter 14 Mechanisms of Infectious Disease 299
W. Michael Dunne Jr. and Nathan A. Ledeboer
Infectious Diseases 299
Epidemiology of Infectious Diseases 307
Diagnosis and Treatment 312
New and Emerging Infectious Diseases 316

Chapter 15 Innate and Adaptive Immunity 319
Cynthia Sommer
Introduction to the Immune System 319
Innate Immunity 326
Adaptive Immunity 332
Developmental Aspects of the Immune System 342

Chapter 16 Disorders of the Immune Response 345
Judith A. Aberg and Jason Faulhaber
Hypersensitivity Disorders 345
Transplantation Immunopathology 353
Autoimmune Disease 355
Immunodeficiency Disorders 359

UNIT 5 Circulatory Function 377

Chapter 17 Control of Cardiovascular Function 377
Organization of the Circulatory System 377
Principles of Blood Flow 380
The Heart as a Pump 384
The Systemic Circulation and Control of Blood Flow 396
Neural Control of Circulatory Function 402

Chapter 18 Disorders of Blood Flow and Blood Pressure 405
Glenn Matfin and Carol M. Porth
Blood Vessel Structure and Function 405
Disorders of the Arterial Circulation 407
Disorders of Arterial Blood Pressure 422
Disorders of the Venous Circulation 439

Chapter 19 Disorders of Cardiac Function 447
Toni Balistrieri and Kathleen Mussatto
Disorders of the Pericardium 447
Coronary Artery Disease 450
Cardiomyopathies 461
Endocardial and Valvular Disorders 466
Heart Disease in Infants and Children 474

Chapter 20 Heart Failure and Circulatory Shock 486
Anna Barkman and Charlotte Pooler
Heart Failure 486
Circulatory Failure (Shock) 499
Heart Failure in Children and the Elderly 508

UNIT 6 Respiratory Function 513

Chapter 21 Control of Respiratory Function 513
Structural Organization of the Respiratory System 513
Exchange of Gases Between the Atmosphere and the Lungs 520
Exchange and Transport of Gases 528
Control of Breathing 536

Chapter 22 Respiratory Tract Infections, Neoplasms, and Childhood Disorders 540
Respiratory Tract Infections 540
Cancer of the Lung 554
Respiratory Disorders in Children 557

Chapter 23 Disorders of Ventilation and Gas Exchange 566
Charlotte Pooler
Physiologic Effects of Ventilation and Diffusion Disorders 566
Disorders of Lung Inflation 569
Obstructive Airway Disorders 573
Interstitial Lung Diseases 586
Disorders of the Pulmonary Circulation 589
Acute Respiratory Disorders 593

UNIT 7 Kidney and Urinary Tract Function 601

Chapter 24 Structure and Function of the Kidney 601
Kidney Structure and Function 601
Tests of Renal Function 616

Chapter 25 Disorders of Renal Function 620
Disorders of Glomerular Function 620
Tubulointerstitial Disorders 627
Cystic Diseases of the Kidney 630
Obstructive Disorders 633
Malignant Tumors of the Kidney 637

Chapter 26 Acute Renal Failure and Chronic Kidney Disease 641
Acute Renal Failure 641
Chronic Kidney Disease 645
Chronic Kidney Disease in Children and Elderly Persons 655

Chapter 27 Disorders of the Bladder and Lower Urinary Tract 659
Control of Urine Elimination 659
Disorders of Bladder Structure and Function 663
Urinary Tract Infections 671
Cancer of the Bladder 675

UNIT 8 Gastrointestinal and Hepatobiliary Function 679

Chapter 28 Structure and Function of the Gastrointestinal System 679
Structure and Organization of the Gastrointestinal Tract 679
Motility 684
Hormonal, Secretory, and Microflora Functions 690
Digestion and Absorption 694
Anorexia, Nausea, and Vomiting 697

Chapter 29 Disorders of Gastrointestinal Function 700
Disorders of the Esophagus 700
Disorders of the Stomach 705
Disorders of the Small and Large Intestines 710

Chapter 30 Disorders of Hepatobiliary and Exocrine Pancreas Function 729
The Liver and Hepatobiliary System 729
Disorders of Hepatic and Biliary Function 737
Disorders of the Gallbladder and Exocrine Pancreas 752

UNIT 9 Endocrine System 761

Chapter 31 Mechanisms of Endocrine Control 761
Glenn Matfin
The Endocrine System 761

Chapter 32 Disorders of Endocrine Control of Growth and Metabolism 774
Glenn Matfin
General Aspects of Altered Endocrine Function 774
Pituitary and Growth Disorders 775
Thyroid Disorders 782
Disorders of Adrenal Cortical Function 790

Chapter 33 Diabetes Mellitus and the Metabolic Syndrome 799
Safak Guven, Glenn Matfin, and Julie A. Kuenzi
Hormonal Control of Nutrient Metabolism and Storage 799
Diabetes Mellitus 805

UNIT 10 Nervous System 829

Chapter 34 Organization and Control of Neural Function 829
Edward W. Carroll and Robin Curtis
Nervous Tissue Cells 829
Nerve Cell Communication 833
Developmental Organization of the Nervous System 837
Spinal Cord and Brain 845
The Autonomic Nervous System 855

Chapter 35 Somatosensory Function, Pain, and Headache 863
Kim A. Noble and Kim Litwack
Organization and Control of Somatosensory Function 863
Pain Sensation 870
Alterations in Pain Sensitivity and Special Types of Pain 880
Headache and Associated Pain 883
Pain in Children and Older Adults 886

Chapter 36 Disorders of Neuromuscular Function 891
Serena W. Hung
Organization and Control of Motor Function 891
Disorders of the Motor Unit 899
Disorders of the Cerebellum and Basal Ganglia 908
Upper Motor Neuron Disorders 913

Chapter 37 Disorders of Brain Function 927
Diane S. Book
Mechanisms and Manifestations of Brain Injury 927
Cerebrovascular Disease 941
Infections and Brain Tumors 951
Seizure Disorders 955
Disorders of Memory and Cognition 959

Chapter 38 Disorders of Special Sensory Function: Vision, Hearing, and Vestibular Function 966
Edward W. Carroll and Scott A. Jens, Disorders of Vision; Susan A. Fontana, Disorders of Hearing and Vestibular Function
The Eye and Disorders of Vision 966
The Ear and Disorders of Auditory Function 988
The Vestibular System and Disorders of Equilibrium 1000

UNIT 11 Genitourinary and Reproductive Function 1009

Chapter 39 Disorders of the Male Genitourinary System 1009
Glenn Matfin
Physiologic Basis of Male Reproductive Function 1009
Disorders of the Penis, the Scrotum and Testes, and the Prostate 1016
Disorders in Childhood and Aging Changes 1028

Chapter 40 Disorders of the Female Genitourinary System 1033
Patricia McCowen Mehring
Structure and Function of the Female Reproductive System 1033
Disorders of the Female Reproductive Organs 1041
Menstrual Disorders 1055
Disorders of the Breast 1059

Chapter 41 Sexually Transmitted Infections 1067
Patricia McCowen Mehring
Infections of the External Genitalia 1068
Vaginal Infections 1072
Vaginal-Urogenital-Systemic Infections 1074

UNIT 12 Musculoskeletal Function 1081

Chapter 42 Structure and Function of the Skeletal System 1081
Structures of the Skeletal System 1081
Joints 1092

Chapter 43 Disorders of the Skeletal System: Trauma, Infections, Neoplasms, and Childhood Disorders 1096
Kathleen E. Gunta
Injury and Trauma of Musculoskeletal Structures 1096
Bone Infections and Osteonecrosis 1109
Neoplasms 1113
Skeletal Disorders in Children 1116

Chapter 44 Disorders of the Skeletal System: Metabolic and Rheumatic Disorders 1130
Kathleen E. Gunta, Metabolic Disorders; Debra Bancroft Rizzo, Rheumatic Disorders
Metabolic Bone Disease 1130
Rheumatic Disorders 1138
Rheumatic Diseases in Children and the Elderly 1153

UNIT 13 Integumentary Function 1159

Chapter 45 Structure and Function of the Skin 1159
Gladys Simandl
Structure and Function of the Skin 1159
Manifestations of Skin Disorders 1166

Chapter 46 Disorders of Skin Integrity and Function 1172
Gladys Simandl
Primary Disorders of the Skin 1172
Ultraviolet Radiation, Thermal, and Pressure Injury 1188
Nevi and Skin Cancers 1194
Age-Related Skin Manifestations 1198

Glossary 1207
Appendix A: Laboratory Values 1217
Index 1219

Introduction to Pathophysiology

The term *pathophysiology,* which is the focus of this book, may be defined as the physiology of altered health. The term combines the words *pathology* and *physiology.* Pathology (from the Greek *pathos,* meaning "disease") deals with the study of the structural and functional changes in cells, tissues, and organs of the body that cause or are caused by disease. Physiology deals with the functions of the human body. Thus, pathophysiology deals not only with the cellular and organ changes that occur with disease, but with the effects that these changes have on total body function. Pathophysiology also focuses on the mechanisms of the underlying disease process and provides the background for preventive as well as therapeutic health care measures and practices.

Disease

A *disease* has been defined as an interruption, cessation, or disorder of a body system or organ structure that is characterized usually by a recognized etiologic agent or agents, an identifiable group of signs and symptoms, or consistent anatomic alterations.[1] The aspects of the disease process include etiology, pathogenesis, morphologic changes, clinical manifestations, diagnosis, and clinical course.

Etiology

The causes of disease are known as *etiologic factors*. Among the recognized etiologic agents are biologic agents (e.g., bacteria, viruses), physical forces (e.g., trauma, burns, radiation), chemical agents (e.g., poisons, alcohol), and nutritional excesses or deficits. At the molecular level, it is important to distinguish between abnormal molecules and molecules that cause disease.[2] This is true of diseases such as cystic fibrosis, sickle cell anemia, and familial hypercholesterolemia, in which the genetic abnormality of a single amino acid, transporter molecule, or receptor protein produces widespread effects on health.

Most disease-causing agents are nonspecific, and many different agents can cause disease of a single organ. On the other hand, a single agent or traumatic event can lead to disease of a number of organs or systems. Although a disease agent can affect more than a single organ and a number of disease agents can affect the same organ, most disease states do not have a single cause. Instead, the majority of diseases are multifactorial in origin. This is particularly true of diseases such as cancer, heart disease, and diabetes. The multiple factors that predispose to a particular disease often are referred to as *risk factors*.

One way to view the factors that cause disease is to group them into categories according to whether they were present at birth or acquired later in life. *Congenital conditions* are defects that are present at birth, although they may not be evident until later in life. Congenital conditions may be caused by genetic influences, environmental factors (e.g., viral infections in the mother, maternal drug use, irradiation, or intrauterine crowding), or a combination of genetic and environmental factors. *Acquired defects* are those that are caused by events that occur after birth. These include injury, exposure to infectious agents, inadequate nutrition, lack of oxygen, inappropriate immune responses, and neoplasia. Many diseases are thought to be the result of a genetic predisposition and an environmental event or events that serve as a trigger to initiate disease development.

Pathogenesis

Pathogenesis is the sequence of cellular and tissue events that take place from the time of initial contact with an etiologic agent until the ultimate expression of a disease. Etiology describes what sets the disease process in motion, and pathogenesis, how the disease process evolves. Although the two terms often are used interchangeably, their meanings are quite different. For example, atherosclerosis often is cited as the cause or etiology of coronary heart disease. In reality, the progression from fatty streak to the occlusive vessel lesion seen in persons with coronary heart disease represents the pathogenesis of the disorder. The true etiology of atherosclerosis remains largely uncertain.

Morphology

Morphology refers to the fundamental structure or form of cells or tissues. *Morphologic changes* are concerned with both the gross anatomic and microscopic changes that are characteristic of a disease. *Histology* deals with the study of the cells and extracellular matrix of body tissues. The most common method used in the study of tissues is the preparation of histologic sections—thin, translucent sections of human tissues and organs—that can be examined with the aid of a microscope. Histologic sections play an important role in the diagnosis of many types of cancer. A *lesion* represents a pathologic or traumatic discontinuity of a body organ or tissue. Descriptions of lesion size and characteristics often can be obtained through the use of radiographs, ultrasonography, and other imaging methods. Lesions also may be sampled by biopsy and the tissue samples subjected to histologic study.

Clinical Manifestations

Diseases can manifest in a number of ways. Sometimes the condition produces manifestations, such as fever, that make it evident that the person is sick. In other cases, the condition is silent at the onset and is detected during examination for other purposes or after the disease is far advanced.

Signs and *symptoms* are terms used to describe the structural and functional changes that accompany a disease. A *symptom* is a subjective complaint that is noted by the person with a disorder, whereas a *sign* is a manifestation that is noted by an observer. Pain, difficulty in breathing, and dizziness are symptoms of a disease. An elevated temperature, a swollen extremity, and changes in pupil size are objective signs that can be observed by someone other than the person with the disease. Signs and symptoms may be related to the primary disorder or they may represent the body's attempt to compensate for the altered function caused by the pathologic condition. Many pathologic states are not observed directly—one cannot see a sick heart or a failing kidney. Instead, what can be observed is the body's attempt to compensate for changes in function brought about by the disease, such as the tachycardia that accompanies blood loss or the increased respiratory rate that occurs with pneumonia.

A *syndrome* is a compilation of signs and symptoms (e.g., chronic fatigue syndrome) that are characteristic of a specific disease state. *Complications* are possible adverse extensions of a disease or outcomes from treatment. *Sequelae* are lesions or impairments that follow or are caused by a disease.

Diagnosis

A *diagnosis* is the designation as to the nature or cause of a health problem (e.g., bacterial pneumonia or hemorrhagic stroke). The diagnostic process usually requires a careful history and physical examination. The history is used to obtain a person's account of his or her symptoms and their progression, and the factors that contribute to a diagnosis. The physical examination is done to observe for signs of altered body structure or function.

The development of a diagnosis involves weighing competing possibilities and selecting the most likely one from among the conditions that might be responsible for the person's clinical presentation. The clinical probability of a given disease in a person of a given age, sex, race, lifestyle, and locality often is influential in arrival at a presumptive diagnosis. Laboratory tests, radiologic studies, computed tomography (CT) scans, and other tests often are used to confirm a diagnosis.

An important factor when interpreting diagnostic test results is the determination of whether they are normal or abnormal. Is a blood count above normal, within the normal range, or below normal? What is termed a *normal* value for a laboratory test is established statistically from test results obtained from a selected sample of people. The normal values refer to the 95% distribution (mean plus or minus two standard deviations [mean ± 2 SD]) of test results for the reference population.[3,4] Thus, the normal levels for serum sodium (136 to 145 mEq/L) represent the mean serum level for the reference population ± 2 SD. The normal values for some laboratory tests are adjusted for sex or age. For example, the normal hemoglobin range for women is 12.0 to 16.0 g/dL, and for men, 14.0 to 17.4 g/dL.[5] Serum creatinine level often is adjusted for age in the elderly, and normal values for serum phosphate differ between adults and children.

The quality of data on which a diagnosis is based may be judged for their validity, reliability, sensitivity, specificity, and predictive value.[6,7] *Validity* refers to the extent to which a measurement tool measures what it is intended to measure. This often is assessed by comparing a measurement method with the best possible method of measure that is available. For example, the validity of blood pressure measurements obtained by a sphygmomanometer might be compared with those obtained by intra-arterial measurements. *Reliability* refers to the extent to which an observation, if repeated, gives the same result. A poorly calibrated blood pressure machine may give inconsistent measurements of blood pressure, particularly of pressures in either the high or low range. Reliability also depends on the persons making the measurements. For example, blood pressure measurements may vary from one observer to another because of the technique that is used (e.g., different observers may deflate the cuff at a different rate, thus obtaining different values), the way the numbers on the manometer are read, or differences in hearing acuity.

In the field of clinical laboratory measurements, *standardization* is aimed at increasing the trueness and reliability of measured values. Standardization relies on the use of written standards, reference measurement procedures, and reference materials.[7] In the United States, the Food and Drug Administration (FDA) regulates in vitro diagnostic devices, including clinical laboratory instruments, test kits, and reagents. Manufacturers who propose to market new diagnostic devices must submit information on their instrument, test kit, or reagent to the FDA, as required by existing statutes and regulations. The FDA reviews this information to decide whether the product may be marketed in the United States.

Measures of sensitivity and specificity are concerned with determining how likely or how well the test or observation will identify people with the disease and people without the disease.[9] *Sensitivity* refers to the proportion of people with a disease who are positive for that disease on a given test or observation (called a *true-positive* result). If the result of a very sensitive test is negative, it tells us the person does not have the disease and the disease has been excluded or "ruled out." *Specificity* refers to the proportion of people without the disease who are negative on a given test or observation (called a *true-negative* result). Specificity can be calculated only from among people who do not have the disease. A test that is 95% specific correctly identifies 95 of 100 normal people. The other 5% are *false-positive* results. A false-positive test result can be unduly stressful for the person being tested, whereas a *false-negative* test result can delay diagnosis and jeopardize the outcome of treatment.

Predictive value is the extent to which an observation or test result is able to predict the presence of a given disease or condition.[8,9] A *positive predictive value* refers to the proportion of true-positive results that occurs in a given population. In a group of women found to have "suspect breast nodules" in a cancer screening program, the proportion later determined to have breast cancer would constitute the positive predictive value. A *negative predictive value* refers to the true-negative observations in

a population. In a screening test for breast cancer, the negative predictive value represents the proportion of women without suspect nodules who do not have breast cancer. Although predictive values rely in part on sensitivity and specificity, they depend more heavily on the prevalence of the condition in the population. Despite unchanging sensitivity and specificity, the positive predictive value of an observation rises with prevalence, whereas the negative predictive value falls.

Clinical Course

The clinical course describes the evolution of a disease. A disease can have an acute, subacute, or chronic course. An *acute disorder* is one that is relatively severe, but self-limiting. *Chronic disease* implies a continuous, long-term process. A chronic disease can run a continuous course or can present with exacerbations (aggravation of symptoms and severity of the disease) and remissions (a period during which there is a decrease in severity and symptoms). *Subacute disease* is intermediate or between acute and chronic: it is not as severe as an acute disease and not as prolonged as a chronic disease.

The spectrum of disease severity for infectious diseases, such as hepatitis B, can range from preclinical to persistent chronic infection. During the *preclinical stage,* the disease is not clinically evident but is destined to progress to clinical disease. As with hepatitis B, it is possible to transmit a virus during the preclinical stage. *Subclinical disease* is not clinically apparent and is not destined to become clinically apparent. It is diagnosed with antibody or culture tests. Most cases of tuberculosis are not clinically apparent, and evidence of their presence is established by skin tests. *Clinical disease* is manifested by signs and symptoms. A persistent chronic infectious disease persists for years, sometimes for life. *Carrier status* refers to an individual who harbors an organism but is not infected, as evidenced by antibody response or clinical manifestations. This person still can infect others. Carrier status may be of limited duration or it may be chronic, lasting for months or years.

Perspectives and Patterns of Disease

The health of individuals is closely linked to the health of the community and to the population it encompasses. The ability to traverse continents in a matter of hours has opened the world to issues of populations at a global level. Diseases that once were confined to local areas of the world now pose a threat to populations throughout the world.

As we move through the 21st century, we are continually reminded that the health care system and the services it delivers are targeted to particular populations. Managed care systems are focused on a population-based approach to planning, delivering, providing, and evaluating health care. The focus of health care also has begun to emerge as a partnership in which individuals are asked to assume greater responsibility for their own health.

Epidemiology and Patterns of Disease

Epidemiology is the study of disease occurrence in human populations.[8] It was initially developed to explain the spread of infectious diseases during epidemics and has emerged as a science to study risk factors for multifactorial diseases, such as heart disease and cancer. Epidemiology looks for patterns of persons affected with a particular disorder, such as age, race, dietary habits, lifestyle, or geographic location. In contrast to biomedical researchers, who seek to elucidate the mechanisms of disease production, epidemiologists are more concerned with whether something happens than how it happens. For example, the epidemiologist is more concerned with whether smoking itself is related to cardiovascular disease and whether the risk of heart disease decreases when smoking ceases. On the other hand, the biomedical researcher is more concerned about the causative agent in cigarette smoke and the pathway by which it contributes to heart disease.

Much of our knowledge about disease comes from epidemiologic studies. Epidemiologic methods are used to determine how a disease is spread, how to control it, how to prevent it, and how to eliminate it. Epidemiologic methods also are used to study the natural history of disease, to evaluate new preventative and treatment strategies, to explore the impact of different patterns of health care delivery, and to predict future health care needs. As such, epidemiologic studies serve as a basis for clinical decision making, allocation of health care dollars, and development of policies related to public health issues.

Measures of disease frequency are an important aspect of epidemiology. They establish a means for predicting what diseases are present in a population and provide an indication of the rate at which they are increasing or decreasing. A *disease case* can be either an existing case or the number of new episodes of a particular illness that is diagnosed within a given period. *Incidence* reflects the number of new cases arising in a population at risk during a specified time. The population at risk is considered to be persons without the disease but who are at risk for developing it. It is determined by dividing the number of new cases of a disease by the population at risk for development of the disease during the same period (e.g., new cases per 1000 or 100,000 persons in the population who are at risk). The cumulative incidence estimates the risk of developing the disease during that period of time. *Prevalence* is a measure of existing disease in a population at a given point in time (e.g., number of existing cases divided by the current population).[8] The prevalence is not an estimate of risk of developing a disease because it is a function of both new cases and how long the cases remain in the population. Incidence and prevalence are always reported as rates (e.g., cases per 100 or cases per 100,000).

Morbidity and mortality statistics provide information about the functional effects (morbidity) and death-producing (mortality) characteristics of a disease. These statistics are useful in terms of anticipating health care needs, planning of public education programs, directing health research efforts, and allocating health care dollars.

Mortality statistics provide information about the causes of death in a given population. In most countries, people are legally required to record certain facts such as age, sex, and cause of death on a death certificate. Internationally agreed on classification procedures (the International Classification of Diseases [ICD] by the WHO) are used for coding the cause of death, and the data are expressed as death rates.[10] Crude mortality rates (i.e., number of deaths in a given period) do not account for age, sex, race, socioeconomic status, and other factors. For this reason, mortality often is expressed as death rates for a specific population, such as the infant mortality rate. Mortality also can be described in terms of the leading causes of death according to age, sex, race, and ethnicity.

Morbidity describes the effects an illness has on a person's life. Many diseases, such as arthritis, have low death rates but a significant impact on a person's life. Morbidity is concerned not only with the occurrence or incidence of a disease but with persistence and the long-term consequences of the disease.

Determination of Risk Factors

Conditions suspected of contributing to the development of a disease are called *risk factors*. They may be inherent to the person (high blood pressure or overweight) or external (smoking or drinking alcohol). There are different types of studies used to determine risk factors, including cross-sectional studies, case-control studies, and cohort studies. *Cross-sectional studies* use the simultaneous collection of information necessary for classification of exposure and outcome status. They can be used to compare the prevalence of a disease in those with the factor (or exposure) with the prevalence of a disease in those who are unexposed to the factor, such as the prevalence of coronary heart disease in smokers and nonsmokers. *Case-control studies* are designed to compare persons known to have the outcome of interest (*cases*) and those known not to have the outcome of interest (*controls*).[8] Information on exposures or characteristics of interest is then collected from persons in both groups. For example, the characteristics of maternal alcohol consumption in infants born with fetal alcohol syndrome (cases) can be compared with those in infants born without the syndrome (controls).

A *cohort* is a group of persons who were born at approximately the same time or share some characteristics of interest.[8] Persons enrolled in a cohort study (also called a *longitudinal study*) are followed over a period of time to observe a specific health outcome. A cohort may consist of a single group of persons chosen because they have or have not been exposed to suspected risk factors; two groups specifically selected because one has been exposed and the other has not; or a single exposed group in which the results are compared with the general population.

One of the best-known examples of a cohort study is the Framingham Study, which was carried out in Framingham, Massachusetts.[11] Framingham was selected because of the size of the population, the relative ease with which the people could be contacted, and the stability of the population in terms of moving into and out of the area. This longitudinal study, which began in 1950, was set up by the U.S. Public Health Service to study the characteristics of people who would later develop coronary heart disease. The study consisted of 5000 persons, aged 30 to 59 years, selected at random and followed for an initial period of 20 years, during which time it was predicted that 1500 of them would develop coronary heart disease. The advantage of such a study is that it can explore a number of risk factors at the same time and determine the relative importance of each. Another advantage is that the risk factors can be related later to other diseases such as stroke.

A second well-known cohort study is the Nurses' Health Study, which was developed by Harvard University and Brigham and Women's Hospital. The study began in 1976 with a cohort of 121,700 female nurses, 30 to 55 years of age, living in the United States.[12] Initially designed to explore the relationship between oral contraceptives and breast cancer, nurses in the study have provided answers to detailed questions about their menstrual cycle, smoking habits, diet, weight and waist measurements, activity patterns, health problems, and medication use. They have collected urine and blood samples, and even provided researchers with their toenail clippings. In selecting the cohort, it was reasoned that nurses would be well organized, accurate, and observant in their responses, and that physiologically they would be no different from other groups of women. It also was anticipated that their childbearing, eating, and smoking patterns would be similar to those of other working women.

Natural History

The *natural history* of a disease refers to the progression and projected outcome of the disease without medical intervention. By studying the patterns of a disease over time in populations, epidemiologists can better understand its natural history. Knowledge of the natural history can be used to determine disease outcome, establish priorities for health care services, determine the effects of screening and early detection programs on disease outcome, and compare the results of new treatments with the expected outcome without treatment.

There are some diseases for which there are no effective treatment methods available, or the current treatment measures are effective only in certain people. In this case, the natural history of the disease can be used as a predictor of outcome. For example, the natural history of hepatitis C indicates that 80% of people who become infected with the virus fail to clear the virus and progress to chronic infection.[13] Information about the natural history of a disease and the availability of effective treatment methods provides directions for preventive measures. In the case of hepatitis C, careful screening of blood donations and education of intravenous drug abusers can be used to prevent transfer of the virus. At the same time, scientists are striving to develop a vaccine that will prevent infection in persons exposed to the virus. The development of vaccines to prevent the spread of infectious diseases such as polio and hepatitis B

undoubtedly has been motivated by knowledge about the natural history of these diseases and the lack of effective intervention measures. With other diseases, such as breast cancer, early detection through use of breast self-examination and mammography increases the chances for a cure.

Prognosis refers to the probable outcome and prospect of recovery from a disease. It can be designated as chances for full recovery, possibility of complications, or anticipated survival time. Prognosis often is presented in relation to treatment options—that is, the expected outcomes or chances for survival with or without a certain type of treatment. The prognosis associated with a given type of treatment usually is presented along with the risk associated with the treatment.

Levels of Prevention

Basically, leading a healthy life contributes to the prevention of disease. There are three fundamental types of prevention: primary prevention, secondary prevention, and tertiary prevention.[8,14] It is important to note that all three levels are aimed at prevention. *Primary prevention* is directed at keeping disease from occurring by removing all risk factors. Examples of primary prevention include the administration of folic acid to pregnant women and women who may become pregnant to prevent fetal neural tube defects, giving immunizations to children to prevent communicable disease, and counseling people to adopt healthy lifestyles as a means of preventing heart disease.[8] Primary prevention is often accomplished outside the health care system at the community level. Some primary prevention measures are mandated by law (e.g., wearing seat belts in automobiles and helmet use on motorcycles). Other primary prevention activities (e.g., use of earplugs or dust masks) occur in specific occupations. *Secondary prevention* detects disease early when it is still asymptomatic and treatment measures can affect a cure or stop it from progressing. The use of a Papanicolaou (Pap) smear for early detection of cervical cancer is an example of secondary prevention. Screening also includes history taking (asking if a person smokes), physical examination (blood pressure measurement), laboratory tests (cholesterol level determination), and other procedures (colonoscopy) that can be "applied reasonably rapidly to asymptomatic people."[8] Most secondary prevention is done in clinical settings. All types of health care professionals (e.g., physicians, nurses, dentists, audiologists, optometrists) participate in secondary prevention. *Tertiary prevention* is directed at clinical interventions that prevent further deterioration or reduce the complications of a disease once it has been diagnosed.

Evidence-Based Practice and Practice Guidelines

Evidence-based practice and evidence-based practice guidelines have recently gained popularity with clinicians, public health practitioners, health care organizations, and the public as a means of improving the quality and efficiency of health care.[15] Their development has been prompted, at least in part, by the enormous amount of published information about diagnostic and treatment measures for various disease conditions, as well as demands for better and more cost-effective health care.

Evidence-based practice has been defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[15] It is based on the integration of the individual expertise of the practitioner with the best external clinical evidence from systematic research.[15] The term *clinical expertise* implies the proficiency and judgment that individual clinicians gain through clinical experience and clinical practice. The best external clinical evidence relies on the identification of clinically relevant research, often from the basic sciences, but especially from patient-centered clinical studies that focus on the accuracy and precision of diagnostic tests and methods, the power of prognostic indicators, and the effectiveness and safety of therapeutic, rehabilitative, and preventive regimens.

Clinical practice guidelines are systematically developed statements intended to inform practitioners and clients in making decisions about health care for specific clinical circumstances.[16,17] They not only should review but also must weigh various outcomes, both positive and negative, and make recommendations. Guidelines are different from systematic reviews. They can take the form of algorithms, which are step-by-step methods for solving a problem, written directives for care, or a combination thereof.

The development of evidence-based practice guidelines often uses methods such as meta-analysis to combine evidence from different studies to produce a more precise estimate of the accuracy of a diagnostic method or the effects of an intervention method.[18] It also requires review: by practitioners with expertise in clinical content, who can verify the completeness of the literature review and ensure clinical sensibility; from experts in guideline development who can examine the method by which the guideline was developed; and by potential users of the guideline.[16]

Once developed, practice guidelines must be continually reviewed and changed to keep pace with new research findings and new diagnostic and treatment methods. For example, the Guidelines for the Prevention, Evaluation, and Treatment of High Blood Pressure (see Chapter 23), first developed in 1972 by the Joint National Committee, have been revised seven times, and the Guidelines for the Diagnosis and Management of Asthma (see Chapter 22), first developed in 1991 by the Expert Panel, have undergone four revisions.

Evidence-based practice guidelines, which are intended to direct client care, are also important in directing research into the best methods of diagnosing and treating specific health problems. This is because health care providers use the same criteria for diagnosing the extent and severity of a particular condition such as hypertension, and because they use the same protocols for treatment.

REFERENCES

1. *Stedman's medical dictionary.* (2006). (28th ed., p. 855). Philadelphia: Lippincott Williams & Wilkins.
2. Waldenstrom J. (1989). Sick molecules and our concepts of illness. *Journal of Internal Medicine* 225, 221–227.
3. Brigden M. L., Heathcote J. C. (2000). Problems with interpreting laboratory tests. Postgraduate Medicine 107(7), 145–162.
4. Mayer D. (2004). Essentials of evidence-based medicine. New York: Cambridge University Press.
5. Fischbach F. (2004). A manual of laboratory and diagnostic tests (7th ed., p. 74, 964). Philadelphia: Lippincott Williams & Wilkins.
6. Dawson B., Trapp R. G., Trapp R. (2004). Basic and clinical biostatistics. New York: Lange Medical Books/McGraw-Hill.
7. World Health Organization. (2007). About WHO: Definition of health; disease eradication/elimination goals. [Online.] Available: www.who.int/about/definition/en/. Accessed January 10, 2009.
8. Michaud G. Y. (2005). The role of standards in the development and implementation of clinical laboratory tests: A domestic and global perspective. Cancer Biomarkers 1, 209–216.
9. Fletcher R. H., Fletcher S. W. (2005). Clinical epidemiology: The essentials (4th ed.). Philadelphia: Lippincott Williams & Wilkins.
10. Montori V. M., Wyer P., Newman T. B., et al. (2005). Tips for learning of evidence-based medicine: 5. The effect of spectrum of disease on performance of diagnostic tests. Canadian Medical Association Journal 173, 385–390.
11. Framingham Heart Study. (2008). Framingham Heart Study: Design, rationale, objectives, and research milestones. [Online]. Available: http://www.framinghamheartstudy.org/research/review.html Accessed January 10, 2009.
12. Channing Laboratory. (2007). Nurses' Health Study. [Online]. Available: http://www.brighamandwomens.org/publicaffairs/NursesHealthStudy.aspx?subID=submenu5 Accessed January 10, 2009.
13. Liang J., Reherman B., Seeff L. B., et al. (2000). Pathogenesis, natural history, treatment, and prevention of hepatitis C. Annals of Internal Medicine 132, 296–305.
14. Stanhope M., Lancaster J. (2000). Community and public health nursing (5th ed., p. 43). St. Louis: Mosby.
15. Sackett D. L. (1996). Evidence based medicine: What it is and what it isn't. British Medical Journal 312, 71–72.
16. Shekelle P. G., Woolff S. H., Eccles M., et al. (1999). Developing guidelines. British Medical Journal 318, 593–596.
17. Natsch S., van der Meer J. W. M. (2003). The role of clinical guidelines, policies, and stewardship. Journal of Hospital Infection 53, 172–176.
18. Acton G. J. (2001). Meta-analysis: A tool for evidence-based practice. AACN Clinical Issues 12, 539–545.

UNIT 1

Cell and Tissue Function

Functional Components of the Cell
- *The Plasma (Cell) Membrane*
- *The Nucleus*
- *The Cytoplasm and Its Organelles*
  - Ribosomes, Endoplasmic Reticulum, and Golgi Apparatus
  - Lysosomes
  - Peroxisomes
  - Proteasomes
  - Mitochondria
- *The Cytoskeleton*
  - Microtubules
  - Microfilaments

Cell Metabolism and Energy Storage
- *Anaerobic Metabolism*
- *Aerobic Metabolism*

Integration of Cell Function
- *Cell Communication Mechanisms*
  - Cell Surface Receptors
  - Intracellular Receptors
- *Membrane Transport Mechanisms*
  - Diffusion
  - Active Transport
  - Vesicular Transport
- *Generation of Membrane Potentials*

Body Tissues
- *Embryonic Origin of Tissue Types*
- *Epithelial Tissue*
  - Simple Epithelium
  - Stratified and Pseudostratified Epithelium
  - Glandular Epithelium
  - Epithelial Cell Renewal
- *Connective Tissue*
  - Loose Connective Tissue
  - Adipose Tissue
  - Reticular and Dense Connective Tissue
- *Muscle Tissue*
  - Skeletal Muscle
  - Smooth Muscle
- *Nervous Tissue*
- *Extracellular Tissue Components*
  - Cell Junctions
  - Extracellular Matrix
  - Cell Adhesion Molecules

Chapter 1

Cell Structure and Function

The cell is the smallest functional unit that an organism can be divided into and retain the characteristics necessary for life. Cells with similar embryonic origin or function are often organized into larger functional units called *tissues*. These tissues in turn combine to form the various body structures and organs. Although the cells of different tissues and organs vary in structure and function, certain characteristics are common to all cells. Cells are remarkably similar in their ability to exchange materials with their immediate environment, obtain energy from organic nutrients, synthesize complex molecules, and replicate themselves. Because most disease processes are initiated at the cellular level, an understanding of cell function is crucial to understanding the disease process. Some diseases affect the cells of a single organ, others affect the cells of a particular tissue type, and still others affect the cells of the entire organism.

This chapter discusses the structural and functional components of the cell, integration of cell function and growth, movement of molecules such as ions across the cell membrane, and tissue types.

Functional Components of the Cell

Although diverse in their organization, all eukaryotic cells (cells with a true nucleus) have in common structures that perform unique functions. Seen under a light microscope, three major components of the eukaryotic cell become evident: the plasma membrane, the nucleus, and the cytoplasm (Fig. 1-1).

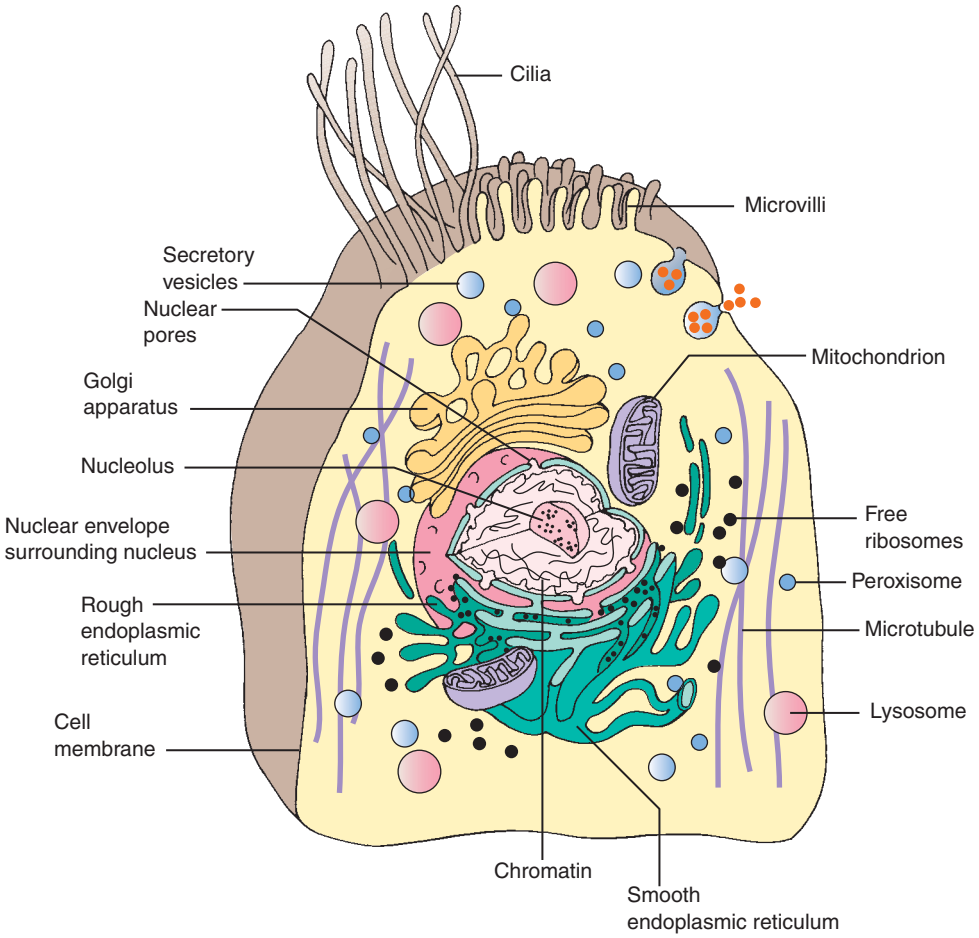


FIGURE 1-1. Composite cell designed to show in one cell all of the various components of the nucleus and cytoplasm.

The living part of the cell is called *protoplasm*. Protoplasm is composed of water, proteins, lipids, carbohydrates, and electrolytes. Two distinct regions of protoplasm exist in the cell: the *cytoplasm*, which lies outside the nucleus, and the *nucleoplasm*, which lies inside the nucleus. The bulk of the cytoplasm is water, in which inorganic and organic chemicals are dissolved. This fluid suspension is called the *cytosol*. The cytosol contains membrane-enclosed compartments or organelles that perform distinctive functions. In addition to the organelles, the cytosol contains a system of tubules and filaments known as the *cytoskeleton* that maintains the shapes of cells and their ability to move. Cells also contain inclusions, which consist of metabolic by-products, storage forms of various nutrients, and inert crystals and pigments.

The Plasma (Cell) Membrane

In many respects, the plasma membrane (also called the cell membrane) is one of the most important parts of the cell. It acts as a semipermeable structure that separates the intracellular and extracellular environments. It controls the transport of materials from the extracellular fluids to the interior of the cell, provides receptors for hormones and other biologically active substances, participates in the generation and conduction of electrical currents that occur in nerve and muscle cells, and aids in the regulation of cell growth and proliferation.

The cell membrane is a dynamic and fluid structure consisting of an organized arrangement of lipids, carbohydrates, and proteins (Fig. 1-2). A main structural component of the membrane is its lipid bilayer. It is a bimolecular layer that consists primarily of phospholipids, with glycolipids and cholesterol. This lipid bilayer provides the basic fluid structure of the membrane and serves as a relatively impermeable barrier to all but lipid-soluble substances. Approximately 75% of the lipids are phospholipids, each with a hydrophilic (water-soluble) head and a hydrophobic (water-insoluble) tail. Phospholipid molecules along with the glycolipids are aligned such that their hydrophilic heads face outward on each side of the membrane and their hydrophobic tails project toward the middle of the membrane. The hydrophilic heads retain water and help cells stick to each other. At normal body temperature, the viscosity of the lipid component of the membrane is equivalent to that of olive oil. The presence of cholesterol stiffens the membrane.

Although the lipid bilayer provides the basic structure of the cell membrane, proteins carry out most of the spe-

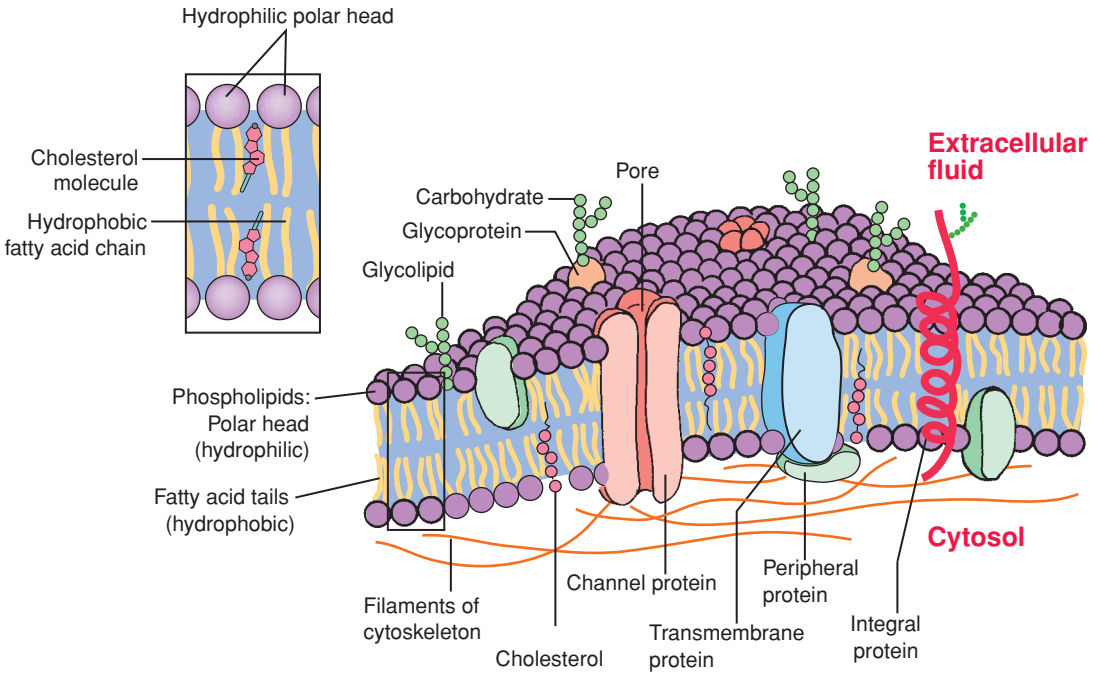


FIGURE 1-2. Structure of the plasma (cell) membrane, showing the hydrophilic (polar) heads and the hydrophobic (fatty acid) tails (*inset*) and the position of the integral and peripheral proteins in relation to the interior and exterior of the cell.

cific functions. The *integral proteins* span the entire lipid bilayer and are essentially part of the membrane. Because most of the integral proteins pass directly through the membrane, they are also referred to as *transmembrane proteins*. Other proteins, called the *peripheral proteins*, are bound to one or the other side of the membrane and do not pass into the lipid bilayer.

The manner in which proteins are associated with the cell membrane often determines their function. Thus, peripheral proteins are associated with functions involving the inner or outer side of the membrane where they are found. Several peripheral proteins serve as receptors or are involved in intracellular signaling systems. By contrast, only the transmembrane proteins can function on both sides of the membrane or transport molecules across it. Many integral transmembrane proteins form the ion channels found on the cell surface. These channel proteins have a complex morphology and are selective with respect to the substances they transmit.

A fuzzy-looking layer, called the *cell coat* or *glycocalyx*, surrounds the cell surface. The structure of the cell coat consists of long, complex carbohydrate chains attached to protein molecules that penetrate the outside portion of the membrane (i.e., glycoproteins); outward-facing membrane lipids (i.e., glycolipids); and carbohydrate-binding proteins called lectins. The cell coat participates in cell-to-cell recognition and adhesion. It contains tissue transplant antigens that label cells as self or nonself. The cell coat of a red blood cell contains the ABO blood group antigens. An intimate relationship exists between the cell membrane and the cell coat.

The Functional Organization of the Cell

- Cells are the smallest functional unit of the body. They contain structures that are strikingly similar to those needed to maintain total body function.
- The nucleus is the control center for the cell. It also contains most of the hereditary material.
- The organelles, which are analogous to the organs of the body, are contained in the cytoplasm. They include the mitochondria, which supply the energy needs of the cell; the ribosomes, which synthesize proteins and other materials needed for cell function; and the lysosomes and proteosomes, which function as the cell's digestive system.
- The cell membrane encloses the cell and provides for intracellular and intercellular communication, transport of materials into and out of the cell, and maintenance of the electrical activities that power cell function.

The Nucleus

The nucleus of a nondividing cell appears as a rounded or elongated structure situated near the center of the cell (see Fig. 1-1). It is enclosed in a nuclear envelope and

contains chromatin, the genetic material of the nucleus, and a distinct region called the *nucleolus*. All eukaryotic cells have at least one nucleus (prokaryotic cells, such as bacteria, lack a nucleus and nuclear membrane).

The nucleus can be regarded as the control center for the cell. It contains the deoxyribonucleic acid (DNA) that is essential to the cell because its genes encode the information necessary for the synthesis of proteins that the cell must produce to stay alive. The genes also represent the individual units of inheritance that transmit information from one generation to another. The nucleus also is the site for the synthesis of the three types of ribonucleic acid (messenger RNA, ribosomal RNA, and transfer RNA) that move to the cytoplasm and carry out the actual synthesis of proteins. Messenger RNA (mRNA) copies and carries the DNA instructions for protein synthesis to the cytoplasm; ribosomal RNA (rRNA) is the site of protein synthesis; and transfer RNA (tRNA) transports amino acids to the site of proteins synthesis for incorporation into the protein being synthesized (see Chapter 5).

The complex structure of DNA and DNA-associated proteins dispersed in the nuclear matrix is called *chromatin*. Depending on its transcriptional activity, chromatin may be condensed as an inactive form of chromatin called *heterochromatin* or extended as a more active form called *euchromatin*. Because heterochromatic regions of the nucleus stain more intensely than regions consisting of euchromatin, nuclear staining can be a guide to cell activity. The nucleus also contains the darkly stained round body called the *nucleolus*. Nucleoli are structures composed of regions from five different chromosomes, each with a part of the genetic code needed for the synthesis of rRNA, which is transcribed exclusively in the nucleolus. Cells that are actively synthesizing proteins can be recognized because their nucleoli are large and prominent and the nucleus as a whole is euchromatic or slightly stained.

Surrounding the nucleus is the *nuclear envelope* formed by an inner and outer nuclear membrane containing a *perinuclear cisternal* space between them (Fig. 1-3). The inner nuclear membrane is supported by a rigid network of protein filaments attached to its inner surface, called *nuclear lamina,* that bind to chromosomes and secure their position in the nucleus. The outer nuclear membrane resembles the membrane of the endoplasmic reticulum and is continuous with it. The nuclear envelope contains many structurally complex circular pores where the two membranes fuse to form a gap filled with a thin protein diaphragm. Many classes of molecules, including fluids, electrolytes, RNA, some proteins, and hormones, can move in both directions through the nuclear pores.

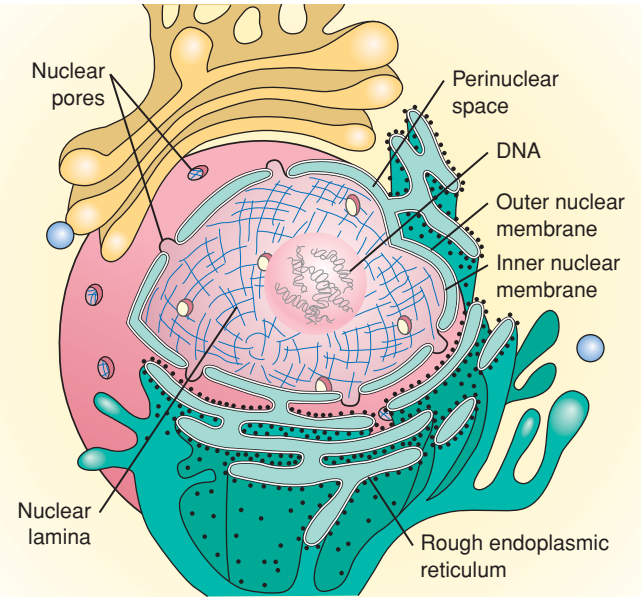


FIGURE 1-3. Schematic drawing of the inner and outer membranes of the nuclear envelope. The double-membrane envelope is penetrated by pores in which nuclear pore complexes are positioned and continuous with the rough endoplasmic reticulum. The nuclear lamina on the surface of the inner membrane bind to DNA and hold the chromosomes in place.

The Cytoplasm and Its Organelles

The cytoplasm surrounds the nucleus, and it is in the cytoplasm that the work of the cell takes place. Embedded in the cytoplasm are various membrane-enclosed compartments (endoplasmic reticulum, Golgi apparatus, mitochondria, lysosomes) that function as the organs of the cells. Most organelles are surrounded by one or two lipid membranes, similar to plasma membrane, that separate the organelles from the cytosol.

Ribosomes, Endoplasmic Reticulum, and Golgi Apparatus

The ribosomes, endoplasmic reticulum, and Golgi apparatus represent the primary sites of protein synthesis in the cell (Fig. 1-4). Because these organelles lack direct communication with the cytosol, they use transport vesicles to move newly synthesized proteins, membrane components, and soluble molecules from one organelle to another. These transport vesicles bud off from the membrane of one organelle and fuse with another, carrying the transported material.

Ribosomes. The ribosomes are small particles of nucleoproteins (rRNA and proteins) that are held together by a strand of mRNA to form polyribosomes (also called polysomes). Polysomes exist as isolated clusters of free ribosomes within the cytoplasm or attached to the membrane of the endoplasmic reticulum (Fig. 1-4). Free ribosomes are involved in the synthesis of proteins, mainly enzymes that aid in the control of cell function, whereas those attached to the endoplasmic reticulum translate mRNAs that code for proteins secreted from the cell or stored within the cell (e.g., granules in white blood cells).

Endoplasmic Reticulum. The endoplasmic reticulum (ER) is an extensive system of paired membranes and flat vesicles that connect various parts of the inner cell

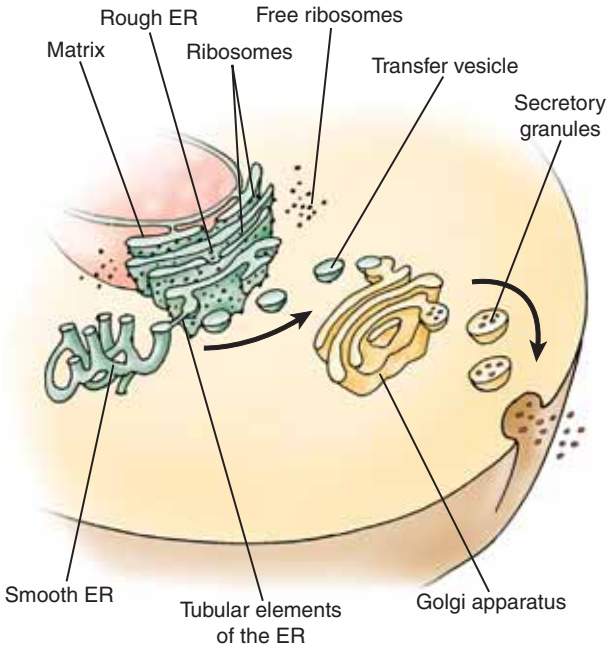


FIGURE 1-4. Three-dimensional view of the rough and the smooth endoplasmic reticula (ER) and the Golgi apparatus. The ER functions as a tubular communication system through which substances can be transported from one part of the cell to another and as the site of protein (rough ER), carbohydrate, and lipid (smooth ER) synthesis. Most of the proteins synthesized by the rough ER are sealed into transfer vesicles and transported to the Golgi apparatus, where they are modified and packaged into secretory granules.

(Fig. 1-4). Between the paired ER membranes is a fluid-filled space called the *matrix*. The matrix connects the space between the two membranes of the nuclear envelope, the cell membrane, and various cytoplasmic organelles. It functions as a tubular communication system for transporting various substances from one part of the cell to another. A large surface area and multiple enzyme systems attached to the ER membranes also provide the machinery for a major share of the cell's metabolic functions.

Two forms of ER exist in cells: rough and smooth. *Rough ER* is studded with ribosomes attached to specific binding sites on the membrane. The ribosomes, with the accompanying strand of mRNA, synthesize proteins. Proteins produced by the rough ER are usually destined to be incorporated into cell membranes, used in the generation of lysosomal enzymes, or exported from the cell. The rough ER segregates these proteins from other components of the cytoplasm and modifies their structure for a specific function. For example, the production of plasma proteins by liver cells takes place in the rough ER.

The *smooth ER* is free of ribosomes and is continuous with the rough ER. It does not participate in protein synthesis; instead, its enzymes are involved in the synthesis of lipid molecules, regulation of intracellular calcium, and metabolism and detoxification of certain hormones and drugs. It is the site of lipid, lipoprotein, and steroid hormone synthesis. The sarcoplasmic reticulum of skeletal and cardiac muscle cells is a form of smooth ER. Calcium ions needed for muscle contraction are stored and released from cisternae of the sarcoplasmic reticulum. The smooth ER of the liver is involved in glycogen storage and metabolism of lipid-soluble drugs.

Golgi Apparatus. The Golgi apparatus, sometimes called the *Golgi complex*, consists of stacks of thin, flattened vesicles or sacs (see Fig. 1-4). These Golgi bodies are found near the nucleus and function in association with the ER. Substances produced in the ER are carried to the Golgi complex in small, membrane-covered transport vesicles. Many cells synthesize proteins that are larger than the active product. The Golgi complex modifies these substances and packages them into secretory granules or vesicles. Insulin, for example, is synthesized as a large, inactive proinsulin molecule that is cut apart to produce a smaller, active insulin molecule within the Golgi complex of the beta cells of the pancreas. In addition to producing secretory granules, the Golgi complex is thought to produce large carbohydrate molecules that combine with proteins produced by the rough ER to form glycoproteins.

Lysosomes

The lysosomes, which can be viewed as the digestive organelles of the cell, are small, membrane-enclosed sacs filled with hydrolytic enzymes. These enzymes can break down excess and worn-out cell parts as well as foreign substances that are taken into the cell. All of the lysosomal enzymes are acid hydrolases, which means that they require an acid environment. The lysosomes provide this environment by maintaining a pH of approximately 5.0 in their interior. The pH of the cytosol and other cellular components is approximately 7.2 and are therefore protected from escaped lysosomal enzymes. Like all other cellular organelles, lysosomes not only contain a unique collection of enzymes, but also have a unique surrounding membrane that prevents the release of its digestive enzymes into the cytosol.

Lysosomes are formed from digestive vesicles called *endosomes*. These vesicles fuse to form multivesicular bodies called *early endosomes* (Fig. 1-5). The early endosomes mature into late *endosomes* as they recycle lipids, proteins, and other membrane components back to the plasma membrane in vesicles called *recycling vesicles*. Lysosomal enzymes are synthesized in the rough ER and then transported to the Golgi apparatus, where they are biochemically modified and packaged for transport to the endosomes. The late endosomes mature into lysosomes as they progressively accumulate newly synthesized acid hydrolases from the Golgi apparatus.

Depending on the nature of the substance, different pathways are used for lysosomal degradation of unwanted materials. Small extracellular particles such as extracellular proteins and plasma membrane proteins form endocytotic vesicles after being internalized by endocytosis and receptor-mediated endocytosis (Fig. 1-5A). These vesicles are converted into early and late endosomes, after which they mature into lysosomes as they accumulate newly

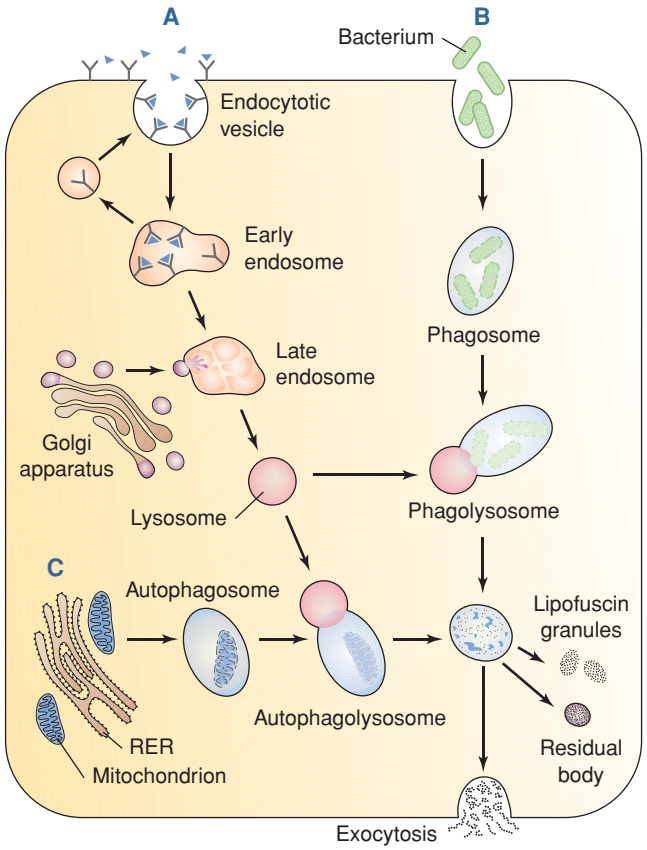


FIGURE 1-5. Pathways for digestion of materials by lysosomes. **(A)** Receptor-mediated endocytosis with formation of lysosomes from early and late endosomes. Vesicle contents are sorted in the early endosome with receptors and lipids being sent back to the membrane. Transport vesicles carry lysosomal enzymes to the late endosomes, converting them into lysosomes that digest proteins and other components acquired from the endocytotic vesicles. **(B)** Phagocytosis involving the delivery of large extracellular particles such as bacteria and cellular debris to the lysosomes via phagosomes. **(C)** Autophagy is the process in which worn-out mitochondria and other cell parts are surrounded by a membrane derived from the rough endoplasmic reticulum (RER). The resulting autophagosome then fuses with a lysosome to form an autophagolysosome. Undigested material may be extruded from the cell or remain in the cytoplasm as lipofuscin granules or membrane-bound residual bodies.

synthesized hydrolases and vesicular proton pumps. Large extracellular particles such as bacteria, cell debris, and other foreign particles are engulfed in a process called *phagocytosis* (Fig. 1-5B). A *phagosome,* formed as the material is internalized within the cell, fuses with a lysosome to form a *phagolysosome*. Intracellular particles, such as entire organelles, cytoplasmic proteins, and other cellular components, are engulfed in a process called autophagy (Fig. 1-5C). These particles are isolated from the cytoplasmic matrix by endoplasmic reticulum membranes to form an *autophagosome*, which then fuses with a lysosome to form an *autophagolysosome*.

Although the lysosomal enzymes can break down most proteins, carbohydrates, and lipids to their basic constituents, some materials remain undigested. These undigested materials may remain in the cytoplasm as *residual bodies* or be extruded from the cell. In some long-lived cells, such as neurons and heart muscle cells, large quantities of residual bodies accumulate as lipofuscin granules or age pigments. Other indigestible pigments, such as inhaled carbon particles and tattoo pigments, also accumulate and may persist in residual bodies for decades.

Lysosomes are also repositories where cells accumulate abnormal substances that cannot be completely digested or broken down. In some inherited diseases known as *lysosomal storage diseases*, a specific lysosomal enzyme is absent or inactive, in which case the digestion of certain cellular substances (e.g., glucocerebrosides, gangliosides, sphingomyelin) does not occur. As a result, these substances accumulate in the cell. In Tay-Sachs disease (see Chapter 6), an autosomal recessive disorder, hexosaminidase A, which is the lysosomal enzyme needed for degrading the GM_2 ganglioside found in nerve cell membranes, is absent. Although the GM_2 ganglioside accumulates in many tissues, such as the heart, liver, and spleen, its accumulation in the nervous system and retina of the eye causes the most damage.

Peroxisomes

Smaller than lysosomes, spherical membrane-bound organelles called *peroxisomes* contain a special enzyme that degrades peroxides (e.g., hydrogen peroxide). Peroxisomes function in the control of free radicals (see Chapter 2). Unless degraded, these highly unstable chemical compounds would damage other cytoplasmic molecules. Peroxisomes also contain the enzymes needed for breaking down very–long-chain fatty acids, which are ineffectively degraded by mitochondrial enzymes. In liver cells, peroxisomal enzymes are involved in the formation of the bile acids.

Proteasomes

Proteasomes are small compartmentalized protein complexes that are responsible for proteolysis of malformed and misfolded proteins. The process of cytosolic proteolysis is carefully controlled by the cell and requires that the protein be targeted for degradation. This process involves *ubiquitination,* a process whereby several small ubiquitin molecules (small 76-amino-acid polypeptide chain) are attached to an amino acid residue of the targeted protein. Once a protein is so tagged, it is degraded by proteasomes. After the targeted protein has been degraded, the resultant amino acids join the intracellular pool of free amino acids and the ubiquitin molecules are released and recycled.

Mitochondria

The mitochondria are literally the "power plants" of the cell because they transform organic compounds into energy that is easily accessible to the cell. They do not make energy, but extract it from organic compounds. Mitochondria contain the enzymes needed for capturing

most of the energy in foodstuffs and converting it into cellular energy. This multistep process requires oxygen and is often referred to as *aerobic metabolism*. Much of this energy is stored in the high-energy phosphate bonds of compounds such as adenosine triphosphate (ATP) that power the various cellular activities. Mitochondria are found close to the site of energy consumption in the cell (e.g., near the myofibrils in muscle cells). The number of mitochondria in a given cell type is largely determined by the type of activity the cell performs and how much energy is needed to undertake the activity. For example, a dramatic increase in mitochondria occurs in skeletal muscle repeatedly stimulated to contract.

The mitochondria are composed of two membranes: an outer membrane that encloses the periphery of the mitochondrion and an inner membrane that forms shelflike projections, called *cristae* (Fig. 1-6). The narrow space between the outer and inner membranes is called the *intermembrane space*, whereas the large space enclosed by the inner membrane is termed the *matrix space*. The outer mitochondrial membrane contains a large number of transmembrane porins, through which water-soluble molecules may pass. The inner membrane contains the respiratory chain enzymes and transport proteins needed for the synthesis of ATP. In certain regions, the outer and inner membranes contact each other; these contact points serve as pathways for proteins and small molecules to enter and leave the matrix space.

Mitochondria contain their own DNA and ribosomes and are self-replicating. The DNA is found in the mitochondrial matrix and is distinct from the chromosomal DNA found in the nucleus. Mitochondrial DNA, known as the "other human genome," is a double-stranded, circular molecule that encodes the rRNA and tRNA required for intramitochondrial synthesis of the proteins needed for the energy-generating function of the mitochondria. Although mitochondrial DNA directs the synthesis of 13 of the proteins required for mitochondrial function, the DNA of the nucleus encodes the structural proteins of the mitochondria and other proteins needed to carry out cellular respiration.

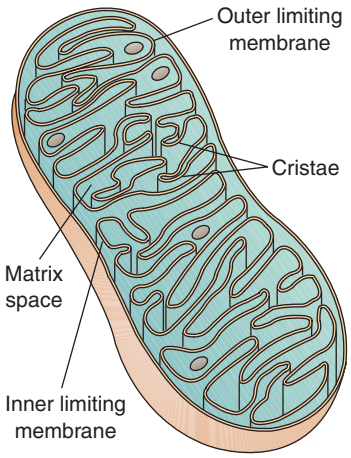


FIGURE 1-6. Mitochondrion. The inner membrane forms transverse folds called cristae, where the enzymes needed for the final step in adenosine triphosphate (ATP) production (i.e., oxidative phosphorylation) are located.

Mitochondrial DNA is inherited matrilineally (i.e., from the mother) and provides a basis for familial lineage studies. Mutations have been found in each of the mitochondrial genes, and an understanding of the role of mitochondrial DNA in certain diseases is beginning to emerge. Most tissues in the body depend to some extent on oxidative metabolism and can therefore be affected by mitochondrial DNA mutations.

Mitochondria also function as key regulators of *apoptosis* or *programmed cell death* (discussed in Chapter 2). The initiation of the mitochondrial pathway for apoptosis results from an increase in mitochondrial membrane permeability and the subsequent release of proapoptotic molecules into the cytoplasm. One of these proapoptotic molecules, cytochrome c, is well known for its role in cellular respiration. In the cytosol, cytochrome c binds to a protein called *apoptosis activating factor-1*, initiating the molecular events involved in the apoptosis cascade. Other apoptotic proteins also enter the cytoplasm, where they bind to and neutralize the various apoptotic inhibitors, whose normal function consists of blocking the apoptotic cascade. Both the formation of reactive oxygen species (e.g., peroxide) and the activation of the p53 tumor-suppressor gene by DNA damage or other means initiate apoptotic signaling through the mitochondria. Dysregulated apoptosis (too little or too much) has been implicated in a wide range of diseases, including cancer, in which there is an inappropriately low rate of apoptosis, and neurodegenerative diseases, in which there is an increased or excessive rate of apoptosis.

The Cytoskeleton

In addition to its organelles, the cytoplasm contains a network of microtubules, microfilaments, intermediate filaments, and thick filaments (Fig. 1-7). Because they control cell shape and movement, these structures are a major component of the structural elements called the *cytoskeleton*.

Microtubules

The microtubules are slender tubular structures composed of globular proteins called *tubulin* (Fig. 1-8). Each microtubule consists of parallel protofilaments, each composed of α- and β-tubulin dimers. Microtubules are dynamic structures that can rapidly disassemble in one location and reassemble in another. During the reassembly process, the tubulin dimers polymerize in an end-to-end fashion to form protofilaments. As a result of the polymerization process, each microtubule possesses a nongrowing "minus" end and a rapidly growing "plus" end. During the disassembly process, the tubulin dimers dissociate from the protofilaments and form a pool of free tubulin in the cytoplasm. This pool is used in the polymerization process for reassembly of the protofilaments.

Microtubules function in many ways, including the development and maintenance of cell form; participation

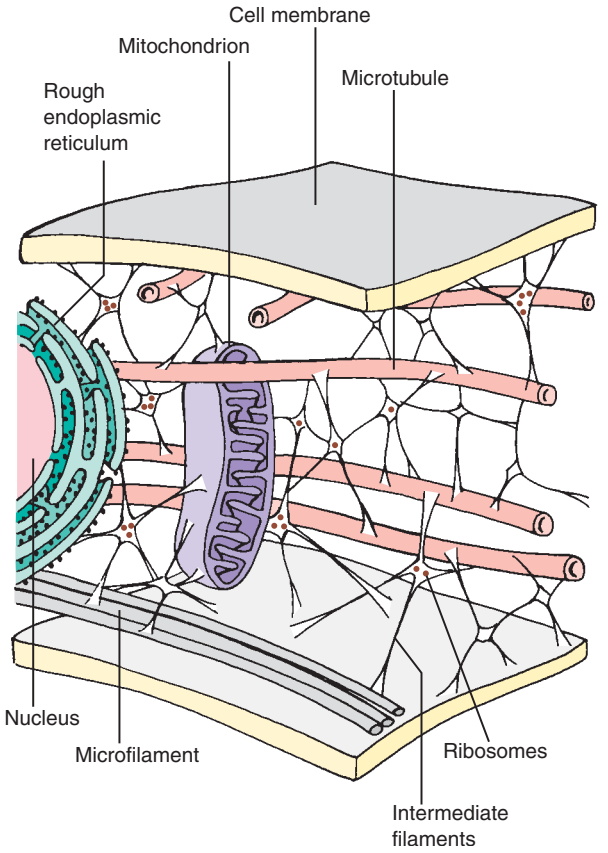


FIGURE 1-7. Three-dimensional view of the rough and smooth endoplasmic reticulum (ER) and the Golgi apparatus. The ER functions as a tubular communication system through which substances can be transported from one part of the cell to another and as the site of protein (rough ER), carbohydrate, and lipid (smooth ER) synthesis. Most of the proteins synthesized by the rough ER are sealed into transfer vesicles and transported to the Golgi apparatus, where they are modified and packaged into secretory granules.

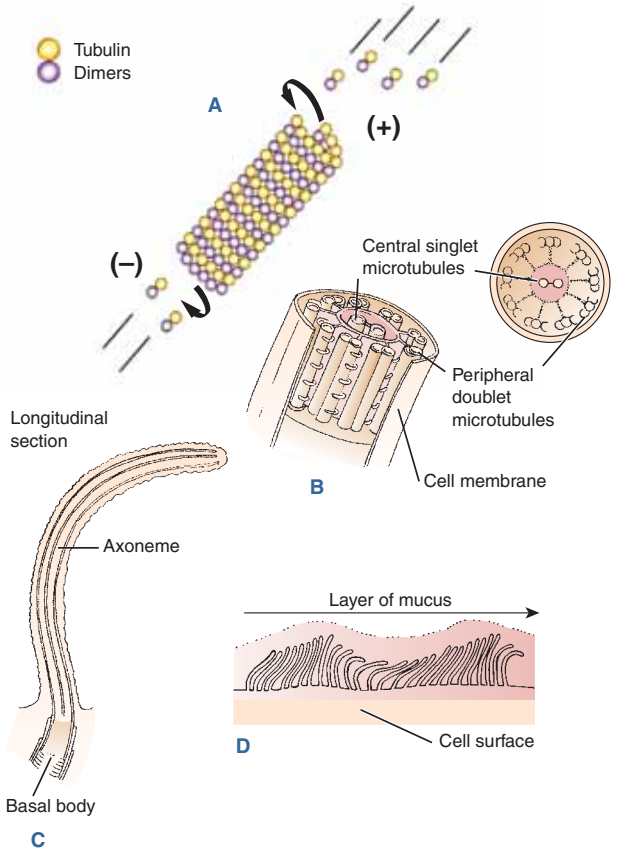


FIGURE 1-8. **(A)** Formation of a microtubule from tubulin dimers, showing the faster growing (+) and the slower growing (−) end. **(B)** Cross-sectional view of microtubule. **(C)** All of the microtubules are anchored to a basal body that is responsible for formation of a core structure called the *axoneme*. **(D)** Sweeping movements of the cilia that move the mucus layer of the respiratory tract.

in intracellular transport mechanisms, including axoplasmic transport in neurons; and formation of the basic structure for several complex cytoplasmic organelles, including the cilia, flagella, and centrioles. *Cilia* and *flagella* are microtubule-filled cellular extensions extending from the cell membrane that are capable of sweeping movements. Cilia are found on the apical (luminal) surfaces of many epithelial linings, including the nasal sinuses or passages such as the upper respiratory system. Removal of mucus from the respiratory passages is highly dependent on the proper functioning of the cilia. Flagella form the tail-like structures that provide motility for sperm. *Centrioles* are small, barrel-shaped bodies oriented at right angles to each other. In dividing cells, the two cylindrical centrioles form the mitotic spindle that aids in the separation and movement of the chromosomes during cell division.

Abnormalities of the microtubules occur in a number of pathologic states. These abnormalities may be manifested by an abnormal appearance and function, aberrant movements of intracellular organelles, and defective cell locomotion. Defective organization of the microtubules can cause sterility by inhibiting sperm motility, as well as defective motility of cilia in the epithelial lining of the respiratory tract, resulting in chronic respiratory tract infections. Proper functioning of the microtubules is also essential for various stages of leukocyte migration. Drugs that bind to tubulin molecules and prevent their assembly of microtubules (*colchicine*) are useful in the treatment of gout, in which symptoms are due to movement of leukocytes toward urate crystals in the tissues. Since microtubules form the mitotic spindle, which is essential for cell proliferation, drugs that bind microtubules (e.g., vinca alkaloids) are useful in the treatment of cancer.

Microfilaments

Microfilaments are thin, threadlike cytoplasmic structures. Three classes of microfilaments exist: *thin microfilaments*, which are equivalent to the thin actin filaments in muscle; *thick myosin filaments*, which are present in muscle cells but may also exist temporarily in other cells; and *intermediate filaments*, which are a heterogeneous group of filaments with diameter sizes between the thick and thin filaments. Muscle contraction depends on the interaction between thin actin filaments and thick myosin filaments.

Microfilaments are present in the superficial zone of the cytoplasm in most cells. Contractile activities involv-

ing the microfilaments and associated thick myosin filaments contribute to associated movement of the cytoplasm and cell membrane during endocytosis and exocytosis. Microfilaments are also present in the microvilli of the intestine. The intermediate filaments function in supporting and maintaining the asymmetric shape of cells. Examples of intermediate filaments are the keratin filaments that are found anchored to the cell membrane of epidermal keratinocytes of the skin and the glial filaments that are found in astrocytes and other glial cells of the nervous system. The *neurofibrillary tangles* found in the brain in Alzheimer disease contain microtubule-associated proteins and neurofilaments, evidence of a disrupted neuronal cytoskeleton.

In summary, the cell is a remarkably autonomous structure that functions in a manner strikingly similar to that of the total organism. The plasma membrane is a lipid bilayer that surrounds the cell and separates it from its surrounding external environment. It contains receptors for hormones and other biologically active substances, participates in the electrical events that occur in nerve and muscle cells, and aids in the regulation of cell growth and proliferation. The cell surface is surrounded by a fuzzy-looking layer called the *cell coat* or *glycocalyx*. The cell coat participates in cell-to-cell recognition and adhesion, and it contains tissue transplant antigens.

The nucleus controls cell function and is the mastermind of the cell. It contains DNA, which provides the information necessary for the synthesis of the various proteins that the cell must produce to stay alive and to transmit information from one generation to another.

The cytoplasm contains the cell's organelles. Ribosomes serve as sites for protein synthesis in the cell. The ER functions as a tubular communication system through which substances can be transported from one part of the cell to another and as the site of protein (rough ER), carbohydrate, and lipid (smooth ER) synthesis. The Golgi apparatus modifies materials synthesized in the ER and packages them into secretory granules for transport within the cell or export from the cell. Lysosomes, which can be viewed as the digestive system of the cell, contain hydrolytic enzymes that digest worn-out cell parts and foreign materials. The mitochondria serve as power plants for the cell because they transform food energy into ATP, which is used to power cell activities. Mitochondria contain their own extrachromosomal DNA, which is used in the synthesis of mitochondrial RNAs and proteins used in oxidative metabolism.

In addition to its organelles, the cytoplasm also contains a network of microtubules and microfilaments called the *cytoskeleton*. Microtubules are slender, stiff tubular structures that influence cell shape, provide a means of moving organelles through the cytoplasm, and effect movement of the cilia and of chromosomes during cell division. Microfilaments are thin threadlike cytoplasmic structures. They include the thin actin and thick myosin filaments, which are present in muscle cells, as well as the intermediate filaments, which function in supporting and maintaining the shape of cells.

Cell Metabolism and Energy Storage

Energy metabolism refers to the chemical processes involved in converting carbohydrates, fats, and proteins from the foods we eat into the energy needed for cell functions. Cells use oxygen to transform the breakdown products of the foods we eat into the energy needed for muscle contraction; the transport of ions and other molecules across cell membranes; and the synthesis of enzymes, hormones, and other macromolecules.

The special carrier for chemical energy in all living cells is ATP. ATP molecules consist of adenosine, a nitrogenous base; ribose, a five-carbon sugar; and three phosphate groups (Fig. 1-9). The last two phosphate groups are attached to the remainder of the molecule by two high-energy bonds. Each bond releases a large amount of energy when hydrolyzed. ATP is hydrolyzed to form adenosine diphosphate (ADP) with the loss of one high-energy bond and to adenosine monophosphate (AMP)

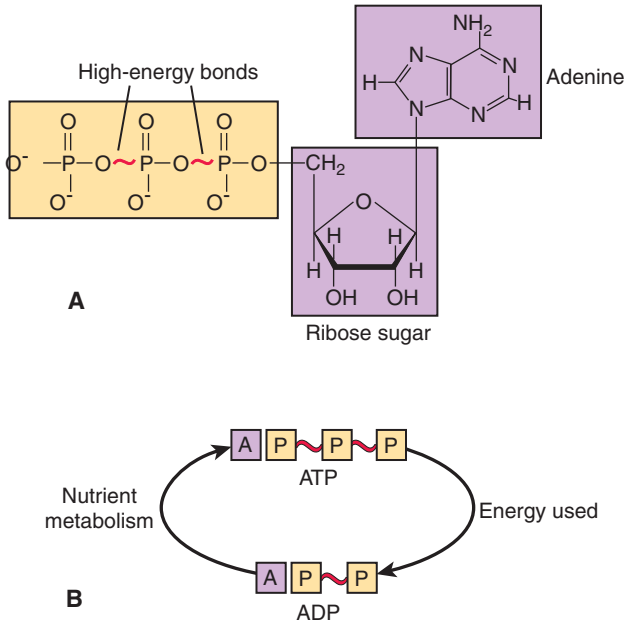


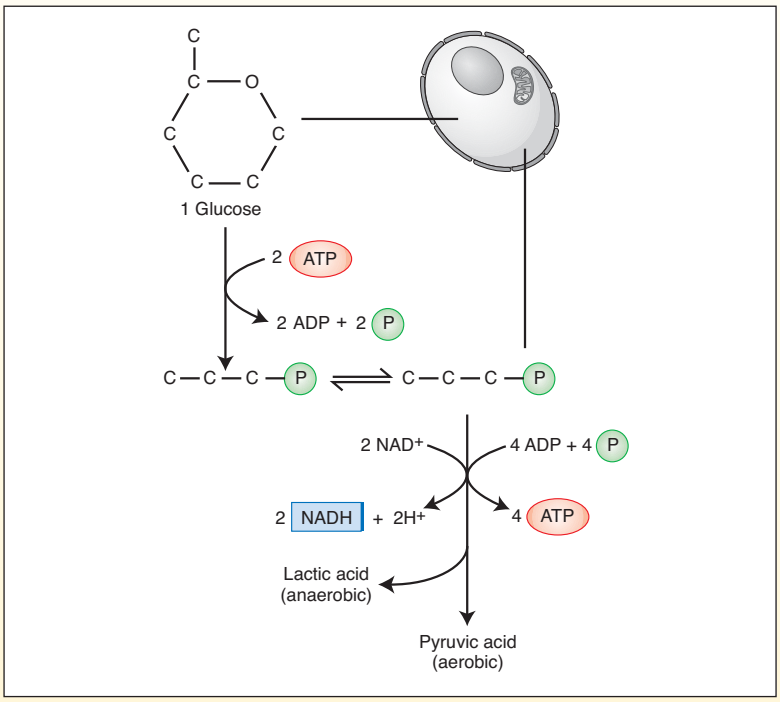
FIGURE 1-9. Adenosine triphosphate (ATP) is the major source of cellular energy. **(A)** Each molecule of ATP contains two high-energy bonds, each containing about 12 kcal of potential energy. **(B)** The high-energy ATP bonds are in constant flux. They are generated by substrate (glucose, amino acid, and fat) metabolism and are consumed as the energy is expended. ADP, adenosine diphosphate.

UNDERSTANDING → Cell Metabolism

Cell metabolism is the process that converts dietary fuels from carbohydrates, proteins, and fats into adenosine triphosphate (ATP), which provides for the energy needs of the cell. ATP is formed through three major pathways: (1) the glycolytic pathway, (2) the citric acid cycle, and (3) the electron transport chain. In fuel metabolism, which is an oxidation–reduction reaction, the fuel donates electrons and is oxidized, and the coenzymes nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) accept electrons and are reduced.

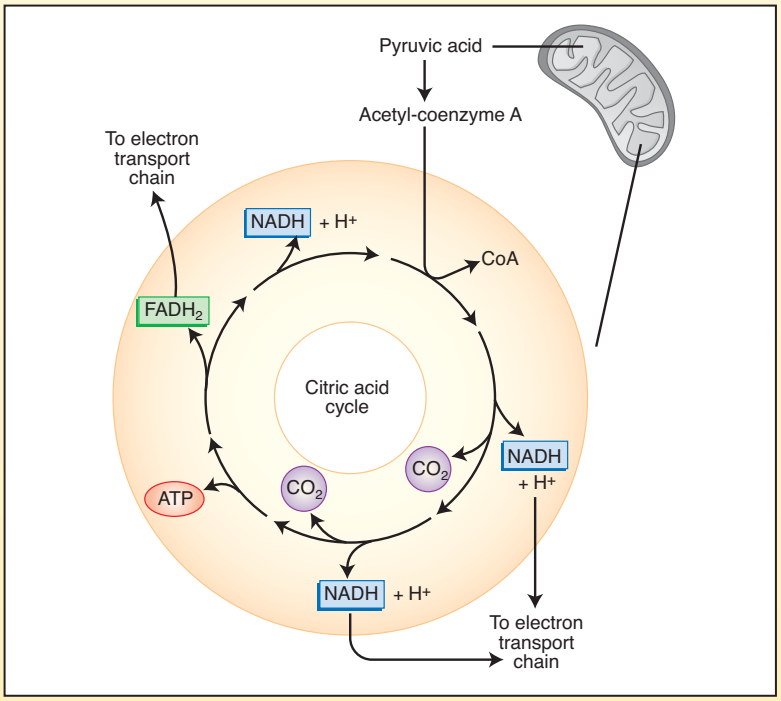
1

Glycolytic pathway. Glycolysis, which occurs in the cytoplasm of the cell, involves the splitting of the six-carbon glucose molecule into two three-carbon molecules of pyruvic acid. Because the reaction that splits glucose requires two molecules of ATP, there is a net gain of only two molecules of ATP from each molecule of glucose that is metabolized. The process is anaerobic and does not require oxygen (O_2) or produce carbon dioxide (CO_2). When O_2 is present, pyruvic acid moves into the mitochondria, where it enters the aerobic citric acid cycle. Under anaerobic conditions, pyruvate is converted to lactic acid, allowing glycolysis to continue as a means of supplying cells with ATP when O_2 is lacking.



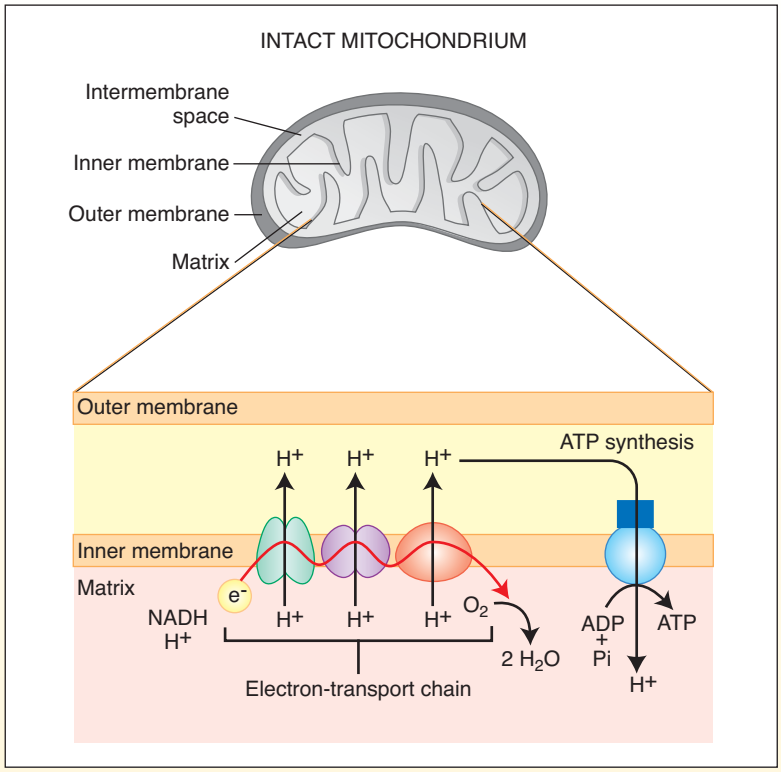
2

Citric acid cycle. Under aerobic conditions, both of the pyruvic acid molecules formed by the glycolytic pathway enter the mitochondria, where each combines with acetyl-coenzyme to form acetyl-coenzyme A (acetyl-CoA). The formation of acetyl-CoA begins the reactions that occur in the citric acid cycle. Some reactions release CO_2 and some transfer electrons from the hydrogen atom to NADH or FADH. In addition to pyruvic acid from the glycolysis of glucose, fatty acid and amino acid breakdown products can also enter the citric acid cycle. Fatty acids, which are the major source of fuel in the body, are oxidized by a process called β-*oxidation* to acetyl-CoA for entry into the citric acid cycle.



3

Electron transport chain. At the completion of the citric acid cycle, each glucose molecule has yielded only four new molecules of ATP (two from glycolysis and two from the citric acid cycle). In fact, the principal function of these earlier stages is to make the electrons (e^-) from glucose and other food substrates available for oxidation. Oxidation of the electrons carried by NADH and $FADH_2$ is accomplished through a series of enzymatically catalyzed reactions in the mitochondrial electron transport chain. During these reactions, protons (H^+) combine with O_2 to form water (H_2O), and large amounts of energy are released and used to add a high-energy phosphate bond to adenosine diphosphate (ADP), converting it to ATP. There is a net yield of 36 molecules of ATP from 1 molecule of glucose (2 from glycolysis, 2 from the citric acid cycle, and 32 from the electron transport chain). In general, the net amount of ATP formed from each gram of protein that is metabolized is less than for glucose, whereas that obtained from fat is greater (e.g., each 16-carbon fatty acid molecule yields about 129 molecules of ATP).



with the loss of two such bonds. The energy liberated from the hydrolysis of ATP is used to drive reactions that require free energy, such as muscle contraction and active transport mechanisms. Energy from foodstuffs is used to convert ADP back to ATP. ATP is often called the *energy currency* of the cell; energy can be "saved" or "spent" using ATP as an exchange currency.

Two types of energy production are present in the cell: the *anaerobic* (i.e., without oxygen) glycolytic pathway, occurring in the cytoplasm, and the *aerobic* (i.e., with oxygen) pathway, occurring in the mitochondria. The glycolytic pathway serves as the prelude to the aerobic pathway.

Anaerobic Metabolism

Glycolysis is the anaerobic process by which energy is liberated from glucose. It is an important source of energy for cells that lack mitochondria. The process also provides a temporary source of energy for cells that are deprived of an adequate supply of oxygen. Glycolysis involves a sequence of reactions that converts glucose to pyruvic acid, with the concomitant production of ATP from ADP. The net gain of energy from the glycolytic metabolism of one molecule of glucose is two ATP molecules. Although relatively inefficient as to energy yield, the glycolytic pathway is important during periods of decreased oxygen delivery, such as occurs in skeletal muscle during the first few minutes of exercise.

Glycolysis requires the presence of nicotinamide adenine dinucleotide (NAD^+), a hydrogen carrier. The end products of glycolysis are pyruvate and NADH (the reduced form of NAD^+) plus H^+. When oxygen is present, pyruvic acid moves into the aerobic mitochondrial pathway, and NAD^+ is regenerated as NADH delivers its electron and proton (H^+) to the oxidative electron transport system. Under anaerobic conditions, such as cardiac arrest or circulatory shock, pyruvic acid is converted to lactic acid, which diffuses out of the cells into the extracellular fluid. Conversion of pyruvate to lactic acid is reversible, and once the oxygen supply has been restored, lactic acid is converted back to pyruvic acid and used directly for energy or to synthesize glucose.

Aerobic Metabolism

Aerobic metabolism, which supplies 90% of the body's energy needs, occurs in the cell's mitochondria and requires oxygen. It is here that the hydrogen and carbon molecules from dietary fats, proteins, and carbohydrates are broken down and combined with molecular oxygen to form carbon dioxide and water as energy is released. Unlike lactic acid, which is an end product of anaerobic metabolism, carbon dioxide and water are relatively harmless and easily eliminated from the body. In a 24-hour period, oxidative metabolism produces 150 to 300 mL of water.

The citric acid cycle, sometimes called the *tricarboxylic acid* (TCA) or *Krebs* cycle, provides the final common pathway for the metabolism of nutrients. In the citric acid cycle, which takes place in the matrix of the mitochondria, an activated two-carbon molecule of acetyl-coenzyme A (acetyl-CoA) condenses with a four-carbon molecule of oxaloacetic acid and moves through a series of enzyme-mediated steps. This process produces hydrogen atoms and carbon dioxide. As hydrogen is generated, it combines with NAD^+ or FAD for transfer to the electron transport system. Besides pyruvate from the glycolysis of glucose, products of amino acid and fatty acid degradation enter the citric acid cycle and contribute to the generation of ATP.

Oxidation of electrons from the hydrogen atoms generated during glycolysis and the citric acid cycle takes place in the electron transport system located on the inner mitochondrial membrane. The electrons are used to reduce elemental oxygen, which combines with hydrogen to form water. During this sequence of oxidative reactions, large amounts of energy are released and used to convert ADP to ATP. Because the formation of ATP involves the addition of a high-energy phosphate bond to ADP, the process is called *oxidative phosphorylation*.

In summary, metabolism is the process whereby the carbohydrates, fats, and proteins from the foods we eat are broken down and subsequently converted into the energy needed for cell function. Energy is stored in the high-energy phosphate bonds of ATP, which serves as the energy currency for the cell. Two sites of energy conversion are present in cells: the anaerobic glycolytic pathway in the cytoplasm and the aerobic pathways in the mitochondria. The most efficient of these pathways is the aerobic citric acid cycle and electron transport chain in the mitochondria. This pathway, which requires oxygen, produces carbon dioxide and water as end products and results in the release of large amounts of energy that is used to convert ADP to ATP. The glycolytic pathway in the cytoplasm involves the breakdown of glucose to form ATP. This pathway can function without oxygen by producing lactic acid.

Integration of Cell Function

Within a complex organism, such as a human being, different organs, tissues, and individual cell types develop specialized functions and needs. Yet each cell must contribute to the integrated life process as the body grows, differentiates, and adapts to changing conditions. Such integration requires that cells have the ability to communicate with one another, transport substances between their intracellular and extracellular environments, and generate and respond to changes in the electrical charge of membrane potentials.

Cell Communication

- Cells communicate with each other and with the internal and external environments by a number of mechanisms, including electrical and chemical signaling systems that control electrical potentials, the overall function of a cell, and gene activity needed for cell division and cell replication.
- Chemical messengers exert their effects by binding to cell membrane proteins or receptors that convert the chemical signal into signals within the cell, in a process called *signal transduction*.
- Cells can regulate their responses to chemical messengers by increasing or decreasing the number of active receptors on their surface.

Cell Communication Mechanisms

Signaling systems consist of receptors that reside either on the cell membrane (surface receptors) or within the cells (intracellular receptors). Receptors are activated by a variety of chemical messengers including neurotransmitters, hormones, growth factors, and other chemical messengers. Some lipid-soluble chemical messengers move through the membrane and bind to cytoplasmic or nuclear receptors to exert their physiologic effects. Signaling systems often rely on the intermediary activity of a separate class of membrane-bound regulatory proteins to convert extracellular signals, or *first messengers,* into intracellular signals, or *second messengers*. Many molecules involved in signal transduction are proteins. A unique property of proteins that allows them to function in this way is their ability to change their shape or conformation, thereby changing their function and consequently the functions of the cell. Proteins often accomplish these conformational changes through enzymes called *protein kinases* that catalyze the phosphorylation of amino acids in the protein structure.

Cell Surface Receptors

Each cell type in the body contains a distinctive set of receptor proteins that enables it to respond to a complementary set of ligands (i.e., molecules with a high affinity for a receptor) or signaling molecules in a specific, preprogrammed way. These receptors, which span the cell membrane, relay information to a series of intracellular intermediates that eventually pass the signal to its final destination. There are three major classes of cell surface receptor proteins: G-protein–linked receptors, enzyme-linked receptors, and ion channel–linked receptors.

G-Protein–Linked Receptors. G-protein–linked receptors mediate cellular responses for numerous types of first messengers, including proteins, small peptides, amino acids, and fatty acid derivatives such as the prostaglandins. Because these regulatory proteins bind to guanine nucleotides such as guanine diphosphate (GDP) and guanine triphosphate (GTP), they are called *G proteins*. With more than 1000 members, G-protein–linked receptors are the largest family of cell surface receptors.

Although there are differences among the G-protein–linked receptors, all share a number of features. They all have a ligand-binding extracellular receptor component, which recognizes a specific ligand or first messenger, and they all undergo conformational changes with receptor binding that activates the G protein (Fig. 1-10). All G proteins are found on the cytoplasmic side of the cell membrane, and all incorporate the *guanosine triphosphatase (GTPase) cycle*, which functions as a molecular switch that exists in two states: an activated (on) state and an inactivated (off) state. Receptor activation causes the α subunit to dissociate from the receptor and the β and γ subunits and transmit the signal from the first messenger to a membrane-bound intermediate called an *effector*. Often, the effector is an enzyme that converts an inactive

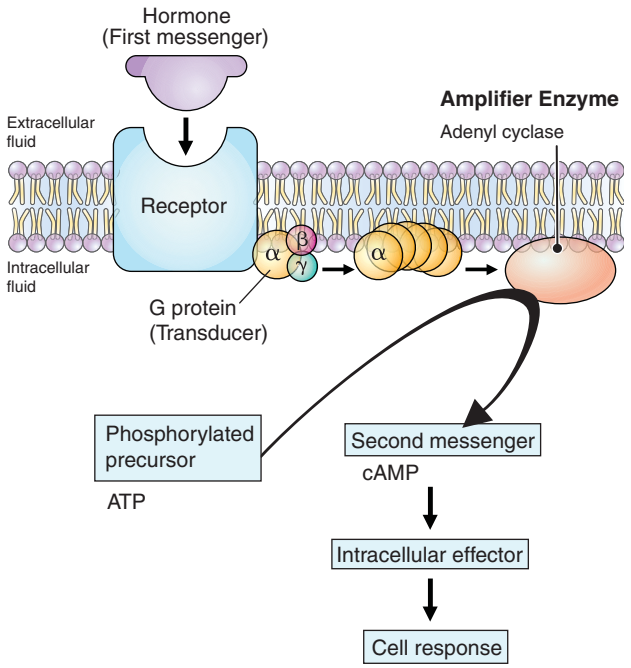


FIGURE 1-10. Activation of a G-protein–linked receptor and production of cyclic adenosine monophosphate (cAMP). Binding of a hormone (the first messenger) causes the activated receptor to interact with the inactive, guanine diphosphate (GDP)–bound G protein. This results in activation of the G protein and dissociation of the G protein α, β, and γ subunits. The activated α subunit of the G protein can then interact with and activate the membrane protein adenyl cyclase to catalyze the conversion of adenosine triphosphate (ATP) to the second messenger cAMP. The second messenger then activates an internal effector, which leads to the cell response.

precursor molecule into a second messenger, which diffuses into the cytoplasm and carries the signal beyond the cell membrane. A common second messenger is cyclic adenosine monophosphate (cAMP). It is activated by the enzyme *adenylyl cyclase,* which generates cAMP by transferring phosphate groups from ATP to other proteins. This transfer changes the conformation and function of these proteins. Such changes eventually produce the cell response to the first messenger, whether it is a secretion, muscle contraction or relaxation, or change in metabolism. Sometimes it is the opening of membrane channels involved in calcium or potassium influx.

Enzyme-Linked Receptors. Like G-protein–linked receptors, enzyme-linked receptors are transmembrane proteins with their ligand-binding site on the outer surface of the cell membrane. Instead of having a cytosolic domain that associates with a G protein, their cytosolic domain either has intrinsic enzyme activity or associates directly with an enzyme. There are several classes of enzyme-linked receptors, including one widely used in hormonal control of cell function. The binding of the hormone to a special transmembrane receptor results in activation of the enzyme *adenylyl cyclase* at the intracellular portion of the receptor. This enzyme then catalyzes the formation of the second messenger, cAMP, which has multiple effects on cell function. Insulin, for example, acts by binding to an enzyme-linked receptor (see Chapter 33).

Ion Channel–Linked Receptors. Ion channel–linked receptors are involved in the rapid synaptic signaling between electrically excitable cells. Many neurotransmitters mediate this type of signaling by transiently opening or closing ion channels formed by integral proteins in the cell membrane (to be discussed). This type of signaling is involved in the transmission of impulses in nerve and muscle cells.

Intracellular Receptors

Some messengers, such as thyroid hormone and steroid hormones, do not bind to membrane receptors but move directly across the lipid layer of the cell membrane and are carried to the cell nucleus, where they influence DNA activity (see Chapter 31). Many of these hormones bind to a cytoplasmic receptor, and together they are carried to the nucleus. In the nucleus, the receptor–hormone complex binds to DNA, thereby increasing transcription of mRNA. The mRNAs are translated in the ribosomes, with the production of increased amounts of proteins that alter cell function.

Membrane Transport Mechanisms

The plasma membrane is a flexible yet sturdy barrier that surrounds the cell and contains the cytoplasm of the cell. The main structural component of the membrane is its lipid bilayer. The lipid layer serves as a barrier against the movement of water and water-soluble substances between the intracellular and extracellular fluids, while allowing a few lipid-soluble (e.g., alcohol, oxygen, nitrogen) and uncharged molecules (glycerol, water) to cross the cell membrane by simple diffusion. The plasma membrane also contains large numbers of protein molecules, many of which travel all the way through the membrane (Fig. 1-11). Most ions and small molecules rely on these proteins for transport.

Different membrane proteins function in different ways. Some, which are called *channel proteins,* have watery spaces all the way through the membrane and allow free movement of water as well as selected ions or molecules. Others, called *membrane transport proteins*, bind with molecules or ions and undergo a series of conformational changes to transfer the bound solute across the membrane. Some transport proteins, called *uniporters*, simply mediate the movement of a single solute from one

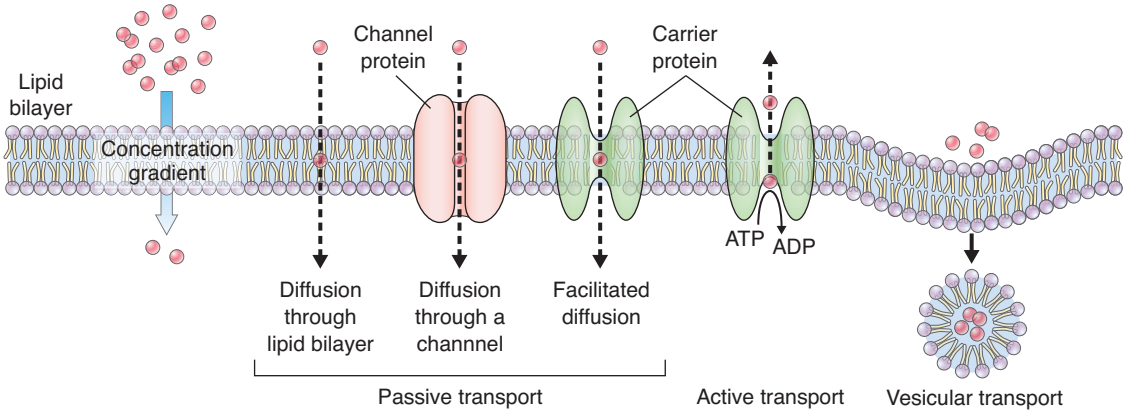


FIGURE 1-11. Mechanisms of membrane transport. Passive transport represents the net movement from a region of higher to lower concentration and active transport (energy requiring) from a region of lower to higher concentration. Vesicular transport involves the formation of membrane-enclosed vesicles or sacs that serve as transport vehicles from extracellular materials that are being moved into the cell (endocytosis) or intracellular materials that are being moved out of the cell (exocytosis).

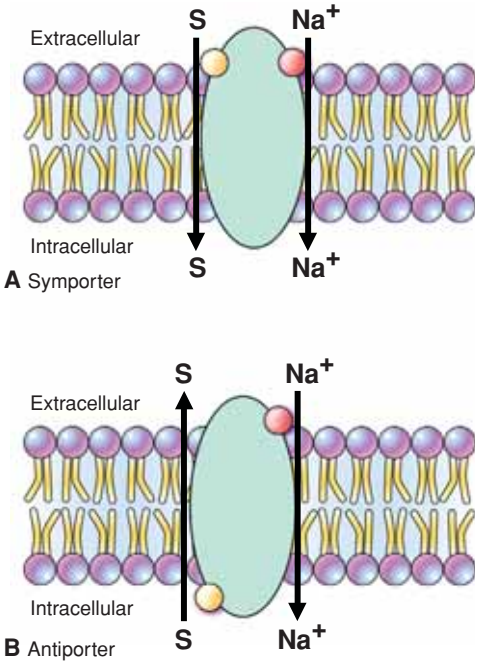


FIGURE 1-12. Secondary active transport systems. **(A)** Symport or cotransport carries the transported solute (S) in the same direction as the sodium (Na^+) ion. **(B)** Antiport or countertransport carries the solute and Na^+ in the opposite direction.

side of the membrane to the other, whereas others function as coupled transporters in which the transfer of one solute depends on the transfer of a second solute (Fig. 1-12). This coupled transport involves either the simultaneous transport in the same direction, performed by transporters called *symporters*, or the transport of a second solute in the opposite direction, by transporters called *antiporters*.

All channels and many transporters allow solutes to cross the membrane only passively by *passive transport* or *facilitated diffusion*. Cells also require transport proteins that actively pump certain solutes across the membrane against an electrochemical gradient, in a process called *active transport*. Active transport is directional and requires an energy source such as ATP. The cell membrane can also engulf substances, forming a membrane-coated vesicle; this membrane-coated vesicle is moved into the cell by *endocytosis* or out of the cell by *exocytosis*.

Many integral transmembrane proteins form the ion channels found on the cell surface. These channel proteins have a complex morphology and are selective with respect to the substances they transmit. Mutations in these channel proteins, often called *channelopathies*, are responsible for a host of genetic disorders. For example, in cystic fibrosis (see Chapter 23), the primary defect resides in an abnormal chloride channel, which results in increased sodium and water reabsorption that causes respiratory tract secretions to thicken and occlude the airways.

Diffusion

Diffusion refers to the process by which molecules and other particles in a solution become widely dispersed and reach a uniform concentration because of energy created by their spontaneous kinetic movements. In the process of reaching a uniform concentration, these molecules and particles move "downhill" from an area of higher to an area of lower concentration. If the molecules or particles carry a net charge, both the concentration gradient and the electrical potential difference across the membrane influence transport.

Lipid-soluble molecules, such as oxygen, carbon dioxide, alcohol, and fatty acids, become dissolved in the lipid matrix of the cell membrane and diffuse through the membrane in the same manner that diffusion occurs in water. Other substances diffuse through minute pores of the cell membrane.

Simple Diffusion. Simple diffusion means that the kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with a carrier protein. The rate of diffusion depends on how many particles are available for diffusion, the kinetic movement of the particles, and the number and size of the openings in the membrane through which the molecules or ions can move.

Facilitated Diffusion. Like simple diffusion, facilitated diffusion occurs down a concentration gradient; thus, it does not require input of metabolic energy. Unlike simple diffusion, however, facilitated diffusion requires a transport protein. Some substances, such as glucose, cannot pass unassisted through the cell membrane because they are not lipid soluble or they are too large to pass through the membrane's pores. These substances combine with special transport proteins at the membrane's outer surface, are carried across the membrane attached to the transporter, and then are released. In facilitated diffusion, a substance can move only from an area of higher concentration to one of lower concentration. The rate at which a substance moves across the membrane because of facilitated diffusion depends on the difference in concentration between the two sides of the membrane. Also important are the availability of transport proteins and the rapidity with which they can bind and release the substance being transported. It is thought that insulin, which facilitates the movement of glucose into cells, acts by increasing the availability of glucose transporters in the cell membrane.

Ion Channels and Gates. Ion channels are integral proteins that span the width of the membrane and are normally composed of several polypeptides or protein subunits that form a gating system (Fig. 1-13). Specific stimuli cause the protein subunits to undergo conformational changes to form an open channel or gate through which the ions can move. In this way, ions do not need to cross the lipid-soluble portion of the membrane but can remain in the aqueous solution that fills the ion channel. Many of the ion channels are highly selective for transport of one or more specific ions or molecules. This selectivity results from the characteristics of the channel itself, such as its diameter, its shape, and the nature of electrical charges and chemical bonds along its inside surface.

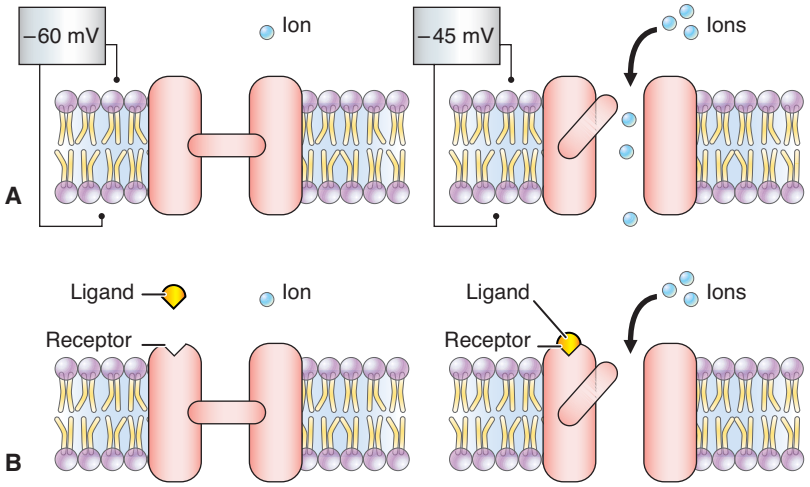


FIGURE 1-13. Gated ion channels that open in response to specific stimuli. **(A)** Voltage-gated channels are controlled by a change in the membrane potential. **(B)** Ligand-gated channels are controlled by binding of a ligand to a receptor.

The plasma membrane contains two basic groups of ion channels: leakage channels and gated channels. Leakage channels are open even in the unstimulated state, whereas gated channels open and close in response to specific stimuli. Three main types of gated channels are present in the plasma membrane: *voltage-gated channels,* which have electrically operated channels that open when the membrane potential changes beyond a certain point; *ligand-gated channels,* which are chemically operated and respond to specific receptor-bound ligands, such as the neurotransmitter acetylcholine; and *mechanically gated channels,* which open or close in response to such mechanical stimulations as vibrations, tissue stretching, or pressure.

Movement of Water across the Plasma Membrane. Water molecules move through adjacent phospholipid molecules in the plasma membrane by osmosis without actually dissolving in the region occupied by the fatty acid side of the chains. Osmosis is regulated by the concentration of nondiffusible particles on either side of membrane, with water moving from the side with the lower concentration of particles to the side with the higher concentration. The plasma membranes of most cells also contain transmembrane proteins, called *aquaporins* that function as water channels. Aquaporins are especially abundant in cells, such as the epithelial cells of the kidney, that must transport water at particularly high rates.

Active Transport

The process of diffusion describes particle movement from an area of higher concentration to one of lower concentration, resulting in an equal distribution across the cell membrane. Sometimes, however, different concentrations of a substance are needed in the intracellular and extracellular fluids. For example, to function, a cell requires a higher intracellular concentration of potassium ions than is present in the extracellular fluid, while maintaining a much lower concentration of sodium ions than the extracellular fluid. In these situations, energy is required to pump the ions "uphill" or against their concentration gradient. When cells use energy to move ions against an electrical or chemical gradient, the process is called *active transport*. Two types of active transport systems exist: primary active transport and secondary active transport.

Primary Active Transport. Among the substances that are transported by *primary active transport* are sodium, potassium, calcium, and hydrogen ions. The active transport system studied in the greatest detail is the sodium/potassium (Na^+/K^+)-adenosine triphosphatase (ATPase) membrane pump. The Na^+/K^+-ATPase membrane pump moves sodium from inside the cell to the extracellular region, where its concentration is approximately 14 times greater than inside; the pump also returns potassium to the inside, where its concentration is approximately 35 times greater than it is outside the cell. If it were not for the activity of the Na^+/K^+-ATPase membrane pump, the osmotically active sodium particles would accumulate in the cell, causing cellular swelling because of an accompanying influx of water.

Secondary Active Transport. *Secondary active transport* mechanisms harness the energy derived from the primary active transport of one substance, usually sodium, for the cotransport of a second substance. For example, when sodium ions are actively transported out of a cell by primary active transport, a large concentration gradient develops (i.e., high concentration on the outside and low on the inside). This concentration gradient represents a large storehouse of energy because sodium ions are always attempting to diffuse into the cell. Similar to facilitated diffusion, secondary transport mechanisms use membrane transport proteins. These proteins have two binding sites: one for sodium and the other for the substance undergoing secondary transport. Secondary transport systems are classified into two groups: cotransport, or symport, systems, in which sodium and the solute are transported in the same direction, and countertransport, or antiport, systems, in

which sodium and the solute are transported in the opposite directions. An example of cotransport occurs in the intestine, where the absorption of glucose and amino acids is coupled with sodium transport.

Vesicular Transport

Vesicular transport is a mechanism in which a cell encloses material in a small spherical membranous sac, or vesicle, formed from the plasma membrane. There are two types of vesicular transport: *endocytosis,* in which materials are moved into a cell in a vesicle formed from the plasma membrane, and *exocytosis,* in which materials are moved out of a cell by fusion of a vesicle with the plasma membrane.

Endocytosis is the process by which cells engulf materials from their surroundings. In the process, the material is progressively enclosed in small portions of the plasma membrane, which first invaginates and then pinches off to become an endocytotic vesicle. If the vesicle is small (>150 nm in diameter), the process is called *pinocytosis,* and the vesicle is called a *pinocytotic vesicle;* if the vesicle is large (>250 nm in diameter), the process is called *phagocytosis*, and the vesicle is called a *phagosome*. The process of pinocytosis, which means "cell drinking," is important in the transport of proteins and strong solutions of electrolytes. Phagocytosis, which means "cell eating," involves the engulfment and subsequent killing or degradation of microorganisms and other particulate matter. Certain cells, such as macrophages and polymorphonuclear leukocytes (neutrophils), are adept at engulfing and disposing of invading organisms, damaged cells, and unneeded extracellular constituents.

Exocytosis is the mechanism for the secretion of intracellular substances into the extracellular spaces. It is the reverse of endocytosis in that a secretory granule fuses to the inner side of the cell membrane, and an opening occurs in the cell membrane. This opening allows the contents of the granule to be released into the extracellular fluid. Exocytosis is important in removing cellular debris and releasing substances, such as hormones, synthesized in the cell. Since a cell's surface area and volume remain unchanged, the same amount of membrane being removed by endocytosis must be added to the plasma membrane by exocytosis. During endocytosis, portions of the cell membrane become an endocytotic vesicle and are removed, and during exocytosis, the vesicular membrane is incorporated into the plasma membrane. In this way, cell membranes can be conserved and reused.

Receptor-mediated endocytosis involves the binding of substances to a receptor on the cell surface. Many cells specialize in the endocytotic ingestion of several types of macromolecules. The most efficient form of capture of these substances depends on the presence of receptor proteins on the cell membrane that bind with a specific ligand or macromolecule. Many of these receptor proteins are concentrated in *clathrin-coated pits,* which are specific areas of the cell where the membrane is lined on its cytoplasmic side by a peripheral protein called *clathrin*. The interaction between the proteins in the receptor–ligand complex causes the membrane to invaginate, or fold inward. Vesicle formation occurs when the edges of the membrane around the clathrin-coated pit fuse and a portion of the membrane pinches off. Almost immediately after it is formed, the vesicle loses its clathrin coat and becomes fused with an early endosome in a manner similar to that involved in non–receptor-mediated endocytosis (see Fig. 1-5). The uptake of cholesterol transported in the blood as low-density lipoprotein (LDL) relies on receptor-mediated removal associated with clathrin-coated pits. This pathway for cholesterol removal is disrupted in persons who inherit defective genes for encoding LDL receptors (see Chapter 18).

In addition to clathrin-coated pits and vesicles, there are other less–well-understood mechanisms by which cells can form endocytotic vesicles. One of these pathways involves the formation of small invaginations or "little cavities" in the cell membrane, called *caveolae*, that extend inward, indenting the plasma membrane and the cytoplasm. These cavities may pinch off and form free vesicles within the cytoplasm. Caveolae are considered to be sites for uptake of material into the cell, for expulsion of material from the cell, and for addition or removal of plasma membrane components. In smooth muscle, caveolae project into the cytoplasm and, analogous to the T tubules in striated muscle, play an important role in regulating intracellular calcium concentration and smooth muscle tone. In addition to transport, caveolae are involved in a number of other functions such as signal transduction and may be involved in the pathogenesis of a number of diseases including muscular dystrophy.

Generation of Membrane Potentials

The human body runs on a system of self-generated electricity. Electrical potentials exist across the membranes of most cells in the body. Because these potentials occur at the level of the cell membrane, they are called *membrane potentials*. In excitable tissues, such as nerve or muscle cells, changes in the membrane potential are necessary for generation and conduction of nerve impulses and muscle contraction. In other types of cells, such as glandular cells, changes in the membrane potential contributes to hormone secretion and other functions.

Electrical potentials describe the ability of separated electrical charges of opposite polarity (+ and −) to do work. In regard to cells, the oppositely charged particles are ions, and the barrier that separates them is the cell membrane. Electrical potentials are measured in volts (V) or units of electromotive force (EMF). Voltage is always measured with respect to two points in a system. For example, the voltage in a car battery (6 or 12 V) is the potential difference between the two battery terminals. In a cell it is the potential difference between the inside and outside of the cell membrane. Because the total amount of charge that can be separated by a biologic membrane is small, the potential differences are small and are therefore measured in millivolts (mV), or 1/1000 of a volt.

There are two main factors that alter membrane potentials: the difference in the concentration of ions on the inside and outside of the membrane and the permeability

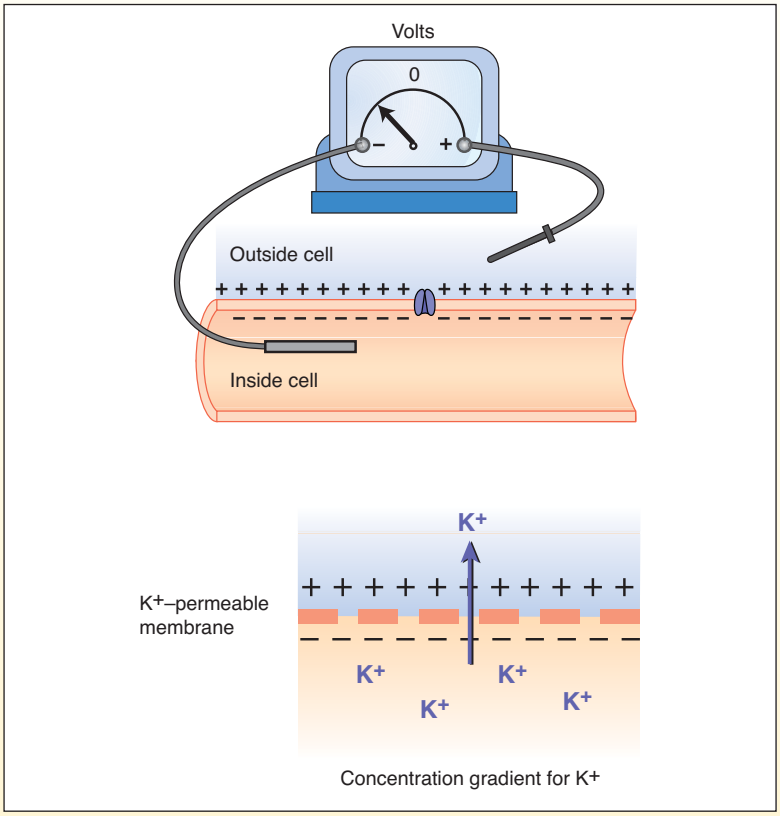
UNDERSTANDING → Membrane Potentials

Electrochemical potentials are present across the membranes of virtually all cells in the body. Some cells, such as nerve and muscle cells, are capable of generating rapidly changing electrical impulses, and transmitting these impulses along their membranes. Generation of membrane potentials relies on (1) diffusion of current-carrying ions, (2) development of an electrochemical equilibrium, and (3) establishment of a resting membrane potential and triggering an action potential.

1

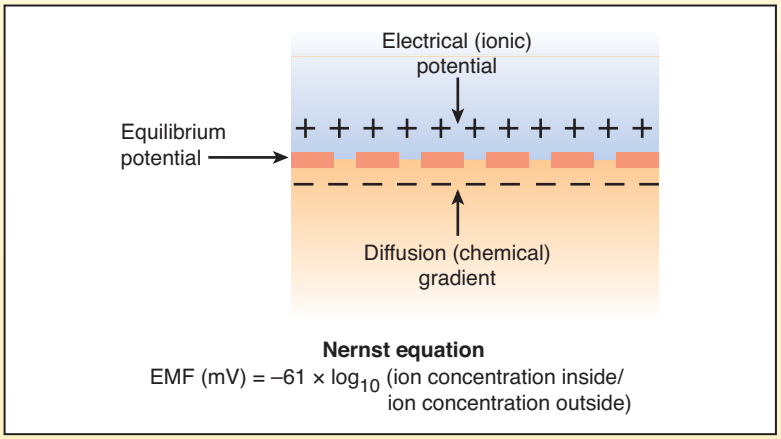
Diffusion Potentials. A diffusion potential is a potential difference generated across a membrane when a current-carrying ion, such as the potassium (K^+) ion, diffuses down its concentration gradient. Two conditions are necessary for this to occur: (1) the membrane must be selectively permeable to a particular ion, and (2) the concentration of the diffusible ion must be greater on one side of the membrane than the other.

The magnitude of the diffusion potential, measured in millivolts, depends on the size of the concentration gradient. The sign (+ or −) or polarity of the potential depends on the diffusing ion. It is negative on the inside when a positively charged ion such as K^+ diffuses from the inside to the outside of the membrane, carrying its charge with it.



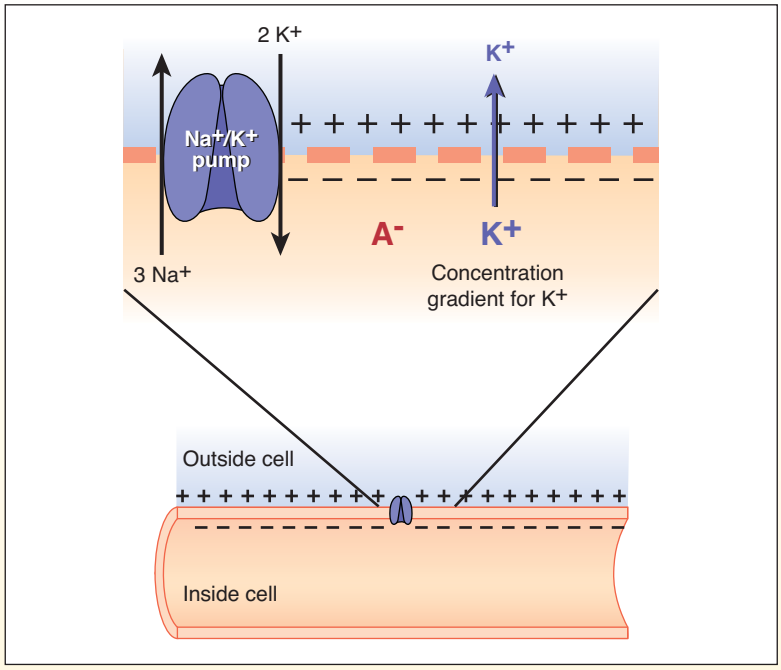
2

Equilibrium Potentials. An equilibrium potential is the membrane potential that exactly balances and opposes the net diffusion of an ion down its concentration gradient. As a cation diffuses down its concentration gradient, it carries its positive charge across the membrane, thereby generating an electrical force that will eventually retard and stop its diffusion. An electrochemical equilibrium is one in which the *chemical forces driving* diffusion and the *repelling electrical forces* are exactly balanced so that no further diffusion occurs. The equilibrium potential (EMF, electromotive force) can be calculated by inserting the inside and outside ion concentrations into the Nernst equation.



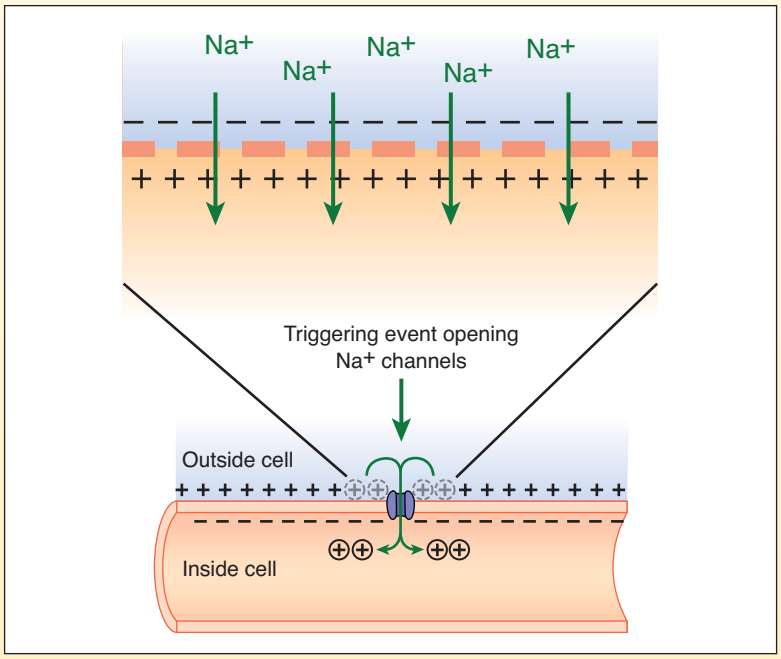
3

Resting Membrane Potential (RMP). The RMP, which is necessary for electrical excitability, is present when the cell is not transmitting impulses. Because the resting membrane is permeable to K^+, it is essentially a K^+ equilibrium potential. This can be explained in terms of the large K^+ concentration gradient (e.g., 140 mEq/L inside and 4 mEq/L outside), which causes the positively charged K^+ to diffuse outward, leaving the nondiffusible, negatively charged intracellular anions (A^-) behind. This causes the membrane to become polarized, with negative charges aligned along the inside and positive charges along the outside. The Na^+/K^+ membrane pump, which removes three Na^+ from inside while returning only two K^+ to the inside, contributes to the maintenance of the RMP.



4

Action Potentials. Action potentials involve rapid changes in the membrane potential. Each action potential begins with a sudden change from the negative RMP to a positive threshold potential, causing an opening of the membrane channels for Na^+ (or other ions of the action potential). Opening of the Na^+ channels allows large amounts of the positively charged Na^+ ions to diffuse to the interior of the cell, causing the membrane potential to undergo depolarization or a rapid change to positive on the inside and negative on the outside. This is rapidly followed by closing of Na^+ channels and opening of the K^+ channels, which leads to a rapid efflux of K^+ from the cell and reestablishment of the RMP.



of the membrane to these ions. Extracellular and intracellular fluids are electrolyte solutions containing approximately 150 to 160 mmol/L of positively charged ions and an equal concentration of negatively charged ions. It is the diffusion of these current-carrying ions that is responsible for generating and conducting membrane potentials. A *diffusion potential* describes the voltage generated by ions that diffuse across the cell membrane.

An *equilibrium potential* is one in which there is no net movement of a particular ion across a membrane because the diffusion potential and electrical forces generated by the movement of the ion are exactly balanced. The magnitude of the equilibrium potential, also known as the *Nernst potential*, is determined by the ratio of the concentration of a specific ion on the two sides of the membrane. The greater the ratio, the greater the tendency for the ion to diffuse in one direction, and therefore the greater the electrical forces required to prevent further diffusion. The Nernst equation (see section on understanding membrane potentials) can be used to calculate the equilibrium potential for any univalent ion at a given concentration difference, assuming that membrane is permeable to the ion. When using the equation, it is generally assumed that the electrical potential of the extracellular fluid outside the membrane remains at zero and the potential being calculated is the electrical potential inside the membrane. It is also assumed that the sign of the potential is negative (−) if a positively charged ion diffuses from the inside to the outside of the membrane and positive (+) if a positively charged ion diffuses from the outside to the inside of the membrane.

The *resting membrane potential* represents the period of time when excitable cells, such as nerve fibers, are not transmitting signals. Because resting cell membranes are more permeable to potassium than sodium, the resting membrane reflects the diffusion of potassium ions. The Na^+/K^+-ATPase membrane pump, which removes three Na^+ from inside the cell while returning two K^+ to the inside, assists in maintaining the resting membrane potential. During an action potential, the cell membrane becomes more permeable to sodium, causing its polarity to change so that it is positive on the inside and negative on the outside (discussed in Chapter 34).

In summary, cells communicate with each other by chemical messenger systems. In some tissues, chemical messengers move from cell to cell through gap junctions without entering the extracellular fluid. Other types of chemical messengers bind to receptors on or near the cell surface. There are three classes of cell surface receptor proteins: G-protein linked, enzyme linked, and ion channel linked. G-protein–linked receptors rely on a class of molecules called G proteins that function as an on–off switch to convert external signals (first messengers) into internal signals (second messengers). Enzyme-linked receptors have intrinsic enzyme activity or rely on enzymes that are closely associated with the receptor they activate. One type of enzyme-linked receptor is widely used in hormonal control of cell function and involves the activation of the enzyme adenylyl cyclase, which catalyzes the formation of cAMP, a second messenger that has multiple effects inside the cell. Ion channel–linked signaling is mediated by neurotransmitters that transiently open or close ion channels formed by integral proteins in the cell membrane.

The movement of materials across the cell's membrane is essential for survival of the cell. *Diffusion* is a process by which substances such as ions move from areas of greater concentration to areas of lesser concentration in an attempt to reach a uniform distribution. Facilitated diffusion is a passive process, in which molecules that cannot normally pass through the cell's membranes do so with the assistance of a carrier molecule. Another type of transport, called *active transport*, requires the cell to expend energy in moving ions against a concentration gradient. The Na^+/K^+-ATPase membrane pump is the best-known type of active transport. *Vesicular transport* is a mechanism in which a cell encloses extracellular material in a small spherical membranous sac, or vesicle, formed from the plasma membrane. There are two types of vesicular transport: *endocytosis,* in which materials are moved into a cell in a vesicle formed from the plasma membrane, and *exocytosis*, in which materials are moved out of a cell by fusion of a vesicle with the plasma membrane.

Electrical potentials, which are measured in volts, describe the ability of separated electrical charges of opposite polarity (+ and −) to do work. In regard to cells, the oppositely charged particles are ions, and the barrier that separates them is the cell membrane. There are two main factors that alter membrane potentials and excitability: the difference in concentration of ions on the inside and outside of the membrane and the permeability of the membrane to these ions. An *equilibrium potential* is one in which there is no net movement of a particular ion across a membrane because the *diffusion* and *electrical forces* generated by the movement of the ions are exactly balanced. The resting membrane potential (+ outside and − inside) is essentially a potassium equilibrium potential that results from the selective permeability of the membrane to the potassium ion and the large difference in potassium concentration that exists between the inside and the outside of the membrane. During an action potential, the cell membrane becomes highly permeable to sodium, causing it to depolarize and reverse its polarity (− inside and + outside).

Body Tissues

In the preceding sections, we discussed the individual cell, its metabolic processes, and mechanisms of communication. Although cells are similar, their structure and function vary according to the specific needs of the body. For example, muscle cells perform different functions

Organization of Cells Into Tissues

- Cells with a similar embryonic origin or function are often organized into larger functional units called *tissues,* and these tissues in turn associate with other, dissimilar tissues to form the various organs of the body.
- Epithelial tissue forms sheets that cover the body's outer surface, lines internal surfaces, and forms glandular tissue. It is supported by a basement membrane, is avascular, and must receive nourishment from capillaries in supporting connective tissues.
- Connective tissue is the most abundant tissue of the body. It is found in a variety of forms, ranging from solid bone to blood cells that circulate in the vascular system.
- Muscle tissue contains actin and myosin filaments that allow it to contract and provide locomotion and movement of skeletal structures (skeletal muscle), pumping of blood through the heart (cardiac muscle), and contraction of blood vessels and visceral organs (smooth muscle).
- Nervous tissue, which consists of two cell types, nerve cells or neurons and glial or supporting cells, is distributed throughout the body, and serves as the body's communication system. The nervous system is divided anatomically into the central nervous system (CNS), which consists of the brain and spinal cord, and the peripheral nervous system (PNS), which is composed of nerve tissue outside the CNS.

from skin cells or nerve cells. Groups of cells that are closely associated in structure and have common or similar functions are called *tissues*. Four categories of tissue exist: (1) epithelial, (2) connective, (3) muscle, and (4) nervous. These tissues do not exist in isolated units but in association with each other and in variable proportions, forming different structures and organs of the body. This section of the chapter provides a brief overview of the cells in each of the four tissue types, the structures that hold these cells together, and the extracellular matrix in which they live.

Embryonic Origin of Tissue Types

After conception, the fertilized ovum undergoes a series of divisions, ultimately forming different cell types that form the various tissues of the body. The formation of different types of cells and the disposition of these cells into tissue types is called *cell differentiation*, a process that is controlled by a system that switches genes on and off (see Chapter 4).

All of the approximately 200 different cells of the body can be classified into the four basic or primary tissue types: epithelial, connective, muscle, and nervous (Table 1-1). These basic tissue types are often described by their embryonic origin. The embryo is essentially a three-layered tubular structure (Fig. 1-14). The outer layer of the tube is called the *ectoderm;* the middle layer, the *mesoderm;* and the inner layer, the *endoderm*. All of the mature tissue types originate from these three cellular layers. Epithelium has its origin in all three embryonic layers, connective tissue and muscle develop mainly from the mesoderm, and nervous tissue develops from the ectoderm.

Epithelial Tissue

Epithelial tissue forms sheets that cover the body's outer surface, line the internal surfaces, and form glandular tissue. Underneath all types of epithelial tissue is an amorphous extracellular layer, called the *basement membrane,* which serves to attach the epithelial cells to adjacent connective tissue and provides them with flexible support.

The cells that make up epithelium have three general characteristics: (1) they are characterized by three distinct surfaces: a free surface or apical surface, a lateral surface, and a basal surface; (2) they are closely apposed and joined by cell-to-cell adhesion molecules, which form specialized cell junctions; and (3) their basal surface is attached to the underlying basement membrane (Fig. 1-15). The characteristics and geometric arrangement of the cells in the epithelium determine their function. The free or apical surface is always directed toward the exterior surface or lumen of an enclosed cavity or tube, the lateral surface communicates with adjacent cells and is characterized by specialized attachment areas, and the basal surface rests on the basement membrane anchoring the cell to the surrounding connective tissue.

Epithelial tissues are classified according to the shape of the cells and the number of layers that are present: simple, stratified, and pseudostratified. Glandular epithelial tissue is formed by cells specialized to produce a fluid secretion. The terms *squamous* (thin and flat), *cuboidal* (cube shaped), and *columnar* (resembling a column) refer to the cells' shape (Fig. 1-16).

Simple Epithelium

Simple epithelium contains a single layer of cells, all of which rest on the basement membrane. Simple squamous epithelium is adapted for filtration; it is found lining the blood vessels, lymph nodes, and alveoli of the lungs. The single layer of squamous epithelium lining the heart and blood vessels is known as the *endothelium*. A similar type of layer, called the *mesothelium*, forms the serous membranes that line the pleural, pericardial, and peritoneal cavities and covers the organs of these cavities. A *simple cuboidal epithelium* is found on the surface of the ovary and in the thyroid. *Simple columnar epithelium* lines the intestine. One form of a simple columnar epithelium has

TABLE 1-1 Classification of Tissue Types

Tissue Type	Location
Epithelial Tissue	
Covering and lining of body surfaces	
Simple epithelium	
Squamous	Lining of blood vessels, body cavities, alveoli of lungs
Cuboidal	Collecting tubules of kidney; covering of ovaries
Columnar	Lining of intestine and gallbladder
Stratified epithelium	
Squamous keratinized	Skin
Squamous nonkeratinized	Mucous membranes of mouth, esophagus, and vagina
Cuboidal	Ducts of sweat glands
Columnar	Large ducts of salivary and mammary glands; also found in conjunctiva
Transitional	Bladder, ureters, renal pelvis
Pseudostratified	Tracheal and respiratory passages
Glandular	
Endocrine	Pituitary gland, thyroid gland, adrenal and other glands
Exocrine	Sweat glands and glands in gastrointestinal tract
Neuroepithelium	Olfactory mucosa, retina, tongue
Reproductive epithelium	Seminiferous tubules of testis; cortical portion of ovary
Connective Tissue	
Embryonic connective tissue	
Mesenchymal	Embryonic mesoderm
Mucous	Umbilical cord (Wharton jelly)
Adult connective tissue	
Loose or areolar	Subcutaneous areas
Dense regular	Tendons and ligaments
Dense irregular	Dermis of skin
Adipose	Fat pads, subcutaneous layers
Reticular	Framework of lymphoid organs, bone marrow, liver
Specialized connective tissue	
Bone	Long bones, flat bones
Cartilage	Tracheal rings, external ear, articular surfaces
Hematopoietic	Blood cells, myeloid tissue (bone marrow)
Muscle Tissue	
Skeletal	Skeletal muscles
Cardiac	Heart muscles
Smooth	Gastrointestinal tract, blood vessels, bronchi, bladder, and others
Nervous Tissue	
Neurons	Central and peripheral neurons and nerve fibers
Supporting cells	Glial and ependymal cells in central nervous system; Schwann and satellite cells in peripheral nervous system

hairlike projections called *cilia*, often with specialized mucus-secreting cells called *goblet cells*. This form of simple columnar epithelium lines the airways of the respiratory tract.

Stratified and Pseudostratified Epithelium

Stratified epithelium contains more than one layer of cells, with only the deepest layer resting on the basement membrane. It is designed to protect the body surface. *Stratified squamous keratinized epithelium* makes up the epidermis of the skin. *Keratin* is a tough, fibrous protein found as filaments in the outer cells of skin. A stratified squamous keratinized epithelium is made up of many layers. The layers closest to the underlying tissues are cuboidal or columnar. The cells become more irregular and thinner as they move closer to the surface. Surface cells become totally filled with keratin and die, are sloughed off, and then replaced by the deeper cells. A stratified squamous nonkeratinized epithelium is found on moist surfaces such as the mouth and tongue. Stratified cuboidal and columnar epithelia are found in the ducts of salivary glands and the larger ducts of the mammary glands. In smokers, the normal columnar ciliated epithelial cells of the trachea and bronchi are often replaced with stratified squamous epithelium cells that are better able to withstand the irritating effects of cigarette smoke.

Pseudostratified epithelium is a type of epithelium in which all of the cells are in contact with the underlying intercellular matrix, but some do not extend to the surface. A pseudostratified ciliated columnar epithelium with goblet cells forms the lining of most of the upper respiratory

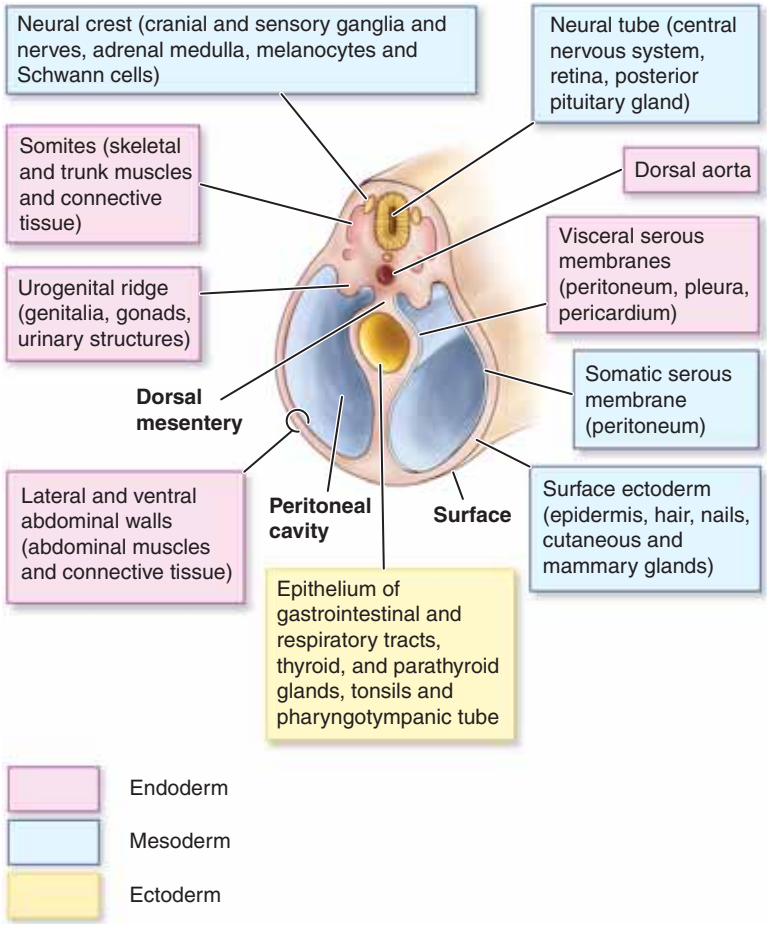


FIGURE 1-14. Cross-section of human embryo illustrating the development of the somatic and visceral structures.

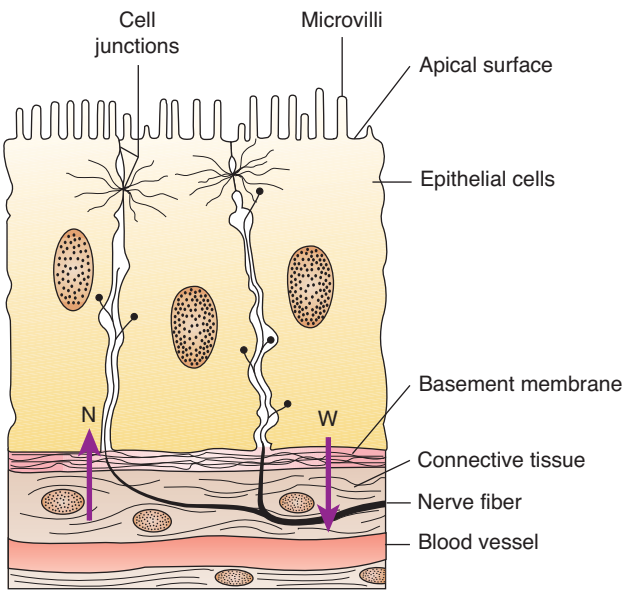


FIGURE 1-15. Typical arrangement of epithelial cells in relation to underlying tissues and blood supply. Epithelial tissue has no blood supply of its own but relies on the blood vessels in the underlying connective tissue for nutrition (N) and elimination of wastes (W).

tract. All of the tall cells reaching the surface of this type of epithelium are either ciliated cells or mucus-producing goblet cells. The basal cells that do not reach the surface serve as stem cells for ciliated and goblet cells. *Transitional epithelium* is a stratified epithelium characterized by cells that can change shape and become thinner when the tissue is stretched. Such tissue can be stretched without pulling the superficial cells apart. Transitional epithelium is well adapted for the lining of organs that are constantly changing their volume, such as the urinary bladder.

Glandular Epithelium

Glandular epithelial tissue is formed by cells specialized to produce a fluid secretion. This process is usually accompanied by the intracellular synthesis of macromolecules. The chemical nature of these macromolecules is variable. The macromolecules typically are stored in the cells in small membrane-bound vesicles called *secretory granules*. For example, glandular epithelia can synthesize, store, and secrete proteins (e.g., insulin), lipids (e.g., adrenocortical hormones, secretions of the sebaceous glands), and complexes of carbohydrates and proteins (e.g., saliva). Less common are secretions that require minimal synthetic activity, such as those produced by the sweat glands.

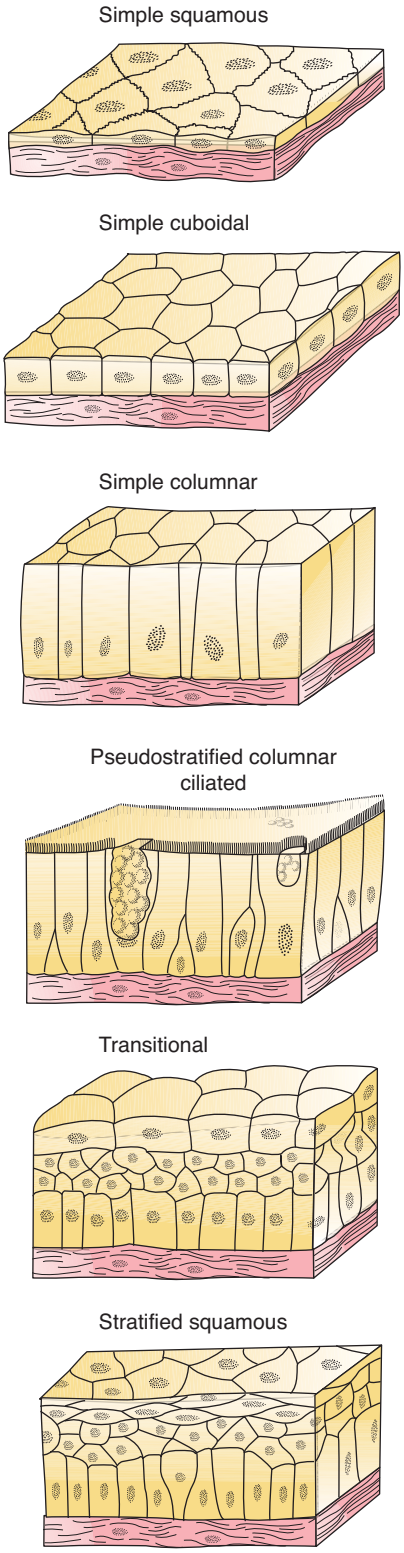


FIGURE 1-16. Representation of the various epithelial tissue types.

All glandular cells arise from surface epithelia by means of cell proliferation and invasion of the underlying connective tissue. Epithelial glands can be divided into two groups: exocrine and endocrine glands. Exocrine glands, such as the sweat glands and lactating mammary glands, retain their connection with the surface epithelium from which they originated. This connection takes the form of epithelium-lined tubular ducts through which the secretions pass to reach the surface. Endocrine glands are epithelial structures that have had their connection with the surface obliterated during development. These glands are ductless and produce secretions (i.e., hormones) that move directly into the bloodstream.

Epithelial Cell Renewal

Cells making up the epithelial tissues generally exhibit a high rate of turnover, which is related to their location and function. The rate of cell turnover is characteristic of specific epithelium. For example, the epithelial cells of the small intestine are renewed every 4 to 6 days by regenerative cells in the lower portion of the intestinal glands (crypts). Similarly, the cells of the stratified squamous epithelium of the skin are constantly being renewed at the basal layer by cell division.

Connective Tissue

Connective or supportive tissue is the most abundant tissue in the body. As its name suggests, it connects and binds or supports the various tissues. Connective tissue is unique in that its cells produce the extracellular matrix that supports and holds tissues together. The proximity of the extracellular matrix to blood vessels allows it to function as an exchange medium through which nutrients and metabolic wastes pass.

The functions of the various connective tissues are reflected by the types of cells and fibers present in the tissue and the characteristics of the extracellular matrix (Fig. 1-17). The capsules that surround organs of the body are composed of connective tissue. Bone, adipose tissue, and cartilage are specialized types of connective tissue that function to support the soft tissues of the body and store fat. One type of cell, the fibroblast, is responsible for synthesis of collagen, elastic, reticular fibers, and ground substance of the extracellular matrix. Other cells, such as lymphocytes, plasma cells, macrophages, and eosinophils, are associated with body defense systems.

Adult connective tissue can be divided into two types: connective tissue proper, which is the focus of the discussion in this chapter, and specialized connective tissue (cartilage, bone, and blood cells), which is discussed in other chapters. There are four recognized types of connective tissue proper: loose (areolar), adipose, reticular, and dense connective tissue.

Loose Connective Tissue

Loose connective tissue, also known as *areolar tissue*, is soft and pliable. It fills spaces between muscle sheaths, forms a layer that encases blood and lymphatic vessels,

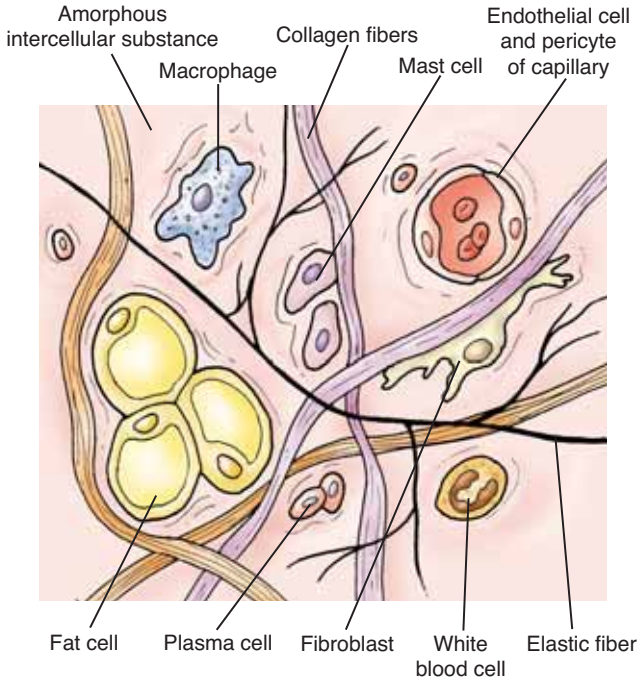


FIGURE 1-17. Diagrammatic representation of cells that may be seen in loose connective tissue. The cells lie in an intercellular matrix that is bathed in tissue fluid that originates in the capillaries.

and provides support for epithelial tissues and the means by which these tissues are nourished. Loose connective tissue is characterized by an abundance of ground substance and tissue fluid housing the fixed connective tissue cells: fibroblasts, mast cells, adipose or fat cells, macrophages, and leukocytes. Fibroblasts are the most abundant of these cells. They are responsible for the synthesis of the fibrous and gel-like substance that fills the intercellular spaces of the body and for the production of collagen, elastic, and reticular fibers.

Adipose Tissue

Adipose tissue is a special form of connective tissue in which adipocytes predominate. Adipocytes do not generate an extracellular matrix but maintain a large intracellular space. These cells store large quantities of triglycerides and are the largest repository of energy in the body. Adipose tissue helps fill spaces between tissues and helps to keep organs in place. The subcutaneous fat helps to shape the body. Because fat is a poor conductor of heat, adipose tissue serves as thermal insulation for the body. Adipose tissue exists in two forms: unilocular and multilocular. Unilocular (white) adipose tissue is composed of cells in which the fat is contained in a single, large droplet in the cytoplasm. Multilocular (brown) adipose tissue is composed of cells that contain multiple droplets of fat and numerous mitochondria.

Reticular and Dense Connective Tissue

Reticular and dense connective tissue is characterized by a network of fibers interspersed with macrophages and fibroblasts that synthesize collagen fibers. *Reticular fibers* provide the framework for capillaries, nerves, and muscle cells. They also constitute the main supporting elements for the blood-forming tissues and the liver.

Dense connective tissue exists in two forms: dense irregular and dense regular. Dense irregular connective tissue consists of the same components found in loose connective tissue but exhibits a predominance of collagen fibers and fewer cells. This type of tissue can be found in the dermis of the skin (i.e., reticular layer), the fibrous capsules of many organs, and the fibrous sheaths of cartilage (i.e., perichondrium) and bone (i.e., periosteum). It also forms the fascia that invests muscles and organs. Dense regular connective tissues are rich in collagen fibers and form the tendons and aponeuroses that join muscles to bone or other muscles and the ligaments that join bone to bone.

Muscle Tissue

Muscle tissue, whose primary function is contraction, is responsible for movement of the body and its parts and for changes in the size and shape of internal organs. Muscle tissue contains two types of fibers that are responsible for contraction: thin actin and thick myosin filaments. The two types of myofilaments occupy the bulk of the cytoplasm, which in muscle cells is called the *sarcoplasm*.

There are three types of muscle tissues: skeletal, cardiac, and smooth. *Skeletal* and *cardiac muscles* are striated muscles, in which the actin and myosin filaments are arranged in large parallel arrays in bundles, giving the muscle fibers a striped or striated appearance when observed with a microscope. *Smooth muscle* lacks striations and is found in the iris of the eye; the walls of blood vessels; hollow organs, such as the stomach and urinary bladder; and hollow tubes, such as the ureters and common bile duct that connect internal organs.

Although the three types of muscle tissues differ significantly in structure, contractile properties, and control mechanisms, they have many similarities. In the following section, the structural properties of skeletal muscle are presented as the prototype of striated muscle tissue. Smooth muscle and the ways in which it differs from skeletal muscle are also discussed. Cardiac muscle is described in Chapter 17.

Skeletal Muscle

Skeletal muscle is the most abundant tissue in the body, accounting for 40% to 45% of the total body weight. Most skeletal muscles are attached to bones, and their contractions are responsible for movements of the skeleton. Skeletal muscle fibers are packaged into skeletal muscles that attach to and cover the body skeleton. Each skeletal muscle is a discrete organ made up of hundreds or thousands of muscle fibers. Although muscle fibers predominate, substantial amounts of connective tissue, blood vessels, and nerve fibers are present. In an intact muscle, several different layers of connective tissue hold the individual muscle fibers together. Skeletal muscles

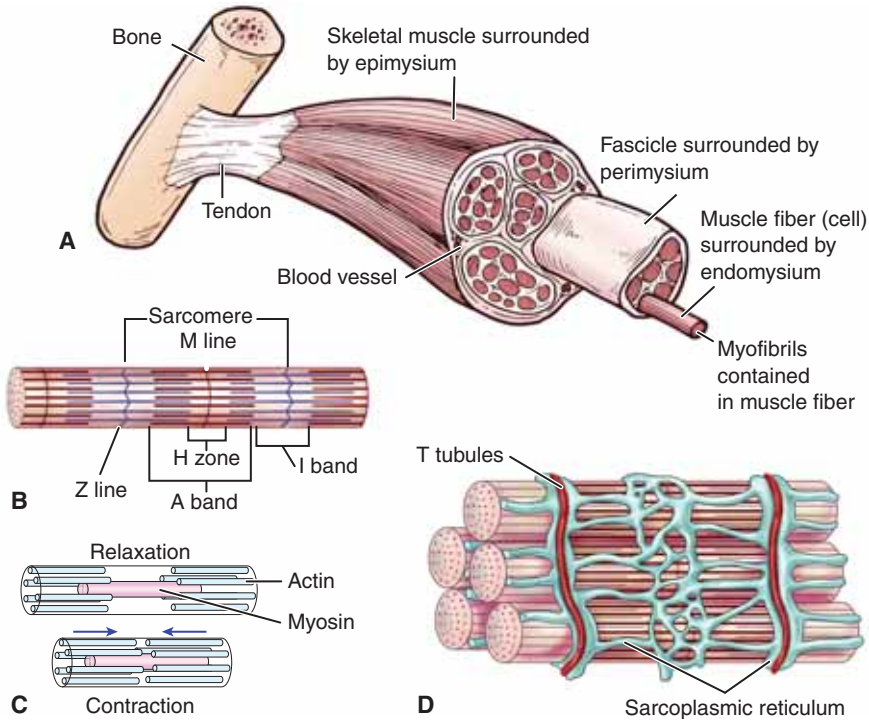


FIGURE 1-18. **(A)** Connective tissue components of a skeletal muscle. **(B)** Striations of the myofibril showing the overlap of contractile proteins and the A and I bands, the H zone, and the Z and M lines. **(C)** The relaxed and contracted states of the myofibril showing the position of actin filaments (blue) between the myosin filaments (pink) in the relaxed muscle (*top*) and pulling of the Z membranes toward each other (*bottom*) as the muscle contracts. **(D)** The sarcoplasmic reticulum with T tubules.

such as the biceps brachii are surrounded by a dense irregular connective tissue covering called the *epimysium* (Fig. 1-18A). Each muscle is subdivided into smaller bundles called *fascicles*, which are surrounded by a connective tissue covering called the *perimysium*. The number of fascicles and their size vary among muscles. Fascicles consist of many elongated structures called *muscle fibers*, each of which is surrounded by connective tissue called the *endomysium*.

Skeletal muscles are syncytial or multinucleated structures, meaning there are no true cell boundaries within a skeletal muscle fiber. The cytoplasm or sarcoplasm of the muscle fiber is contained within the sarcolemma, which represents the cell membrane. Embedded throughout the sarcoplasm are the contractile elements actin and myosin, which are arranged in parallel bundles (i.e., *myofibrils*). Each myofibril consists of regularly repeating units along the length of the myofibril called *sarcomeres*.

Sarcomeres, which are the structural and functional units of striated muscle, extend from one Z line to another Z line (Fig. 1-18B). The central portion of the sarcomere contains the dark band (A band) consisting mainly of myosin filaments, with some overlap with actin filaments. Straddling the Z line, the lighter I band contains only actin filaments; therefore, it takes two sarcomeres to complete an I band. An H zone is found in the middle of the A band and represents the region where only myosin filaments are found. In the center of the H zone is a thin, dark band, the M band or M line, produced by linkages between the myosin filaments. Z lines consist of short elements that interconnect and provide the thin actin filaments from two adjoining sarcomeres with an anchoring point. Muscle contraction involves sliding of the actin filaments inward among the myosin filaments (Fig. 1-18C). In the relaxed state, the ends of the actin filaments extend from two successive Z lines, barely overlapping one another. In the contracted state, these actin filaments have been pulled inward among the myosin filaments so their ends overlap one another.

The *sarcoplasmic reticulum*, which is comparable to the smooth ER, is composed of longitudinal tubules that run parallel to the muscle fiber and surround each myofibril (Fig 1-18D). This network ends in enlarged, saclike regions called the *lateral sacs* or *terminal cisternae*. These sacs store calcium that is released during muscle contraction. A second system of tubules consists of the *transverse* or *T tubules*, which are extensions of the plasma membrane and run perpendicular to the muscle fiber. The hollow portion or lumen of the T tubule is continuous with the extracellular fluid compartment. Action potentials, which are rapidly conducted over the surface of the muscle fiber, are in turn propagated by the T tubules into the sarcoplasmic reticulum. As the action potential moves through the lateral sacs, the sacs release calcium, initiating muscle contraction. The membrane of the sarcoplasmic reticulum also has an active transport mechanism for pumping calcium ions back into the reticulum. This prevents interactions between calcium ions and the actin and myosin myofilaments after cessation of a muscle contraction.

Skeletal Muscle Contraction. Muscle contraction involves the sliding of the thick myosin and thin actin filaments over each other to produce shortening of the muscle fiber, while the actual length of the individual thick and thin filaments remains unchanged. The thick myosin filaments consist of a thin tail, which provides the structural backbone for the filament, and a globular head that

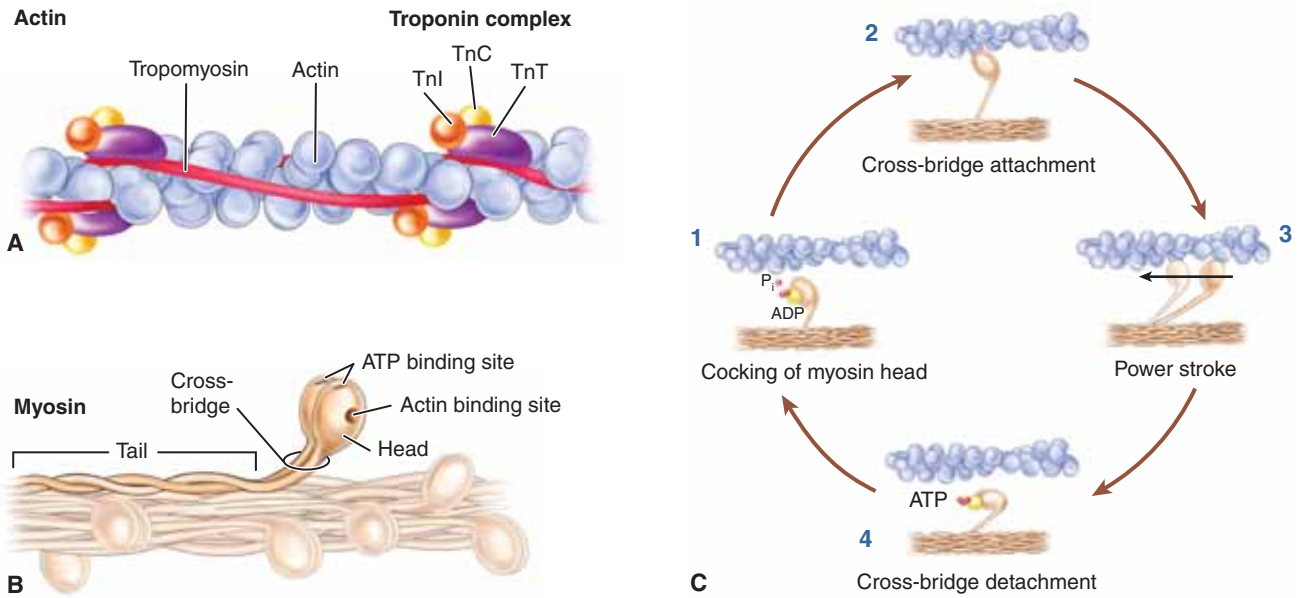


FIGURE 1-19. Molecular structure of the thin actin filament **(A)** and the thicker myosin filament **(B)** of striated muscle. The thin filament is a double-stranded helix of actin molecules with tropomyosin and troponin molecules lying along the grooves of the actin strands. **(C)** Sequence of events involved in sliding of adjacent actin and myosin filaments: (1) cocking of the myosin head, which occurs as adenosine triphosphate (ATP) is split to adenosine diphosphate (ADP); (2) cross-bridge attachment; (3) power stroke during which the myosin head bends as it moves the actin forward; and (4) cross-bridge detachment, which occurs as a new ATP attaches to the myosin head.

forms cross-bridges with the thin actin filaments (Fig. 1-19B). Myosin molecules are bundled together side by side in the thick filaments such that one half have their heads toward one end of the filament and their tails toward the other end, and the other half are arranged in the opposite manner. Each globular myosin head contains a binding site able to bind to a complementary site on the actin molecule. Besides the binding site for actin, each myosin head has a separate active site that catalyzes the breakdown of ATP to provide the energy needed to activate the myosin head so it can form a cross-bridge with actin. After contraction, myosin also binds ATP, thus breaking the linkage between actin and myosin.

The thin filaments are composed mainly of actin, a globular protein lined up in two rows that coil around each other to form a long helical strand (Fig. 1-19A). Associated with each actin filament are two regulatory proteins, tropomyosin and troponin. *Tropomyosin*, which lies in grooves of the actin strand, provides the site for attachment of the globular heads of the myosin filament. In the noncontracted state, *troponin* covers the tropomyosin-binding sites and prevents formation of cross-bridges between the actin and myosin. During an action potential, calcium ions released from the sarcoplasmic reticulum diffuse to the adjacent myofibrils, where they bind to troponin. The binding of calcium to troponin uncovers the tropomyosin-binding sites such that the myosin heads can attach and form cross-bridges.

Muscle contraction begins with activation of the cross-bridges from the myosin filaments and uncovering of the tropomyosin-binding sites on the actin filament (Fig. 1-19C). When activated by ATP, the heads of the myosin filaments swivel in a fixed arc, much like the oars of a boat, as they become attached to the actin filament. During contraction, each myosin head undergoes its own cycle of movement, forming a bridge attachment and releasing it, and moving to another site where the same sequence of movement occurs. This pulls the thin and thick filaments past each other. Energy from ATP is used to break the actin and myosin cross-bridges, stopping the muscle contraction. After the linkage between actin and myosin, the concentration of calcium around the myofibrils decreases as calcium is actively transported into the sarcoplasmic reticulum by a membrane pump that uses energy derived from ATP.

Smooth Muscle

Smooth muscle is often called *involuntary muscle* because its activity arises spontaneously or through the activity of the autonomic nervous system. Smooth muscle is usually arranged in sheets or bundles and its contractions are slower and more sustained than skeletal or cardiac muscle contractions.

Smooth muscle cells are spindle shaped and smaller than skeletal muscle fibers. Each smooth muscle cell has one centrally positioned nucleus. Z bands and M lines are not present in smooth muscle fibers, and the cross-striations are absent because the bundles of filaments are not parallel but crisscross obliquely through the cell. Instead, the actin filaments are attached to structures called dense bodies. Some dense bodies are attached to

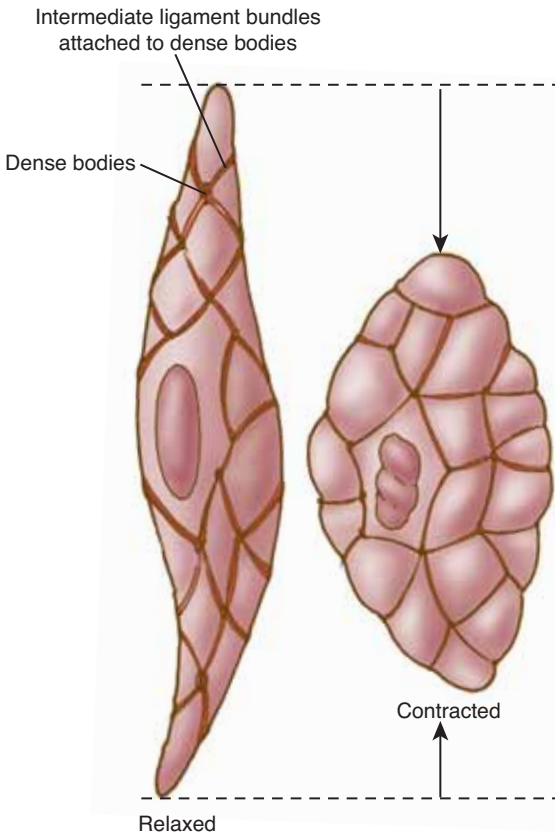


FIGURE 1-20. Structure of smooth muscle showing the dense bodies. In smooth muscle, the force of contraction is transmitted to the cell membrane by bundles of intermediate fibers.

the cell membrane, and others are dispersed in the cell and linked together by structural proteins (Fig. 1-20).

The lack of Z lines and regular overlapping of contractile elements provide a greater range of tension development. This is important in hollow organs that undergo changes in volume, with consequent changes in the length of the smooth muscle fibers in their walls. Even with the distention of a hollow organ, the smooth muscle fiber retains some ability to develop tension, whereas such distention would stretch skeletal muscle beyond the area where the thick and thin filaments overlap.

Smooth Muscle Contraction. As with cardiac and skeletal muscle, smooth muscle contraction is initiated by an increase in intracellular calcium. However, smooth muscle differs from skeletal muscle in the way its cross-bridges are formed. The sarcoplasmic reticulum of smooth muscle is less developed than in skeletal muscle, and no transverse tubules are present. Smooth muscle relies on the entrance of extracellular calcium for muscle contraction. This dependence on movement of extracellular calcium across the cell membrane during muscle contraction is the basis for the action of calcium-blocking drugs used in the treatment of cardiovascular disease.

Smooth muscle also lacks the calcium-binding regulatory protein troponin, which is found in skeletal and cardiac muscle. Instead, it relies on another cytoplasmic protein called calmodulin. The calcium–calmodulin complex binds to and activates the myosin-containing thick filaments, which interact with actin.

Nervous Tissue

Nervous tissue is distributed throughout the body as an integrated communication system. Anatomically, the nervous system is divided into the central nervous system (CNS), which consists of the brain and spinal cord, and the peripheral nervous system (PNS), which consists of nerve fibers and ganglia that exist outside the CNS. Nerve cells develop from the embryonic ectoderm. Nerve cells are highly differentiated and therefore incapable of regeneration in postnatal life. Embryonic development of the nervous system and the structure and functions of the nervous system are discussed more fully in Chapter 34.

Structurally, nervous tissue consists of two cell types: nerve cells or neurons and supporting cells or neuroglia. Most nerve cells consist of three parts: the soma or cell body, dendrites, and the axon. The cytoplasm-filled dendrites, which are multiple elongated processes, receive and carry stimuli from the environment, from sensory epithelial cells, and from other neurons to the cell. The axon, which is a single cytoplasm-filled process, is specialized for generating and conducting nerve impulses away from the cell body to other nerve cells, muscle cells, and glandular cells.

Neurons can be classified as afferent and efferent neurons according to their function. Afferent or sensory neurons carry information toward the CNS; they are involved in the reception of sensory information from the external environment and from within the body. Efferent or motor neurons carry information away from the CNS; they are needed for control of muscle fibers and endocrine and exocrine glands.

Communication between neurons and effector organs, such as muscle cells, occurs at specialized structures called *synapses*. At the synapse, chemical messengers (i.e., neurotransmitters) alter the membrane potential to conduct impulses from one nerve to another or from a neuron to an effector cell. In addition, electrical synapses exist in which nerve cells are linked through gap junctions that permit the passage of ions from one cell to another.

Neuroglia (*glia* means "glue") are the cells that support neurons, form myelin, and have trophic and phagocytic functions. Four types of neuroglia are found in the CNS: astrocytes, oligodendrocytes, microglia, and ependymal cells. Astrocytes are the most abundant of the neuroglia. They have many long processes that surround blood vessels in the CNS. They provide structural support for the neurons, and their extensions form a sealed barrier that protects the CNS. The oligodendrocytes provide myelination of neuronal processes in the CNS. The microglia are phagocytic cells that represent the mononuclear phagocytic system in the nervous system. Ependymal cells line the cavities of the brain and spinal cord and are in contact with the cerebrospinal

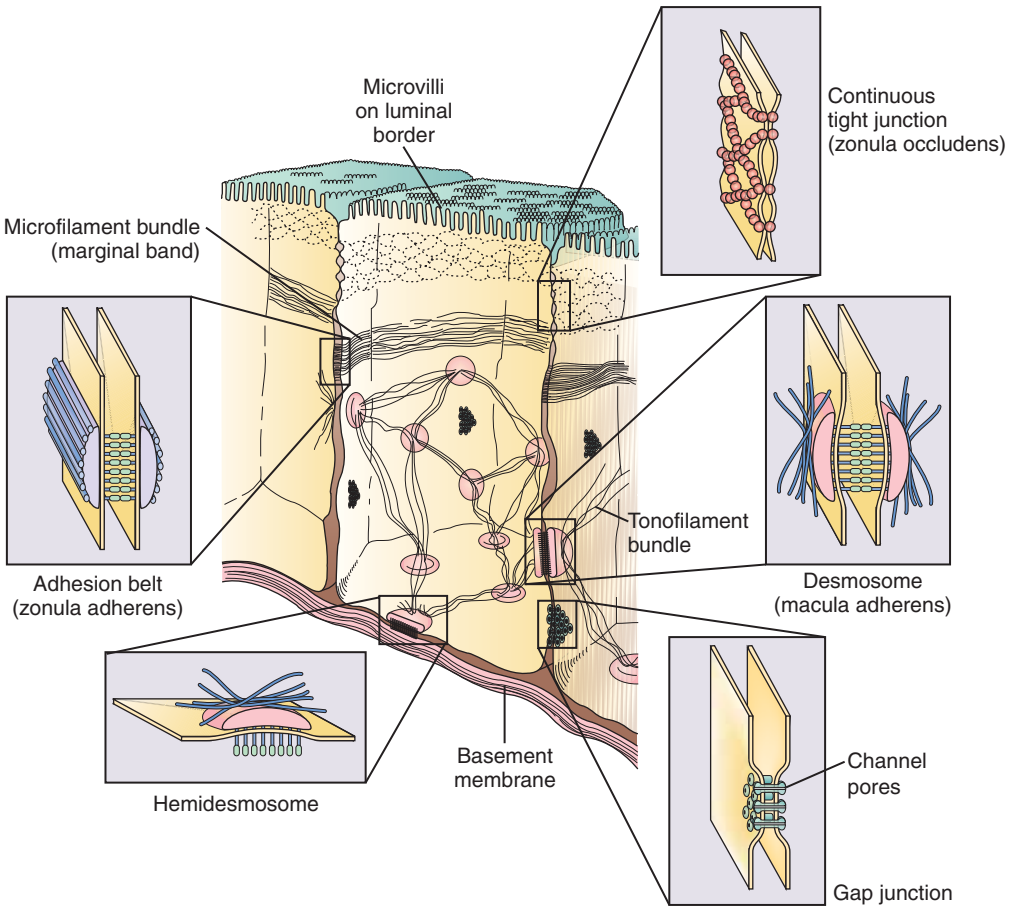


FIGURE 1-21. Three types of intercellular junctions found in epithelial tissue: the continuous tight junction (zonula occludens); the adhering junction, which includes the adhesion belt (zonula adherens), desmosomes (macula adherens), and hemidesmosomes; and the gap junction.

fluid. In the PNS, supporting cells consist of the Schwann and satellite cells. The Schwann cells provide myelination of the axons and dendrites, and the satellite cells enclose and protect the dorsal root ganglia and autonomic ganglion cells.

Extracellular Tissue Components

The discussion thus far has focused on the cellular components of the different tissue types. Within tissues, cells are held together by cell junctions; the space between cells is filled with an extracellular matrix; and adhesion molecules form intercellular contacts.

Cell Junctions

The junctions between tissue cells are important in governing the shape of the body, transmitting mechanical stresses from one cell to another, and creating pathways for communication. Cell junctions occur at many points in cell-to-cell contact, but they are particularly plentiful and important in epithelial tissue. These specialized junctions enable cells to form barriers to the movement of water, solutes, and cells from one body compartment to the next. Three basic types of intercellular junctions are observed: tight junctions, adhering junctions, and gap junctions (Fig. 1-21).

Continuous tight or *occluding junctions* (i.e., zonula occludens), which are found only in epithelial tissue, seal the surface membranes of adjacent cells together. This type of intercellular junction prevents materials such as macromolecules present in the intestinal contents from entering the intercellular space.

Adhering junctions represent sites of strong adhesion between cells. The primary role of adhering junctions may be that of preventing cell separation. Adhering junctions are not restricted to epithelial tissue; they provide adherence between adjacent cardiac muscle cells as well. Adhering junctions are found as continuous, beltlike adhesive junctions (i.e., zonula adherens) or scattered, spotlike adhesive junctions, called *desmosomes* (i.e., macula adherens). A special feature of the adhesion belt junction is that it provides an anchoring site to the cell membrane for microfilaments. In epithelial desmosomes, bundles of keratin-containing intermediate filaments (i.e., tonofilaments) are anchored to the junction on the cytoplasmic area of the cell membrane. A primary disease of desmosomes is pemphigus, which is caused by a buildup

of antibodies to the desmosome proteins. Affected persons have skin and mucous membrane blistering. *Hemidesmosomes*, which resemble a half desmosome, are another type of junction. They are found at the base of epithelial cells and help attach the epithelial cell to the underlying connective tissue.

Gap or *nexus junctions* involve the close adherence of adjoining cell membranes with the formation of channels that link the cytoplasm of the two cells. Because they are low-resistance channels, gap junctions are important in cell-to-cell conduction of electrical signals (e.g., between cells in sheets of smooth muscle or between adjacent cardiac muscle cells, where they function as electrical synapses). These multiple communication channels also enable ions and small molecules to pass directly from one cell to another.

Extracellular Matrix

Tissues are not made up solely of cells. A large part of their volume is made up of an extracellular matrix. This matrix is composed of a variety of proteins and polysaccharides (i.e., a molecule made up of many sugars). These proteins and polysaccharides are secreted locally and are organized into a supporting meshwork in close association with the cells that produced them. The amount and composition of the matrix vary with the different tissues and their function. In bone, for example, the matrix is more plentiful than the cells that surround it; in the brain, the cells are much more abundant and the matrix is only a minor constituent.

Two main classes of extracellular macromolecules make up the extracellular matrix. The first is an amorphous gel-like material called *ground substance*. Ground substance is composed of polysaccharide chains of proteins called *glycosaminoglycans* (GAGs), which are usually found linked to protein as proteoglycans. The second type consists of the fibrous proteins (i.e., collagen and elastin) and the fibrous adhesive proteins (i.e., fibronectin and laminin) that are found in the basement membrane. Members of each of these two classes of extracellular macromolecules come in a variety of shapes and sizes.

Ground Substance. The proteoglycan and GAG molecules in connective tissue form a highly hydrated, gel-like substance, or tissue gel, in which the fibrous proteins are embedded. The polysaccharide gel resists compressive forces; the collagen fibers strengthen and help organize the matrix; the rubberlike elastin adds resilience; and the adhesive proteins help cells attach to the appropriate part of the matrix. Polysaccharides in the tissue gel are highly hydrophilic, and they form gels even at low concentrations. They also produce a negative charge that attracts cations such as sodium, which are osmotically active, causing large amounts of water to be sucked into the matrix. This creates a swelling pressure, or turgor, that enables the matrix to withstand extensive compressive forces. For example, the cartilage matrix that lines the knee joint can support pressures of hundreds of atmospheres by this mechanism.

Fibrous Proteins. Three types of fibers are found in the extracellular space: collagen, elastin, and reticular fibers. *Collagen* is the most common protein in the body. It is a tough, nonliving, white fiber that serves as the structural framework for skin, ligaments, tendons, and many other structures. *Elastin* acts like a rubber band; it can be stretched and then returns to its original form. Elastin fibers are abundant in structures subjected to frequent stretching, such as the aorta and some ligaments. *Reticular fibers* are extremely thin fibers that create a flexible network in organs subjected to changes in form or volume, such as the spleen, liver, uterus, or intestinal muscle layer.

Cell Adhesion Molecules

Important classes of extracellular macromolecules are the cell adhesion molecules (CAMs). CAMs can be cell-to-cell or cell-to-matrix adhesion molecules. There are four major classes of CAMS: cadherins, selectins, integrins, and the immunoglobulin (Ig) superfamily of proteins. These proteins are located on the cell surface where they function as receptors, or they can be stored in the cytoplasm. As receptors, CAMs can bind to similar or different molecules in other cells, providing for interaction between the same cell types or different cell types.

Cadherins. Cadherins are the major CAMs responsible for calcium-dependent cell-to-cell adhesion junctions. The word *cadherin* is derived from the term "calcium-dependent adhesion protein." There are over 90 members of the cadherin superfamily. The first three cadherins that were discovered were named according to the main tissues in which they were found: the E-cadherins, which are present in many types of epithelial cells; the N-cadherins, which are present in nerve and muscle cells; and the P-cadherins, which are found on cells in the placenta and epidermis. All are found in various other tissues; N-cadherin, for example, is expressed in fibroblasts, and E-cadherin is expressed in parts of the brain.

Most cadherins function as transmembrane adhesive proteins that indirectly link the actin cytoskeletons of cells they join together, an arrangement that occurs in adhering junctions. Cadherins also form desmosomes that interact with intermediate filaments of the cytoskeleton, rather than the actin filaments. Cell-to-cell interactions mediated by cadherins play a major role in regulating cell motility, proliferation, and differentiation.

Selectins. Selectins are cell surface carbohydrate-binding proteins (lectins) that mediate a variety of transient, cell-to-cell adhesion interactions in the bloodstream. They are found on activated endothelial cells of blood vessels, on leukocytes, and on platelets. Selectins, together with integrins and immunoglobulins, participate in leukocyte movement through the endothelial lining of blood vessels during inflammation.

Integrins. Integrins usually assist in attaching epithelial cells to the underlying basement membrane. Extracellu-

larly, they are attached to fibronectin and laminin, the two major components of the basement membrane. Like the cadherins, their intracellular portion is linked to actin. One group of integrins is associated with hemidesmosomes, whereas others are associated with the surface of white blood cells, macrophages, and platelets. Integrins usually have a weak affinity for their ligands unless they are associated with cellular focal contacts and hemidesmosomes. This allows some movement between cells except where a firm attachment is required to attach epithelial cells to the underlying connective tissue.

Certain integrins play an important role in allowing white blood cells to pass through the vessel wall, a process called *transmigration*. Persons affected with leukocyte adhesion deficiency are unable to synthesize appropriate integrin molecules. As a result, they experience repeated bacterial infections because their white blood cells are not able to transmigrate through vessel walls.

Immunoglobulin Superfamily. The Ig superfamily consists of a group of one or more immunoglobulin-like adhesion proteins that are similar structurally to those of antibody molecules. They have many functions outside the immune system that are unrelated to immune defenses. The best-studied example of Ig superfamily proteins are the neural cell adhesion molecules (N-CAMs), which are expressed in a variety of cells, including most nerve cells. During early development, N-CAMs play an important role in connecting the neurons of the developing nervous system.

In summary, body cells are organized into four basic tissue types: epithelial, connective, muscle, and nervous. The epithelium covers and lines the body surfaces and forms the functional components of glandular structures. Epithelial tissue is classified into three types according to the shape of the cells and the number of layers that are present: simple, stratified, and pseudostratified.

Connective tissue supports and connects body structures; it forms the bones and skeletal system, the joint structures, the blood cells, and the cells that produce the extracellular matrix. Fibroblasts are the most abundant of these cells. They are responsible for the synthesis of collagen, elastic, and reticular fibers and the gel-like substance that fills the intercellular spaces of the body. Specialized connective tissue includes bone and cartilage, hematopoietic and lymphatic tissue, blood cells, and adipose tissue.

Muscle tissue is a specialized tissue designed for contractility. Three types of muscle tissue exist: skeletal, cardiac, and smooth. Actin and myosin filaments interact to produce muscle shortening, a process activated by the presence of calcium. In skeletal muscle, calcium is released from the sarcoplasmic reticulum in response to an action potential. Smooth muscle is often called *involuntary muscle* because it contracts spontaneously or through the activity of the autonomic nervous system. It differs from skeletal muscle in that its sarcoplasmic reticulum is less defined and it depends on the entry of extracellular calcium ions for muscle contraction.

Nervous tissue is designed for communication purposes and includes the neurons, the supporting neural structures, and the ependymal cells that line the ventricles of the brain and the spinal canal.

Within tissues, cells are held together by cell junctions; the space between cells is filled with an extracellular matrix; and adhesion molecules attach cells to the extracellular matrix. There are three basic types of cell junctions: tight junctions, adhering or adhesive-type junctions, and gap junctions. The extracellular matrix, which fills the space between the cells of tissue, is made up of a gel-like ground substance with collagen, reticular, and elastic fibers embedded in it. The ability of cells to adhere to components of the extracellular matrix is mediated by cell adhesion molecules (cadherins, selectins, integrins, and the immunoglobulin superfamily of proteins).

REVIEW EXERCISES

1. Persons who drink sufficient amounts of alcohol display rapid changes in central nervous system function, including both motor and behavioral changes, and the odor of alcohol can be detected on their breath.

A. Use the concepts related to the lipid bilayer structure of the cell membrane to explain these observations.

2. Tattoos consist of pigments that have been injected into the skin.

A. Explain what happens to the dye once it has been injected and why it does not eventually wash away.

3. Insulin is synthesized in the beta cells of the pancreas as a prohormone and then secreted as an active hormone.

A. Using your knowledge of the function of DNA, the RNAs, the endoplasmic reticulum, and the Golgi complex, propose a pathway for the synthesis of insulin.

4. Mitochondrial disorders, whether due to mutations in mitochondrial or nuclear genes, often produce muscle weakness, sometimes with severe involvement of the muscles that move the eyes, other neurologic symptoms, lactic acidosis, and cardiomyopathy.

A. Mitochondrial disorders that are responsible for these manifestations are often classified as

mitochondrial encephalomyopathies. Propose an explanation for the propensity to develop encephalopathies and myopathies with mitochondrial disorders rather than disorders of other body systems such as the kidney or digestive tract.

B. Relate the function of the mitochondria in terms of oxidative metabolism to the development of lactic acidosis.

5. The absorption of glucose from the intestine involves a cotransport mechanism in which the active primary transport of sodium is used to provide for the secondary transport of glucose.

A. Hypothesize how this information might be used to design an oral rehydration solution for someone who is suffering from diarrhea.

BIBLIOGRAPHY

Alberts B., Johnson A., Lewis J., et al. (2008). *Molecular biology of the cell* (5th ed.). New York and London: Garland Publishing.

Ashcroft F.M. (2000). *Ion channels and disease.* San Diego: Academic Press.

Chatterjee A., Mambo E., Sidransky D. (2006). Mitochondrial DNA mutations in human cancer. *Oncogene* 25, 4663–4674.

Cohen A.W., Hnasko R., Schuber W., et al. (2004). Role of caveolae and caveolins in health and disease. *Physiology Review* 84, 1341–1379.

Costanzo L.S. (2002). *Physiology* (2nd ed.). Philadelphia: W.B. Saunders.

Dalely W.P. (2007). Extracellular matrix dynamics in development and regenerative medicine. *Journal of Cell Science* 121, 255–264.

DeMartino G.N. (2007). Proteasomes: Machines for all reasons. *Cell* 129, 659–662.

Dubyak G.R. (2004). Ion homeostasis, channels, and transporters: An update on cellular mechanisms. *Advances in Physiological Education* 28, 143–154.

Gartner L.P., Hiatt J.L. (2007). *Color textbook of histology* (3rd ed.). Philadelphia: Saunders.

Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed.). Philadelphia: Elsevier Saunders.

Joachim F. (1998). How the ribosome works. *American Scientist* 86, 428–439.

Kierszenbaum A.L. (2007). *Histology and cell biology: An introduction to pathology* (2nd ed., pp. 67–75, 101–102). St. Louis: Mosby.

Kumar V., Abbas A.K., Fausto N., et al., (Eds.). (2010). *Robbins and Cotran pathologic basis of disease* (8th ed.). Philadelphia: Saunders Elsevier.

Lodish H., Berk A., Matsudaria P. (2004). *Molecular cell biology* (5th ed., pp. 147–231, 779, 817–897). New York: W. H. Freeman.

Rhoades R.A., Tanner G.A. (2003). *Medical physiology* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins.

Ross M.H., Kaye G.I., Pawlina W. (2006). *Histology: A text and atlas* (5th ed.). Philadelphia: Lippincott Williams & Wilkins.

Rubin E., Strayer R.S. (2008). *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed.). Philadelphia: Lippincott Williams & Wilkins.

Smith C., Marks A.D., Lieberman M. (2005). *Marks' basic medical biochemistry: A clinical approach* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins.

Tortora G.J., Derrickson B. (2009). *Principles of anatomy and physiology* (11th ed., pp. 61–103, 301–332, 415–454). New York: John Wiley & Sons.

Voeltz G.V., Rolls M.M., Rapoport T.A. (2002). Structural organization of the endoplasmic reticulum. *EMBO Reports* 3, 944–950.

Cellular Responses to Persistent Stress
Adaptations of Growth and Differentiation
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia
Intracellular Accumulations
Pathologic Calcifications
Dystrophic Calcification
Metastatic Calcification
Cell Injury, Death, and Senescence
Causes of Cell Injury
Injury from Physical Agents
Radiation Injury
Chemical Injury
Injury from Biologic Agents
Injury from Nutritional Imbalances
Mechanisms of Cell Injury
Free Radical Injury
Hypoxic Cell Injury
Impaired Calcium Homeostasis
Reversible Cell Injury and Cell Death
Reversible Cell Injury
Programmed Cell Death
Necrosis
Cellular Aging
Replicative Senescence
Genetic Influences
Accumulation of Environmental and Genetic Damage
Syndromes of Premature Aging

Chapter 2

Cellular Responses to Stress, Injury, and Aging

In their simplest form, all diseases exert their effects on the smallest living unit of the body, namely, the cell. When confronted with stresses that endanger its normal structure and function, the cell undergoes adaptive changes that permit survival and maintenance of function. It is only when the stress is overwhelming or adaptation is ineffective that injury, maladaptive changes, and cell death occur. Biologic aging produces its own changes in cell structure and function.

Cellular Responses to Persistent Stress

Cells adapt to changes in the internal environment just as the total organism adapts to changes in the external environment. Cells may adapt by undergoing changes in size, number, and type. These changes, occurring singly or in combination, may lead to atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia (Fig. 2-1). Cellular stresses also include intracellular accumulations and storage of products in abnormal amounts.[1,2]

Adaptations of Growth and Differentiation

There are numerous molecular mechanisms mediating cellular adaptation, including factors produced by other cells or by the cells themselves. These mechanisms depend largely on signals transmitted by chemical messengers that exert their effects by altering gene function. In general, the genes expressed in all cells fall into two categories: genes that are necessary for the normal function of a cell and genes that determine the differentiating characteristics of a particular cell type. In many adaptive cellular responses, the expression of the differentiation genes is altered, whereas its functional genes remain unaffected. Thus, a cell is able to change size or form

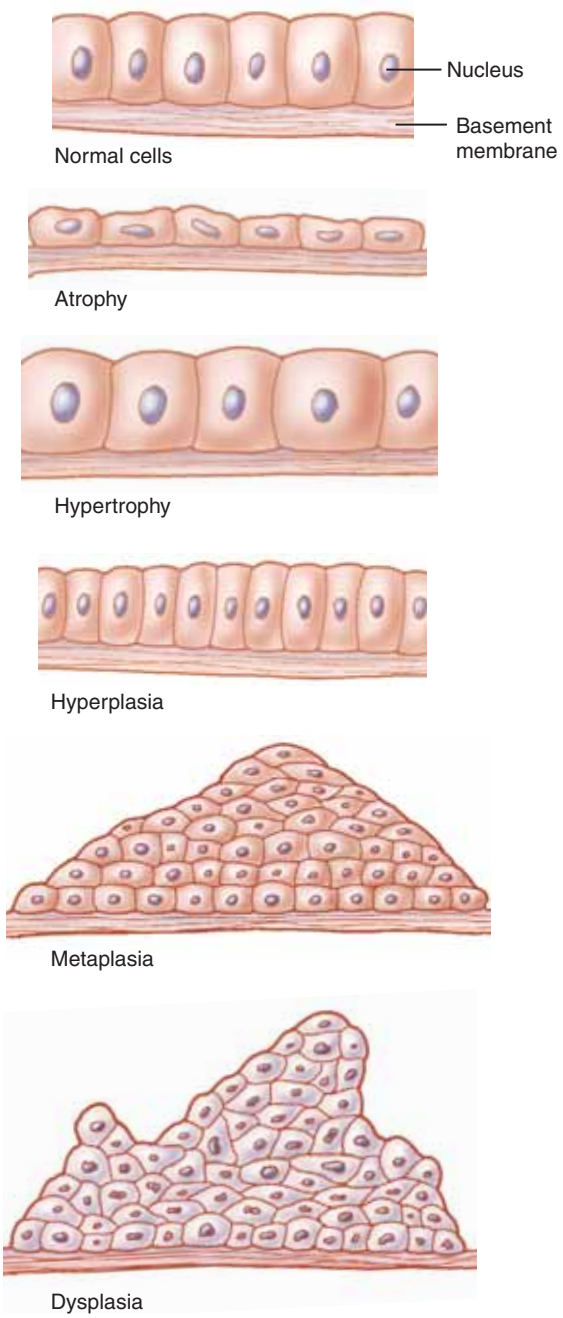


FIGURE 2-1. Adaptive cell and tissue responses involving a change in cell size (hypertrophy and atrophy), number (hyperplasia), cell type (metaplasia), or size, shape, and organization (dysplasia). (From Anatomical Chart Company. [2002]. *Atlas of pathophysiology* [p. 4]. Springhouse, PA: Springhouse.)

without compromising its function. Once the stimulus for adaptation is removed, the effect on expression of the differentiating genes is removed and the cell resumes its previous state of specialized function. Whether adaptive cellular changes are normal or abnormal depends on whether the response was mediated by an appropriate stimulus. Normal adaptive responses occur in response to need and an appropriate stimulus. After the need has been removed, the adaptive response ceases.

Cellular Adaptations

- Cells are able to adapt to increased work demands or threats to survival by changing their size (atrophy and hypertrophy), number (hyperplasia), and form (metaplasia).
- Normal cellular adaptation occurs in response to an appropriate stimulus and ceases once the need for adaptation has ceased.

Atrophy

When confronted with a decrease in work demands or adverse environmental conditions, most cells are able to revert to a smaller size and a lower and more efficient level of functioning that is compatible with survival.[1,2] This decrease in cell size is called *atrophy*. Cells that are atrophied reduce oxygen consumption and other cellular functions by decreasing the number and size of their organelles and other structures. There are fewer mitochondria, myofilaments, and endoplasmic reticulum structures. When a sufficient number of cells are involved, the entire tissue atrophies.

Cell size, particularly in muscle tissue, is related to workload. As the workload of a cell declines, oxygen consumption and protein synthesis decrease. Furthermore, proper muscle mass is maintained by sufficient levels of insulin/insulin-like growth factor-1 (IGF-1). When insulin/IGF-1 levels are low or catabolic signals are present, muscle atrophy occurs by mechanisms that include reduced synthetic processes, increased proteolysis by the ubiquitin-proteasome system, and apoptosis or programmed cell death (to be discussed).[3] In the ubiquitin-proteasome system, intracellular proteins destined for destruction are covalently bonded to a small protein called *ubiquitin* and then degraded by small cytoplasmic organelles called *proteasomes* (see Chapter 1).

The general causes of atrophy can be grouped into five categories: (1) disuse, (2) denervation, (3) loss of endocrine stimulation, (4) inadequate nutrition, and (5) ischemia or decreased blood flow. Disuse atrophy occurs when there is a reduction in skeletal muscle use. An extreme example of disuse atrophy is seen in the muscles of extremities that have been encased in plaster casts. Because atrophy is adaptive and reversible, muscle size is restored after the cast is removed and muscle use is resumed. Denervation atrophy is a form of disuse atrophy that occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation produces a form of disuse atrophy. In women, the loss of estrogen stimulation during menopause results in atrophic changes in the reproductive organs. With malnutrition and decreased blood flow, cells decrease their size and energy requirements as a means of survival.

Hypertrophy

Hypertrophy represents an increase in cell size and with it an increase in the amount of functioning tissue mass.

It results from an increased workload imposed on an organ or body part and is commonly seen in cardiac and skeletal muscle tissue, which cannot adapt to an increase in workload through mitotic division and formation of more cells. Hypertrophy involves an increase in the functional components of the cell that allows it to achieve equilibrium between demand and functional capacity. For example, as muscle cells hypertrophy, additional actin and myosin filaments, cell enzymes, and adenosine triphosphate (ATP) are synthesized.

Hypertrophy may occur as the result of normal physiologic or abnormal pathologic conditions. The increase in muscle mass associated with exercise is an example of physiologic hypertrophy. Pathologic hypertrophy occurs as the result of disease conditions and may be adaptive or compensatory. Examples of adaptive hypertrophy are the thickening of the urinary bladder from long-continued obstruction of urinary outflow and the myocardial hypertrophy from valvular heart disease or hypertension. Compensatory hypertrophy is the enlargement of a remaining organ or tissue after a portion has been surgically removed or rendered inactive. For instance, if one kidney is removed, the remaining kidney enlarges to compensate for the loss.

The initiating signals for hypertrophy appear to be complex and related to ATP depletion, mechanical forces such as stretching of the muscle fibers, activation of cell degradation products, and hormonal factors. In the case of the heart, initiating signals can be divided into two broad categories: (1) biomechanical and stretch-sensitive mechanisms and (2) neurohumoral mechanisms associated with the release of hormones, growth factors, cytokines, and chemokines.[4] Internal stretch-sensitive receptors for the biochemical signals and an array of membrane-bound receptors for the specific neurohumoral ligands, such as IGF-1 and epidermal growth factor (EGF), activate specific signal transduction pathways. These pathways control myocardial growth by altering gene expression to increase protein synthesis and reduce protein degradation, thereby causing hypertrophic enlargement of the heart. A limit is eventually reached beyond which further enlargement of the tissue mass is no longer able to compensate for the increased work demands. The limiting factors for continued hypertrophy might be related to limitations in blood flow. In hypertension, for example, the increased workload required to pump blood against an elevated arterial pressure results in a progressive increase in left ventricular muscle mass and need for coronary blood flow (Fig. 2-2).

There continues to be interest in the signaling pathways that control the arrangement of contractile elements in myocardial hypertrophy. Research suggests that certain signal molecules can alter gene expression controlling the size and assembly of the contractile proteins in hypertrophied myocardial cells. For example, the hypertrophied myocardial cells of well-trained athletes have proportional increases in width and length. This is in contrast to the hypertrophy that develops in dilated cardiomyopathy, in which the hypertrophied cells have a relatively greater increase in length than width. In pressure overload, as occurs with hypertension, the hypertrophied cells have greater width than length.[5] It is anticipated that further elucidation of the signal pathways that determine the adaptive and nonadaptive features of cardiac hypertrophy will lead to new targets for treatment.

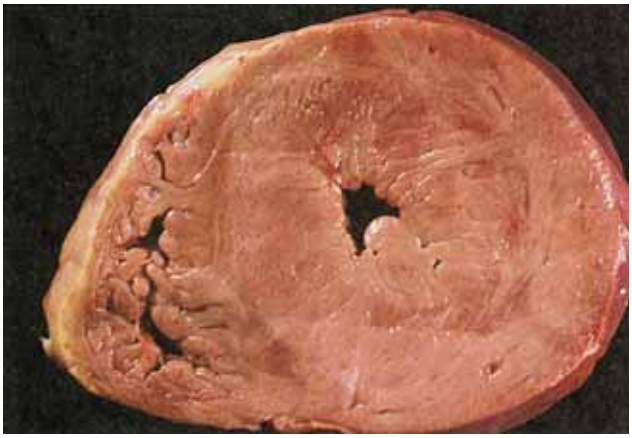


FIGURE 2-2. Myocardial hypertrophy. Cross-section of the heart in a patient with long-standing hypertension. (From Strayer D.S., Rubin E. [2008]. Cell injury. In Rubin D.S., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 5]. Philadelphia: Lippincott Williams & Wilkins.)

Hyperplasia

Hyperplasia refers to an increase in the number of cells in an organ or tissue. It occurs in tissues with cells that are capable of mitotic division, such as the epidermis, intestinal epithelium, and glandular tissue.[1,2] Certain cells, such as neurons, rarely divide and therefore have little capacity, if any, for hyperplastic growth. There is evidence that hyperplasia involves activation of genes controlling cell proliferation and the presence of intracellular messengers that control cell replication and growth. As with other normal adaptive cellular responses, hyperplasia is a controlled process that occurs in response to an appropriate stimulus and ceases after the stimulus has been removed.

The stimuli that induce hyperplasia may be physiologic or nonphysiologic. There are two common types of physiologic hyperplasia: hormonal and compensatory. Breast and uterine enlargement during pregnancy are examples of a physiologic hyperplasia that results from estrogen stimulation. The regeneration of the liver that occurs after partial hepatectomy (i.e., partial removal of the liver) is an example of compensatory hyperplasia. Hyperplasia is also an important response of connective tissue in wound healing, during which proliferating fibroblasts and blood vessels contribute to wound repair. Although hypertrophy and hyperplasia are two distinct processes, they may occur together and are often triggered by the same mechanism.[1] For example, the pregnant uterus undergoes both hypertrophy and hyperplasia as a result of estrogen stimulation.

Most forms of nonphysiologic hyperplasia are due to excessive hormonal stimulation or the effects of growth

factors on target tissues.[2] Excessive estrogen production can cause endometrial hyperplasia and abnormal menstrual bleeding (see Chapter 40). Benign prostatic hyperplasia, which is a common disorder of men older than 50 years of age, is thought to be related to the action of androgens (see Chapter 39). Skin warts are an example of hyperplasia caused by growth factors produced by certain viruses, such as the papillomaviruses.

Metaplasia

Metaplasia represents a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.[1,2] These changes are thought to involve the reprogramming of undifferentiated stem cells that are present in the tissue undergoing the metaplastic changes.

Metaplasia usually occurs in response to chronic irritation and inflammation and allows for substitution of cells that are better able to survive under circumstances in which a more fragile cell type might succumb. However, the conversion of cell type never oversteps the boundaries of the primary tissue type (e.g., one type of epithelial cell may be converted to another type of epithelial cell, but not to a connective tissue cell). An example of metaplasia is the adaptive substitution of stratified squamous epithelial cells for the ciliated columnar epithelial cells in the trachea and large airways of a habitual cigarette smoker. Although the squamous epithelium is better able to survive in these situations, the protective function that the ciliated epithelium provides for the respiratory tract is lost. Also, continued exposure to the influences that cause metaplasia may predispose to cancerous transformation of the metaplastic epithelium.

Dysplasia

Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and organization. Minor degrees of dysplasia are associated with chronic irritation or inflammation.[1] The pattern is most frequently encountered in areas of metaplastic squamous epithelium of the respiratory tract and uterine cervix. Although dysplasia is abnormal, it is adaptive in that it is potentially reversible after the irritating cause has been removed. Dysplasia is strongly implicated as a precursor of cancer. In cancers of the respiratory tract and the uterine cervix, dysplastic changes have been found adjacent to the foci of cancerous transformation. Through the use of the Papanicolaou (Pap) smear, it has been documented that cancer of the uterine cervix develops in a series of incremental epithelial changes ranging from severe dysplasia to invasive cancer (discussed in Chapter 40). However, dysplasia is an adaptive process and as such does not necessarily lead to cancer. In many cases, the dysplastic cells revert to their former structure and function.

Intracellular Accumulations

Intracellular accumulations represent the buildup of substances that cells cannot immediately use or eliminate. The substances may accumulate in the cytoplasm (frequently in the lysosomes) or in the nucleus. In some cases the accumulation may be an abnormal substance that the cell has produced, and in other cases the cell may be storing exogenous materials or products of pathologic processes occurring elsewhere in the body. These substances can be grouped into three categories: (1) normal body substances, such as lipids, proteins, carbohydrates, melanin, and bilirubin, that are present in abnormally large amounts; (2) abnormal endogenous products, such as those resulting from inborn errors of metabolism; and (3) exogenous products, such as environmental agents and pigments that cannot be broken down by the cell.[2] These substances may accumulate transiently or permanently, and they may be harmless or, in some cases, toxic.

Under some conditions cells may accumulate abnormal amounts of various substances, some of which may be harmless while others may be associated with varying degrees of injury. The substance may accumulate in the cytoplasm, the organelles (such as lysosomes), or the nucleus. These accumulations may be produced by an exogenous substance or a normal substance that is synthesized at a rate that exceeds its metabolism or removal. An example of this type of process is fatty changes in the liver due to intracellular accumulation of triglycerides. Liver cells normally contain some fat, which is either oxidized and used for energy or converted to triglycerides. This fat is derived from free fatty acids released from adipose tissue. Abnormal accumulation occurs when the delivery of free fatty acids to the liver is increased, as in starvation and diabetes mellitus, or when the intrahepatic metabolism of lipids is disturbed, as in alcoholism.

Intracellular accumulation can result from genetic disorders that disrupt the enzymatic degradation of selected substances or their transport to other sites. A normal enzyme may be replaced with an abnormal one, resulting in the formation of a substance that cannot be used or eliminated from the cell, or an enzyme may be missing, so that an intermediate product accumulates in the cell. For example, there are at least 10 genetic disorders that affect glycogen metabolism, most of which lead to the accumulation of intracellular glycogen stores. In the most common form of this disorder, von Gierke disease, large amounts of glycogen accumulate in the liver and kidneys because of a deficiency of the enzyme glucose-6-phosphatase. Without this enzyme, glycogen cannot be broken down to form glucose. The disorder leads not only to an accumulation of glycogen but also to a reduction in blood glucose levels. In Tay-Sachs disease, another genetic disorder, abnormal lipids accumulate in the brain and other tissues, causing motor and mental deterioration beginning at approximately 6 months of age, followed by death at 2 to 3 years of age (see Chapter 6).

Pigments are colored substances that may accumulate in cells. They can be endogenous (i.e., arising from within the body) or exogenous (i.e., arising from outside the body). Icterus, also called *jaundice*, is characterized by a yellow discoloration of tissue due to the retention of bilirubin, an endogenous bile pigment. This condition

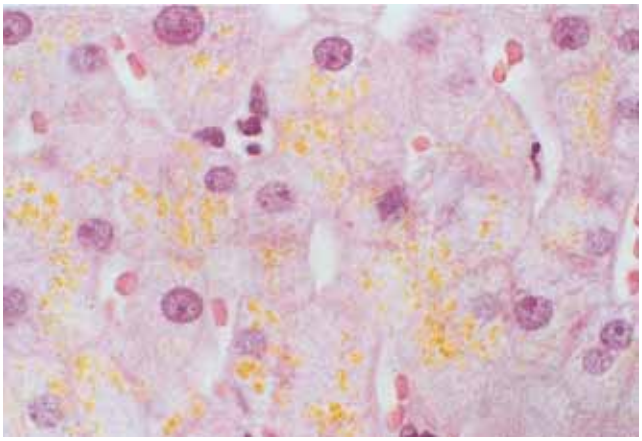


FIGURE 2-3. Accumulation of intracellular lipofuscin. A photomicrograph of the liver of an 80-year-old man shows golden cytoplasmic granules, which represent lysosomal storage of lipofuscin. (From Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 13]. Philadelphia: Lippincott Williams & Wilkins.)

may occur because of increased bilirubin production from red blood cell destruction, obstruction of bile passage into the intestine, or toxic diseases that affect the liver's ability to remove bilirubin from the blood. Lipofuscin is a yellow-brown pigment that results from the accumulation of the indigestible residues produced during normal turnover of cell structures (Fig. 2-3). The accumulation of lipofuscin increases with age and is sometimes referred to as the *wear-and-tear pigment*. It is more common in heart, nerve, and liver cells than other tissues and is seen more often in conditions associated with atrophy of an organ.

One of the most common exogenous pigments is carbon in the form of coal dust. In coal miners or persons exposed to heavily polluted environments, the accumulation of carbon dust blackens the lung tissue and may cause serious lung disease. The formation of a blue lead line along the margins of the gum is one of the diagnostic features of lead poisoning. Tattoos are the result of insoluble pigments introduced into the skin, where they are engulfed by macrophages and persist for a lifetime.

The significance of intracellular accumulations depends on the cause and severity of the condition. Many accumulations, such as lipofuscin and mild fatty changes, have no effect on cell function. Some conditions, such as the hyperbilirubinemia that causes jaundice, are reversible. Other disorders, such as glycogen storage diseases, produce accumulations that result in organ dysfunction and other alterations in physiologic function.

Pathologic Calcifications

Pathologic calcification involves the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals. It is known as *dystrophic calcification* when it occurs in dead or dying tissue and as *metastatic calcification* when it occurs in normal tissue.[1,2]

Dystrophic Calcification

Dystrophic calcification represents the macroscopic deposition of calcium salts in injured tissue. It is often visible to the naked eye as deposits that range from gritty sand-like grains to firm, hard, rock material. The pathogenesis of dystrophic calcification involves the intracellular or extracellular formation of crystalline calcium phosphate. The components of the calcium deposits are derived from the bodies of dead or dying cells as well as from the circulation and interstitial fluid.

Dystrophic calcification is commonly seen in atheromatous lesions of advanced atherosclerosis, areas of injury in the aorta and large blood vessels, and damaged heart valves. While the presence of calcification may only indicate the presence of previous cell injury, as in healed tuberculosis lesions, it is also a frequent cause of organ dysfunction. For example, calcification of the aortic valve is a frequent cause of aortic stenosis in the elderly (Fig. 2-4).

Metastatic Calcification

In contrast to dystrophic calcification, which occurs in injured tissues, metastatic calcification occurs in normal tissues as the result of increased serum calcium levels (hypercalcemia). Almost any condition that increases the serum calcium level can lead to calcification in inappropriate sites such as the lung, renal tubules, and blood vessels. The major causes of hypercalcemia are hyperparathyroidism, either primary or secondary to phosphate retention in renal failure; increased mobilization of calcium from bone as in Paget disease, cancer with metastatic bone lesions, or immobilization; and vitamin D intoxication.

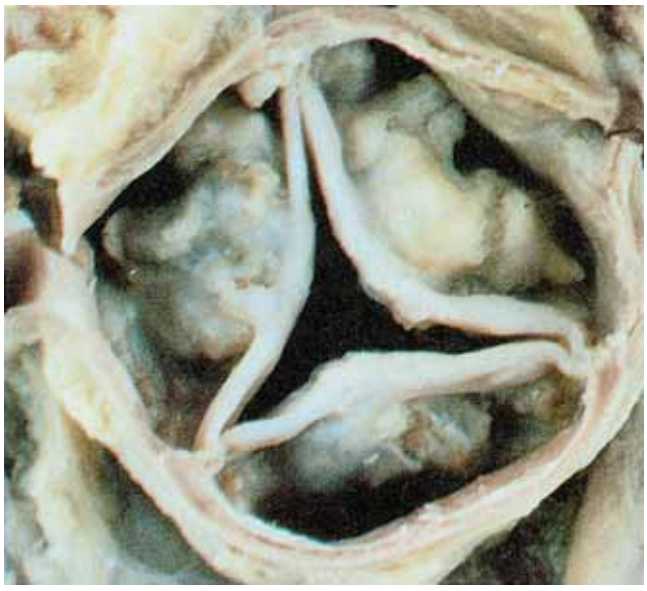


FIGURE 2-4. Calcific aortic stenosis. Large deposits of calcium salts are evident in the cusps and free margins of the thickened aortic valve as viewed from above. (From Strayer D.S., Rubin E. [2008] In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 8]. Philadelphia: Lippincott Williams & Wilkins.)

In summary, cells adapt to changes in their environment and in their work demands by changing their size, number, and characteristics. These adaptive changes are consistent with the needs of the cell and occur in response to an appropriate stimulus. The changes are usually reversed after the stimulus has been withdrawn.

When confronted with a decrease in work demands or adverse environmental conditions, cells atrophy or reduce their size and revert to a lower and more efficient level of functioning. Hypertrophy results from an increase in work demands and is characterized by an increase in tissue size brought about by an increase in cell size and functional intracellular components. An increase in the number of cells in an organ or tissue that are still capable of mitotic division is called hyperplasia. Metaplasia occurs in response to chronic irritation and represents the substitution of cells of a type that are better able to survive under circumstances in which a more fragile cell type might succumb. Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and appearance. It is often a precursor of cancer.

Under some circumstances, cells may accumulate abnormal amounts of various substances. If the accumulation reflects a correctable systemic disorder, such as the hyperbilirubinemia that causes jaundice, the accumulation is reversible. If the disorder cannot be corrected, as often occurs in many inborn errors of metabolism, the cells become overloaded, causing cell injury and death.

Pathologic calcification involves the abnormal tissue deposition of calcium salts. Dystrophic calcification occurs in dead or dying tissue. While the presence of dystrophic calcification may only indicate the presence of previous cell injury, it is also a frequent cause of organ dysfunction (e.g., when it affects the heart valves). Metastatic calcification occurs in normal tissues as the result of elevated serum calcium levels. Almost any condition that increases the serum calcium level can lead to calcification in inappropriate sites such as the lung, renal tubules, and blood vessels.

Cell Injury, Death, and Senescence

Cells can be injured in many ways. The extent to which any injurious agent can cause cell injury and death depends in large measure on the intensity and duration of the injury and the type of cell that is involved. Cell injury is usually reversible up to a certain point, after which irreversible cell injury and death occur. Whether a specific stress causes irreversible or reversible cell injury depends on the severity of the insult and on variables such as blood supply, nutritional status, and regenerative capacity. Cell injury and death are ongoing processes, and in the healthy state, they are balanced by cell renewal.

Cell Injury

- Cells can be damaged in a number of ways, including physical trauma, extremes of temperature, electrical injury, exposure to damaging chemicals, radiation damage, injury from biologic agents, and nutritional factors.
- Most injurious agents exert their damaging effects through uncontrolled free radical production, impaired oxygen delivery or utilization, or the destructive effects of uncontrolled intracellular calcium release.
- Cell injury can be reversible, allowing the cell to recover, or it can be irreversible, causing cell death and necrosis.
- In contrast to necrosis, which results from tissue injury, apoptosis is a normal physiologic process designed to remove injured or worn-out cells.

Causes of Cell Injury

Cell damage can occur in many ways. For purposes of discussion, the ways by which cells are injured have been grouped into five categories: (1) injury from physical agents, (2) radiation injury, (3) chemical injury, (4) injury from biologic agents, and (5) injury from nutritional imbalances.

Injury from Physical Agents

Physical agents responsible for cell and tissue injury include mechanical forces, extremes of temperature, and electrical forces. They are common causes of injuries due to environmental exposure, occupational and transportation accidents, and physical violence and assault.

Mechanical Forces. Injury or trauma due to mechanical forces occurs as the result of body impact with another object. The body or the mass can be in motion or, as sometimes happens, both can be in motion at the time of impact. These types of injuries split and tear tissue, fracture bones, injure blood vessels, and disrupt blood flow.

Extremes of Temperature. Extremes of heat and cold cause damage to the cell, its organelles, and its enzyme systems. Exposure to low-intensity heat (43°C to 46°C), such as occurs with partial-thickness burns and severe heat stroke, causes cell injury by inducing vascular injury, accelerating cell metabolism, inactivating temperature-sensitive enzymes, and disrupting the cell membrane. With more intense heat, coagulation of blood vessels and tissue proteins occurs. Exposure to cold increases blood viscosity and induces vasoconstriction by direct action on blood vessels and through reflex activity of the sympathetic nervous system. The resultant decrease in blood

flow may lead to hypoxic tissue injury, depending on the degree and duration of cold exposure. Injury from freezing probably results from a combination of ice crystal formation and vasoconstriction. The decreased blood flow leads to capillary stasis and arteriolar and capillary thrombosis. Edema results from increased capillary permeability.

Electrical Forces. Injuries due to electrical forces can affect the body through extensive tissue injury and disruption of neural and cardiac impulses. The effect of electricity on the body is mainly determined by its voltage, the type of current (i.e., direct or alternating), its amperage, the resistance of the intervening tissue, the pathway of the current, and the duration of exposure.[6]

Lightning and high-voltage wires that carry several thousand volts produce the most severe damage.[2] Alternating current (AC) is usually more dangerous than direct current (DC) because it causes violent muscle contractions, preventing the person from releasing the electrical source and sometimes resulting in fractures and dislocations. In electrical injuries, the body acts as a conductor of the electrical current. The current enters the body from an electrical source, such as an exposed wire, and passes through the body and exits to another conductor, such as the moisture on the ground or a piece of metal the person is holding. The pathway that a current takes is critical because the electrical energy disrupts impulses in excitable tissues. Current flow through the brain may interrupt impulses from respiratory centers in the brain stem, and current flow through the chest may cause fatal cardiac arrhythmias.

The resistance to the flow of current in electrical circuits transforms electrical energy into heat. This is why the elements in electrical heating devices are made of highly resistive metals. Much of the tissue damage produced by electrical injuries is caused by heat production in tissues that have the highest electrical resistance.[2,7] Resistance to electrical current varies from the greatest to the least in bone, fat, tendons, skin, muscles, blood, and nerves. The most severe tissue injury usually occurs at the skin sites where the current enters and leaves the body (Fig. 2-5). After electricity has penetrated the skin, it passes rapidly through the body along the lines of least resistance—through body fluids and nerves. Degeneration of vessel walls may occur, and thrombi may form as current flows along the blood vessels. This can cause extensive muscle and deep tissue injury. Thick, dry skin is more resistant to the flow of electricity than thin, wet skin. It is generally believed that the greater the skin resistance, the greater is the amount of local skin burn, and the less the resistance, the greater are the deep and systemic effects.

FIGURE 2-5. Electrical burn of the skin. The victim was electrocuted after attempting to stop a fall from a ladder by grasping a high-voltage line. (From Strayer D.S., Rubin E. [2008]. Environmental and nutritional pathology. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 272]. Philadelphia: Lippincott Williams & Wilkins.)

Radiation Injury

Electromagnetic radiation comprises a wide spectrum of wave-propagated energy, ranging from ionizing gamma rays to radiofrequency waves. A photon is a particle of radiation energy. Radiation energy with frequencies above the ultraviolet (UV) range is called *ionizing radiation* because the photons have enough energy to knock electrons off atoms and molecules. *Nonionizing radiation* refers to radiation energy at frequencies below those of visible light. *UV radiation* represents the portion of the spectrum of electromagnetic radiation just above the visible range.

Ionizing Radiation. Ionizing radiation affects cells by causing ionization of molecules and atoms in the cell, by directly hitting the target molecules in the cell, or by producing free radicals that interact with critical cell components.[2,7] It can immediately kill cells, interrupt cell replication, or cause a variety of genetic mutations, which may or may not be lethal. Most radiation injury is caused by localized irradiation that is used in the treatment of cancer (see Chapter 7). Except for unusual circumstances such as the use of high-dose irradiation that precedes bone marrow transplantation, exposure to whole-body irradiation is rare.

The injurious effects of ionizing radiation vary with the dose, dose rate (a single dose can cause greater injury than divided or fractionated doses), and the differential sensitivity of the exposed tissue to radiation injury. Because of the effect on deoxyribonucleic acid (DNA) synthesis and interference with mitosis, rapidly dividing cells of the bone marrow and intestine are much more vulnerable to radiation injury than tissues such as bone and skeletal muscle. Over time, occupational and accidental exposure to ionizing radiation can result in increased risk for the development of various types of cancers, including skin cancers, leukemia, osteogenic sarcomas, and lung cancer.

Many of the clinical manifestations of radiation injury result from acute cell injury, dose-dependent changes in the blood vessels that supply the irradiated tissues, and fibrotic tissue replacement. The cell's initial response to radiation injury involves swelling, disruption of the

mitochondria and other organelles, alterations in the cell membrane, and marked changes in the nucleus. The endothelial cells in blood vessels are particularly sensitive to irradiation. During the immediate postirradiation period, only vessel dilatation is apparent (e.g., the initial erythema of the skin after radiation therapy). Later or with higher levels of radiation, destructive changes occur in small blood vessels such as the capillaries and venules. Acute reversible necrosis is represented by such disorders as radiation cystitis, dermatitis, and diarrhea from enteritis. More persistent damage can be attributed to acute necrosis of tissue cells that are not capable of regeneration and chronic ischemia. Chronic effects of radiation damage are characterized by fibrosis and scarring of tissues and organs in the irradiated area (e.g., interstitial fibrosis of the heart and lungs after irradiation of the chest). Because the radiation delivered in radiation therapy inevitably travels through the skin, radiation dermatitis is common. There may be necrosis of the skin, impaired wound healing, and chronic radiation dermatitis.

Ultraviolet Radiation. UV radiation contains increasingly energetic rays that are powerful enough to disrupt intracellular bonds and cause sunburn and increase the risk of skin cancers (see Chapter 46). The degree of risk depends on the type of UV rays, the intensity of exposure, and the amount of protective melanin pigment in the skin. Skin damage induced by UV radiation is thought to be caused by reactive oxygen species and by damage to melanin-producing processes in the skin. UV radiation also damages DNA, resulting in the formation of pyrimidine dimers (i.e., the insertion of two identical pyrimidine bases into replicating DNA instead of one). Other forms of DNA damage include the production of single-stranded breaks and formation of DNA–protein cross-links. Normally, errors that occur during DNA replication are repaired by enzymes that remove the faulty section of DNA and repair the damage. The importance of DNA repair in protecting against UV radiation injury is evidenced by the vulnerability of persons who lack the enzymes needed to repair UV-induced DNA damage. In a genetic disorder called *xeroderma pigmentosum*, an enzyme needed to repair sunlight-induced DNA damage is lacking. This autosomal recessive disorder is characterized by extreme photosensitivity and a 2000-fold increased risk of skin cancer in sun-exposed skin.[2]

Nonionizing Radiation. Nonionizing radiation includes infrared light, ultrasound, microwaves, and laser energy.[1] Unlike ionizing radiation, which can directly break chemical bonds, nonionizing radiation exerts its effects by causing vibration and rotation of atoms and molecules. All of this vibrational and rotational energy is eventually converted to thermal energy. Low-frequency nonionizing radiation is used widely in radar, television, industrial operations (e.g., heating, welding, melting of metals, processing of wood and plastic), household appliances (e.g., microwave ovens), and medical applications (e.g., diathermy). Isolated cases of skin burns and thermal injury to deeper tissues have occurred in industrial settings and from improperly used household microwave ovens. Injury from these sources is mainly thermal and, because of the deep penetration of the infrared or microwave rays, tends to involve dermal and subcutaneous tissue injury.

Chemical Injury

Chemicals capable of damaging cells are everywhere around us. Air and water pollution contain chemicals capable of tissue injury, as does tobacco smoke and some processed or preserved foods. Some of the most damaging chemicals exist in our environment, including gases such as carbon monoxide, insecticides, and trace metals such as lead.

Chemical agents can injure the cell membrane and other cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of the cell. Corrosive substances such as strong acids and bases destroy cells as the substances come into contact with the body. Other chemicals may injure cells in the process of metabolism or elimination. Carbon tetrachloride (CCl_4), for example, causes little damage until it is metabolized by liver enzymes to a highly reactive free radical ($CCl_3\bullet$). Carbon tetrachloride is extremely toxic to liver cells.

Drugs. Many drugs—alcohol, prescription drugs, over-the-counter drugs, and street drugs—are capable of directly or indirectly damaging tissues. Ethyl alcohol can harm the gastric mucosa, liver (see Chapter 30), developing fetus (see Chapter 6), and other organs. Antineoplastic (anticancer) and immunosuppressant drugs can directly injure cells. Other drugs produce metabolic end products that are toxic to cells. Acetaminophen, a commonly used over-the-counter analgesic drug, is detoxified in the liver, where small amounts of the drug are converted to a highly toxic metabolite. This metabolite is detoxified by a metabolic pathway that uses a substance (i.e., glutathione) normally present in the liver. When large amounts of the drug are ingested, this pathway becomes overwhelmed and toxic metabolites accumulate, causing massive liver necrosis.

Lead Toxicity. Lead is a particularly toxic metal. Small amounts accumulate to reach toxic levels. There are innumerable sources of lead in the environment, including flaking paint, lead-contaminated dust and soil, pottery glazes, traditional remedies, cosmetics, and wild game contaminated by lead shot. Adults often encounter lead through occupational exposure. Lead and other metal smelters, miners, welders, storage battery workers, and pottery makers are particularly at risk.[2,7] Children are exposed to lead through ingestion of peeling lead paint, by breathing dust from lead paint (e.g., during remodeling), playing in contaminated soil, or playing with toys or items made or decorated with lead.[8,9] Factors that increase the risk of lead toxicity include preschool age, low socioeconomic status, and living in older housing built primarily before 1960.[9]

Lead is absorbed through the gastrointestinal tract or the lungs into the blood. A deficiency in calcium, iron, or

zinc increases lead absorption. In children, most lead is absorbed through the lungs. Although infants and children may have the same or a lower intake of lead as compared to adults, their absorption is greater. Also, the more permeable blood-brain barrier of infants and children makes them highly susceptible to brain damage.[2,7,9] Lead crosses the placenta, exposing the fetus to levels of lead that are comparable with those of the mother. Lead is stored in bone and eliminated by the kidneys. Most of the absorbed lead (80% to 85%) is stored in bone (and teeth of young children), 5% to 10% remains in the blood, and the remainder accumulates in soft tissue deposits.[2] Although the half-life of lead is hours to days, bone deposits serve as a repository from which blood levels are maintained. In a sense, bone protects other tissues, but the slow turnover maintains blood levels for months to years.

The toxicity of lead is related to its multiple biochemical effects.[2,7] It has the ability to inactivate enzymes, compete with calcium for incorporation into bone, and interfere with nerve transmission and brain development. The major targets of lead toxicity are the red blood cells, the gastrointestinal tract, the kidneys, and the nervous system. Anemia is a cardinal sign of lead toxicity. Lead competes with the enzymes required for hemoglobin synthesis and with the membrane-associated enzymes that prevent hemolysis of red blood cells. The resulting red cells are coarsely stippled and hypochromic, resembling those seen in iron-deficiency anemia. The life span of the red cell is also decreased. The gastrointestinal tract is the main source of symptoms in the adult. This is characterized by "lead colic," a severe and poorly localized form of acute abdominal pain. A lead line formed by precipitated lead sulfite may appear along the gingival margins. The lead line is seldom seen in children. The kidneys are the major route for excretion of lead. Lead can cause diffuse kidney damage, eventually leading to renal failure. Even without overt signs of kidney damage, lead toxicity leads to hypertension.

In the nervous system, lead toxicity is characterized by demyelination of cerebral and cerebellar white matter and death of cortical cells. When this occurs in early childhood, it can affect neurobehavioral development and result in lower IQ levels and poorer classroom performance.[9] Peripheral demyelinating neuropathy may occur in adults. The most serious manifestation of lead poisoning is acute encephalopathy. It is manifested by persistent vomiting, ataxia, seizures, papilledema, impaired consciousness, and coma. Acute encephalopathy may manifest suddenly, or it may be preceded by other signs of lead toxicity such as behavioral changes or abdominal complaints.

The threshold level at which lead causes subclinical and clinical disturbances has been redefined a number of times over the past 50 years. At one time, a blood level of 25 μg/dL was considered safe. Subsequent surveys showed abnormally low IQs in children with levels as low as 10 to 15 μg/dL. Since 1991, the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, and Health Canada considered a blood lead level of up to 10 μg/dL to be acceptable.[8–10] Recent research suggests that even levels below 10 μg/dL are associated with declines in children's IQ at 3 to 5 years of age.[11]

Approximately 99% of children are identified by screening procedures, which are recommended for high-risk populations based on the likelihood of lead exposure. A screening value greater than 10 μg/dL requires repeat testing for a diagnosis and to determine the need for treatment. Treatment involves removal of the lead source and, in cases of severe toxicity, administration of a chelating agent. A public health team should evaluate the source of lead because meticulous removal is needed.

Mercury Toxicity. Mercury has been used for industrial and medical purposes for hundreds of years. Mercury is toxic, and the hazards of mercury-associated occupational and accidental exposures are well known. In recent times, the primary concern of the general public to the potential hazards of mercury has focused on exposure from eating certain fish, amalgams used in dentistry, and vaccines.[12] Mercury is toxic in four primary forms: mercury vapor, inorganic divalent mercury, methyl mercury, and ethyl mercury.[12] Depending on the form of mercury exposure, toxicity involving the central nervous system and kidney can occur.

In the case of dental fillings, the concern involves mercury vapor being released into the mouth. However, the amount of mercury vapor released from fillings is very small. There is no clear evidence supporting health risk from this type of exposure, and removal of amalgams may temporarily increase blood levels of mercury.[12] The main source of methyl mercury exposure is from consumption of long-lived fish, such as tuna and swordfish. Fish concentrate mercury from sediment in the water. It is important to note that only certain types of fish pose potential risk, and types such as salmon have miniscule or absent amounts of mercury. Because the developing brain is more susceptible to mercury-induced damage, it is recommended that young children and pregnant and nursing women avoid consumption of fish known to contain high mercury content. Thimerosal is an ethyl mercury–containing preservative that helps prevent microorganism growth in vaccines. Concern about potential adverse effects have led to the making of single-dose vials that eliminate the need for thimerosal.[12] In the United States and Canada, most vaccines are either free of thimerosal or contain only trace amounts.

Injury from Biologic Agents

Biologic agents differ from other injurious agents in that they are able to replicate and can continue to produce their injurious effects (see Chapter 14). These agents range from submicroscopic viruses to the larger parasites. Biologic agents injure cells by diverse mechanisms. Viruses enter the cell and become incorporated into its DNA synthetic machinery. Certain bacteria elaborate exotoxins that interfere with cellular production of ATP. Other bacteria, such as the gram-negative bacilli, release endotoxins that cause cell injury and increased capillary permeability.

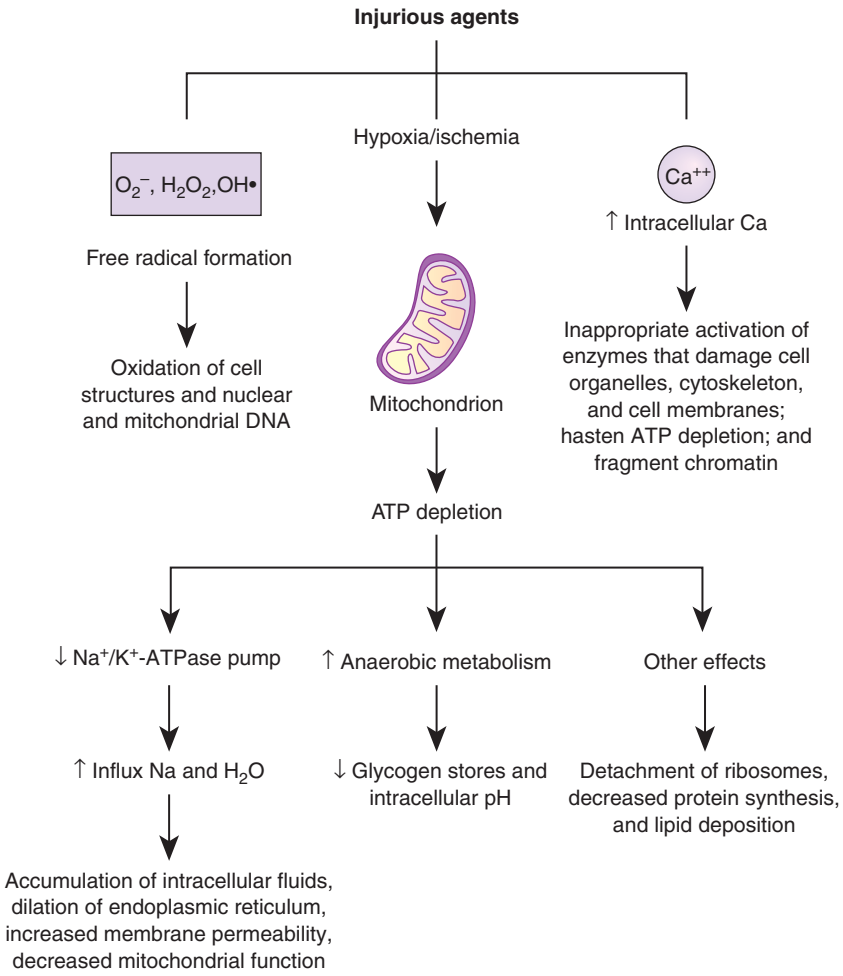


FIGURE 2-6. Mechanisms of cell injury. ATP, adenosine triphosphate.

Injury from Nutritional Imbalances

Nutritional excesses and nutritional deficiencies predispose cells to injury. Obesity and diets high in saturated fats are thought to predispose persons to atherosclerosis. The body requires more than 60 organic and inorganic substances in amounts ranging from micrograms to grams. These nutrients include minerals, vitamins, certain fatty acids, and specific amino acids. Dietary deficiencies can occur in the form of starvation, in which there is a deficiency of all nutrients and vitamins, or because of a selective deficiency of a single nutrient or vitamin. Iron-deficiency anemia, scurvy, beriberi, and pellagra are examples of injury caused by a lack of specific vitamins or minerals. The protein and calorie deficiencies that occur with starvation cause widespread tissue damage.

Mechanisms of Cell Injury

The mechanisms by which injurious agents cause cell injury and death are complex. Some agents, such as heat, produce direct cell injury; other factors, such as genetic derangements, produce their effects indirectly through metabolic disturbances and altered immune responses. There seem to be at least three major mechanisms whereby most injurious agents exert their effects: free radical formation, hypoxia and ATP depletion, and disruption of intracellular calcium homeostasis (Fig. 2-6).

Free Radical Injury

Many injurious agents exert damaging effects through reactive chemical species known as *free radicals*.[1,2,13–15] Cell injury in many circumstances involves damage by free radicals. These situations include ischemia-reperfusion injury, chemical and radiation injury, toxicity from oxygen and other gases, cellular aging, microbial killing of microbial agents, and tissue injury caused by inflammation.

Free radicals are highly reactive chemical species with an unpaired electron in the outer orbit (valence shell) of the molecule. In the literature, the unpaired electron is denoted by a dot, for example, NO•. The unpaired electron causes free radicals to be unstable and highly reactive, so that they react nonspecifically with molecules in the vicinity. Moreover, free radicals can establish chain reactions consisting of many events that generate new free radicals. In cells and tissues, free radicals react with proteins, lipids, and carbohydrates, thereby damaging

cell membranes, inactivating enzymes, and damaging nucleic acids that make up DNA.

Reactive oxygen species (ROS) are oxygen-containing molecules that include free radicals, such as superoxide (O_2^-) and hydroxyl radical (OH•), and nonradicals, such as hydrogen peroxide (H_2O_2). These reactive species are normal products of the mitochondrial respiration and energy generation of cells, but they are removed by cellular defense systems. Exogenous causes, including ionizing and UV radiation, can also cause ROS production in the body. *Oxidative stress* is a condition that occurs when the generation of ROS exceeds the ability of the body to neutralize and eliminate ROS. Oxidative stress can lead to oxidation of cell components, activation of signal transduction pathways, DNA damage, and changes in gene expression. In addition to focusing on nuclear DNA as a target of oxidative injury, current studies are focusing on mitochondrial DNA as a target of oxidation and subsequent cause of mitochondrial dysfunction.[16]

Although ROS and oxidative stress are clearly associated with cell and tissue damage, recent evidence suggests that ROS are not always acting in a random and damaging manner. Current studies are finding that ROS are also important signaling molecules that are used in healthy cells to regulate normal functions such as vascular smooth muscle tone, insulin and vascular endothelial growth factor (VEGF) signaling, and even a preconditioning function to protect cells from injury due to high levels of ROS.[17]

Antioxidants are natural and synthetic molecules that inhibit the reactions of ROS with biologic structures or that prevent the uncontrolled formation of ROS. Antioxidants include enzymatic and nonenzymatic compounds. Enzymes known to function as antioxidants include superoxide dismutase (SOD), catalase, glutathione peroxidase, and thioreductase. SOD forms hydrogen peroxide from superoxide. Catalase, present in peroxisomes, catalyzes the reaction that forms water from hydrogen peroxide. Nonenzymatic antioxidants include carotenes (e.g., vitamin A), tocopherols (e.g., vitamin E), ascorbate (vitamin C), glutathione, and flavonoids, as well as micronutrients such as selenium and zinc.[18] Nonenzymatic antioxidants often directly react with oxidants to "disarm" them. For example, vitamin C directly scavenges superoxide and hydroxyl radicals.[19]

Oxidative damage has been implicated in many diseases. Mutations in the gene for SOD are associated with amyotrophic lateral sclerosis (ALS; so-called *Lou Gehrig disease*).[20] Oxidative stress is thought to have an important role in the development of cancer.[21] Reestablishment of blood flow following loss of perfusion, as occurs during heart attack and stroke, is associated with oxidative injury to vital organs. The endothelial dysfunction that contributes to the development, progression, and prognosis of cardiovascular diseases is thought to be caused in part by oxidative stress.[22] In addition to the many diseases and altered health conditions that have been associated with oxidative damage, oxidative stress has been associated with age-related functional declines that underlie the process of aging.[23]

Hypoxic Cell Injury

Hypoxia deprives the cell of oxygen and interrupts oxidative metabolism and the generation of ATP. The actual time necessary to produce irreversible cell damage depends on the degree of oxygen deprivation and the metabolic needs of the cell. Some cells, such as those in the heart, brain, and kidney, require large amounts of oxygen to provide the energy to perform their functions. Brain cells, for example, begin to undergo permanent damage after 4 to 6 minutes of oxygen deprivation. A thin margin can exist between the time involved in reversible and irreversible cell damage. A classic study found that the epithelial cells of the proximal tubule of the kidney in the rat could survive 20 but not 30 minutes of ischemia.[24] Recent work has identified a group of proteins called *hypoxia-inducible factors* (HIFs). During hypoxic conditions, HIFs cause the expression of genes that stimulate red blood cell formation, manufacture glycolytic enzymes that produce ATP in the absence of oxygen, and increase angiogenesis[25] (i.e., the formation of new blood vessels).

Hypoxia can result from an inadequate amount of oxygen in the air, respiratory disease, ischemia (i.e., decreased blood flow due to vasoconstriction or vascular obstruction), anemia, edema, or inability of the cells to use oxygen. Ischemia is characterized by impaired oxygen delivery and impaired removal of metabolic end products such as lactic acid. In contrast to pure hypoxia, which depends on the oxygen content of the blood and affects all cells in the body, ischemia commonly depends on blood flow through limited numbers of blood vessels and produces local tissue injury. In some cases of edema, the distance for diffusion of oxygen may become a limiting factor in the delivery of oxygen. In hypermetabolic states, the cells may require more oxygen than can be supplied by normal respiratory function and oxygen transport. Hypoxia also serves as the ultimate cause of cell death in other injuries. For example, a physical agent such as cold temperature can cause severe constriction and impair blood flow.

Hypoxia causes a power failure in the cell, with widespread effects on the cell's structural and functional components. As oxygen tension in the cell falls, oxidative metabolism ceases, and the cell reverts to anaerobic metabolism, using its limited glycogen stores in an attempt to maintain vital cell functions. Cellular pH falls as lactic acid accumulates in the cell. This reduction in pH can have adverse effects on intracellular structures and biochemical reactions. Low pH can alter cell membranes and cause chromatin clumping and cell shrinkage.

An important effect of reduced ATP is acute cell swelling caused by failure of the energy-dependent sodium/potassium (Na^+/K^+)-adenosine triphosphatase (ATPase) membrane pump, which extrudes sodium from and returns potassium to the cell. With impaired function of this pump, intracellular potassium levels decrease,

and sodium and water accumulate in the cell. The movement of water and ions into the cell is associated with dilation of the endoplasmic reticulum, increased membrane permeability, and decreased mitochondrial function.[2] To a point, the cellular changes due to hypoxia are reversible if oxygenation is restored. If the oxygen supply is not restored, however, there is a continued loss of enzymes, proteins, and ribonucleic acid through the hyperpermeable cell membrane. Injury to the lysosomal membranes results in the leakage of destructive lysosomal enzymes into the cytoplasm and enzymatic digestion of cell components. Leakage of intracellular enzymes through the permeable cell membrane into the extracellular fluid provides an important clinical indicator of cell injury and death. These enzymes enter the blood and can be measured by laboratory tests.

Impaired Calcium Homeostasis

Calcium functions as an important second messenger and cytosolic signal for many cell responses. Various calcium-binding proteins, such as troponin and calmodulin, act as transducers for the cytosolic calcium signal. Calcium/calmodulin–dependent kinases indirectly mediate the effects of calcium on responses such as smooth muscle contraction and glycogen breakdown. Normally, intracellular calcium ion levels are kept extremely low compared with extracellular levels. These low intracellular levels are maintained by energy-dependent membrane-associated calcium/magnesium (Ca^{2+}/ Mg^{2+})-ATPase exchange systems[2] and sequestration of calcium ions within organelles such as the mitochondria and smooth endoplasmic reticulum. Ischemia and certain toxins lead to an increase in cytosolic calcium because of increased influx across the cell membrane and the release of calcium from intracellular stores. The increased calcium level may inappropriately activate a number of enzymes with potentially damaging effects. These enzymes include the phospholipases that are responsible for damaging the cell membrane, proteases that damage the cytoskeleton and membrane proteins, ATPases that break down ATP and hasten its depletion, and endonucleases that fragment chromatin. Although it is known that injured cells accumulate calcium, it is unknown whether this is the ultimate cause of irreversible cell injury.

Reversible Cell Injury and Cell Death

The mechanisms of cell injury can produce sublethal and reversible cellular damage or lead to irreversible injury with cell destruction or death (Fig. 2-7). Cell destruction and removal can involve one of two mechanisms: apoptosis, which is designed to remove injured or worn-out cells, or cell death or necrosis, which occurs in irreversibly damaged cells.

Reversible Cell Injury

Reversible cell injury, although impairing cell function, does not result in cell death. Two patterns of reversible cell injury can be observed under the microscope: cellular swelling and fatty change. Cellular swelling occurs with impairment of the energy-dependent Na^+/K^+-ATPase membrane pump, usually as the result of hypoxic cell injury.

Fatty changes are linked to intracellular accumulation of fat. When fatty changes occur, small vacuoles of fat disperse throughout the cytoplasm. The process is usually more ominous than cellular swelling, and although it is reversible, it usually indicates severe injury. These fatty changes may occur because normal cells are presented with an increased fat load or because injured cells are unable to metabolize the fat properly. In obese persons, fatty infiltrates often occur within and between the cells of the liver and heart because of an increased fat load. Pathways for fat metabolism may be impaired during cell injury, and fat may accumulate in the cell as production exceeds use and export. The liver, where most fats are synthesized and metabolized, is particularly susceptible to fatty change, but fatty changes may also occur in the kidney, the heart, and other organs.

Programmed Cell Death

In most normal nontumor cells, the number of cells in tissues is regulated by balancing cell proliferation and

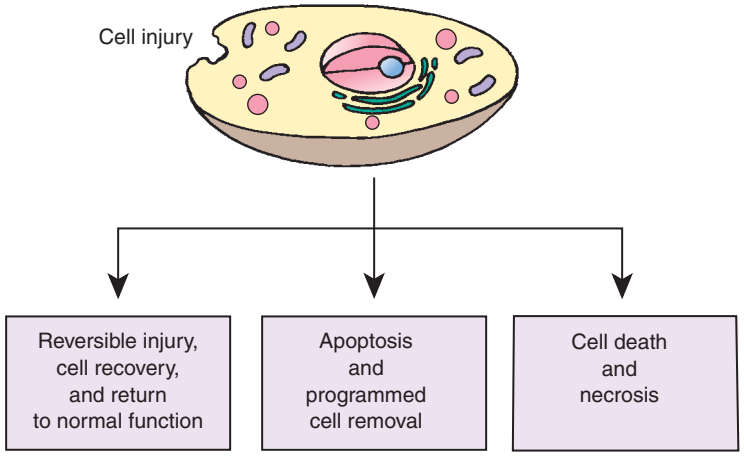


FIGURE 2-7. Outcomes of cell injury: reversible cell injury, apoptosis and programmed cell removal, cell death, and necrosis.

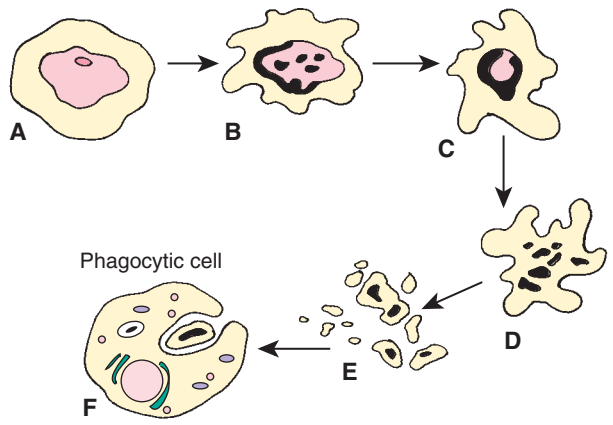


FIGURE 2-8. Apoptotic cell removal. **(A)** Shrinking of the cell structures. **(B, C)** Condensation and fragmentation of the nuclear chromatin. **(D, E)** Separation of nuclear fragments and cytoplasmic organelles into apoptotic bodies. **(F)** Engulfment of apoptotic fragments by phagocytic cell.

cell death. Cell death occurs by necrosis or a form of programmed cell death called *apoptosis*.

Apoptosis, from the Greek *apo* for "apart" and *ptosis* for "fallen," means "fallen apart." Apoptosis was discovered in 1972 and continues to be one of the most investigated processes in biologic and pathobiologic research.[26] Apoptosis is a highly selective process that eliminates injured and aged cells, thereby controlling tissue regeneration. Cells undergoing apoptosis have characteristic morphologic features, as well as biochemical changes. As shown in Figure 2-8, shrinking and condensation of the nucleus and cytoplasm occur. The chromatin aggregates at the nuclear envelope, and DNA fragmentation occurs. Then, the cell becomes fragmented into multiple apoptotic bodies in a manner that maintains the integrity of the plasma membrane and does not initiate inflammation. Changes in the plasma membrane induce phagocytosis of the apoptotic bodies by macrophages and other cells, thereby completing the degradation process.

Apoptosis is thought to be responsible for several normal physiologic processes, including the programmed destruction of cells during embryonic development, hormone-dependent involution of tissues, death of immune cells, cell death by cytotoxic T cells, and cell death in proliferating cell populations. During embryogenesis, in the development of a number of organs such as the heart, which begins as a pulsating tube and is gradually modified to become a four-chambered pump, apoptotic cell death allows for the next stage of organ development. It also separates the webbed fingers and toes of the developing embryo. Apoptotic cell death occurs in the hormone-dependent involution of endometrial cells during the menstrual cycle and in the regression of breast tissue after weaning from breast-feeding. The control of immune cell numbers and destruction of autoreactive T cells in the thymus have been credited to apoptosis. Cytotoxic T cells and natural killer cells are thought to destroy target cells by inducing apoptotic cell death.

Apoptosis is linked to many pathologic processes and diseases. For example, interference with apoptosis is known to be a mechanism that contributes to carcinogenesis.[27] Apoptosis is also known to be involved in the cell death associated with viral infections, such as hepatitis B and C.[27,28] Apoptosis may also be implicated in neurodegenerative disorders such as ALS, Alzheimer disease, and Parkinson disease. However, the exact mechanisms involved in these diseases remains under investigation.

Two basic pathways for apoptosis have been described (Fig. 2-9). These are the extrinsic pathway, which is death receptor dependent, and the intrinsic pathway, which is

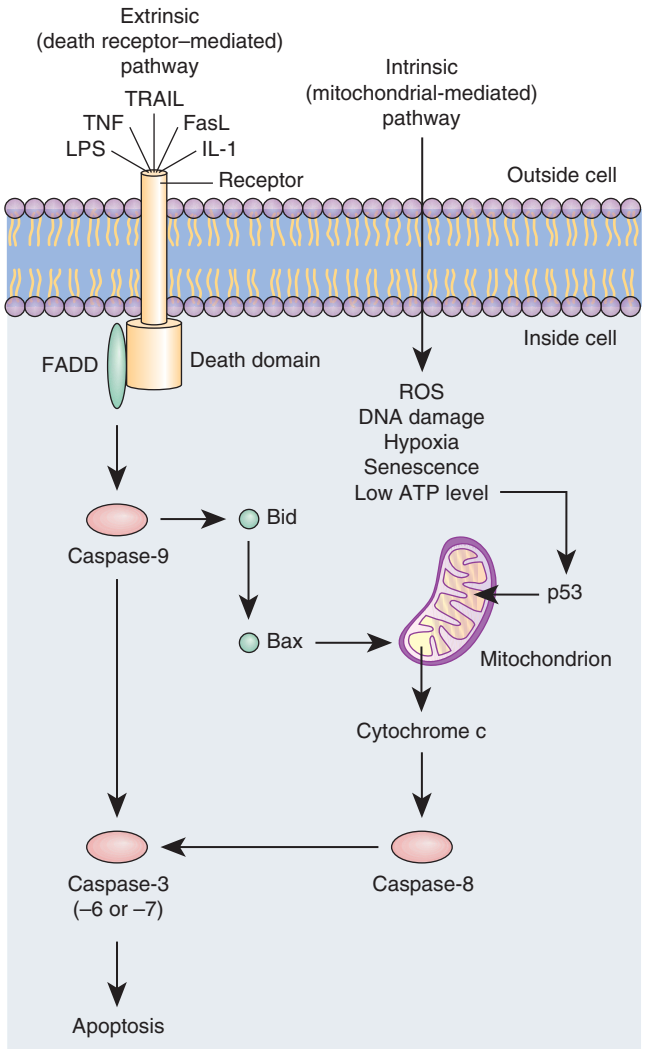


FIGURE 2-9. Pathways for apoptosis. The *extrinsic pathway* is activated by signals such as TNF-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL) that, upon binding to the Fas receptor, form a death-inducing complex by joining the Fas-associated death domain (FADD) to the death domain of the Fas receptor. The *intrinsic pathway* is activated by signals, such as reactive oxygen species (ROS) and DNA damage, that induce the release of cytochrome c from mitochondria into the cytoplasm. Both pathways activate caspases to execute apoptosis, with activation of the proapoptotic proteins Bid and Bax by caspase-8 serving to bridge the two systems.

death receptor independent. The execution phase of both pathways is carried out by proteolytic enzymes called *caspases* (cysteine proteases that cleave aspartate residues), which are present in the cell as *procaspases* and are activated by cleavage of an inhibitory portion of their polypeptide chain.[2,29]

The *extrinsic pathway* involves extracellular signaling proteins that bind to cell surface molecules called *death receptors* and trigger apoptosis. The prototype death receptors are tumor necrosis factor (TNF) receptor and the Fas ligand receptor.[29] Fas ligand may be expressed on the surface of certain cells, such as cytotoxic T cells, or appear in a soluble form. When Fas ligand binds to its receptor, proteins congregate at the cytoplasmic end of the Fas receptor to form a death-initiating complex. The complex then converts procaspase-8 to caspase-8. Caspase-8, in turn, activates a cascade of caspases that execute the process of apoptosis. The end result includes activation of endonucleases that cause fragmentation of DNA and cell death. In addition to TNF and Fas ligand, primary signaling molecules known to activate the extrinsic pathway include TNF-related apoptosis-inducing ligand (TRAIL); the cytokine interleukin-1 (IL-1); and lipopolysaccharide (LPS), the endotoxin found in the outer cell membrane of gram-negative bacteria.

The *intrinsic pathway,* or *mitochondrion-induced pathway,* of apoptosis is activated by conditions such as DNA damage, ROS, hypoxia, decreased ATP levels, cellular senescence, and activation of the p53 protein by DNA damage. The intrinsic pathway is tightly regulated to ensure that cells kill themselves only when appropriate. A major class of intracellular regulators of apoptosis is the Bc12 family of proteins. Some of these proteins insert into the mitochondrial membrane opening channels through which proteins escape into the cytoplasm.[29] A crucial protein released from the mitochondria is cytochrome c, a component of the mitochondrial electron transport chain (see Chapter 1). When released into the cytoplasm, cytochrome c binds to a procaspase-activating protein that activates caspases, including caspase-3. Caspase-3 activation is a common step to both the extrinsic and intrinsic pathways. Activation of caspase-8 in the extrinsic pathway can also lead to activation of proapoptotic proteins, such as Bid and Bax, thereby bridging the two pathways for apoptosis.[2,29] While some members of the Bc12 family are proapoptotic, others are antiapoptotic and inhibit apoptosis by binding to proapoptotic proteins, either on the mitochondrial membranes or in the cytoplasm.

Inhibitors of apoptosis are thought to contribute to cancer and autoimmune diseases.[29–31] The Bc12 gene was first identified in B-cell lymphoma, in which a chromosomal translocation causes excessive production of Bc12, giving the gene its name.[29] Excessive levels of Bcl2 in the lymphocytes that carry the translocation promote the development of cancer by inhibiting apoptosis. Similarly, mutation of the genes encoding the tumor-suppressor protein p53 so that it no longer suppresses apoptosis or cell cycle arrest in response to DNA damage is implicated in a number of other cancers (see Chapter 7). The therapeutic actions of certain drugs may induce or facilitate apoptosis. Apoptosis continues to be an active area of investigation to better understand and treat a variety of diseases.

Necrosis

Necrosis refers to cell death in an organ or tissue that is still part of a living person.[32] Necrosis differs from apoptosis in that it involves unregulated enzymatic digestion of cell components, loss of cell membrane integrity with uncontrolled release of the products of cell death into the intracellular space, and initiation of the inflammatory response.[32] In contrast to apoptosis, which functions in removing cells so new cells can replace them, necrosis often interferes with cell replacement and tissue regeneration.

With necrotic cell death, there are marked changes in the appearance of the cytoplasmic contents and the nucleus. These changes often are not visible, even under the microscope, for hours after cell death. The dissolution of the necrotic cell or tissue can follow several paths. The cell can undergo liquefaction (i.e., liquefaction necrosis); it can be transformed to a gray, firm mass (i.e., coagulation necrosis); or it can be converted to a cheesy material by infiltration of fatlike substances (i.e., caseous necrosis). *Liquefaction necrosis* occurs when some of the cells die but their catalytic enzymes are not destroyed. An example of liquefaction necrosis is the softening of the center of an abscess with discharge of its contents. During *coagulation necrosis*, acidosis develops and denatures the enzymatic and structural proteins of the cell. This type of necrosis is characteristic of hypoxic injury and is seen in infarcted areas. *Infarction* (i.e., tissue death) occurs when an artery supplying an organ or part of the body becomes occluded and no other source of blood supply exists. As a rule, the shape of the infarction is conical and corresponds to the distribution of the artery and its branches. An artery may be occluded by an embolus, a thrombus, disease of the arterial wall, or pressure from outside the vessel.

Caseous necrosis is a distinctive form of coagulation necrosis in which the dead cells persist indefinitely as soft, cheeselike debris.[1] It is most commonly found in the center of tuberculosis granulomas, or tubercles, and is thought to result from immune mechanisms (see Chapter 22).

Gangrene. The term *gangrene* is applied when a considerable mass of tissue undergoes necrosis. Gangrene may be classified as dry or moist. In dry gangrene, the part becomes dry and shrinks, the skin wrinkles, and its color changes to dark brown or black. The spread of dry gangrene is slow, and its symptoms are not as marked as those of wet gangrene. The irritation caused by the dead tissue produces a line of inflammatory reaction (i.e., line of demarcation) between the dead tissue of the gangrenous area and the healthy tissue (Fig. 2-10). Dry gangrene usually results from interference with arterial blood supply to a part without interference with venous return and is a form of coagulation necrosis.

In moist or wet gangrene, the area is cold, swollen, and pulseless. The skin is moist, black, and under tension. Blebs form on the surface, liquefaction occurs, and a foul odor is caused by bacterial action. There is no line of demarcation between the normal and diseased tissues, and the spread of tissue damage is rapid. Systemic symptoms

FIGURE 2-10. Gangrenous toes. (Biomedical Communications Group, Southern Illinois University School of Medicine, Springfield, IL.)

are usually severe, and death may occur unless the condition can be arrested. Moist or wet gangrene primarily results from interference with venous return from the part. Bacterial invasion plays an important role in the development of wet gangrene and is responsible for many of its prominent symptoms. Dry gangrene is confined almost exclusively to the extremities, but moist gangrene may affect the internal organs or the extremities. If bacteria invade the necrotic tissue, dry gangrene may be converted to wet gangrene.

Gas gangrene is a special type of gangrene that results from infection of devitalized tissues by one of several *Clostridium* bacteria, most commonly *Clostridium perfringens*. These anaerobic and spore-forming organisms are widespread in nature, particularly in soil; gas gangrene is prone to occur in trauma and compound fractures in which dirt and debris are embedded. Some species have been isolated in the stomach, gallbladder, intestine, vagina, and skin of healthy persons. The bacteria produce toxins that dissolve cell membranes, causing death of muscle cells, massive spreading edema, hemolysis of red blood cells, hemolytic anemia, hemoglobinuria, and renal failure.[33] Characteristic of this disorder are the bubbles of hydrogen sulfide gas that form in the muscle. Gas gangrene is a serious and potentially fatal disease. Antibiotics are used to treat the infection and surgical methods are used to remove the infected tissue. Amputation may be required to prevent spreading infection involving a limb. Hyperbaric oxygen therapy has been used, but clinical data supporting its efficacy has not been rigorously assessed.

Cellular Aging

Aging is a complex natural process in which there are physiologic and structural alterations in almost all organ systems.[1,2,34–38] Even in the absence of disease, beginning in the fourth decade of life, there is a progressive decline in muscle strength, cardiac reserve, vital capacity, nerve conduction time, and glomerular filtration rate. Although the biologic basis of aging is poorly understood, there is general consensus that its elucidation should be sought at the cellular level. A number of cell functions decline with age. Oxidative phosphorylation by the mitochondria is reduced, as is synthesis of nucleic acids and transcription factors, cell receptors, and cell proteins.

A number of theories have been proposed to explain the cause of aging. The main theories are based on scientific observations at the molecular, cellular, organ, and system levels. In general, these theories can be divided into either programmed or error theories. The *programmed theories* propose that the changes that occur with aging are genetically programmed, whereas the *damage* or *error theories* maintain that the changes result from an accumulation of random events or environmental agents or influences that is associated with DNA damage.[35–39] Evidence suggests that the process of aging and longevity is multifaceted, with both genetic and environmental factors playing a role. In animal studies, genetics accounted for less than 35% of the effects of aging, whereas environmental influences accounted for over 65%.[36] In humans, long life appears to have a stronger genetic basis, which explains why centenarians and near centenarians tend to cluster in families.[40]

Replicative Senescence

Replicative senescence implies that cells have limited capacity for replication. At the cellular level, Hayflick and Moorhead observed more than 40 years ago that cultured human fibroblasts have a limited ability to replicate (approximately 50 population doublings) and then die.[41] Before achieving this maximum, they slow their rate of division and manifest identifiable and predictable morphologic changes characteristic of senescent cells.

One explanation of replicative senescence is related to the length of the outermost tails of the chromosome arms, called *telomeres*, that contain short repeat sequences of DNA bases.[1,2,35] During mitosis, the molecular machinery that replicates DNA cannot copy the extreme ends of the chromosome. Thus, with each cell division, a small segment of telomeric DNA is lost. Over time, it is theorized that as the telomeres become progressively shorter, the DNA at the ends of the chromosomes cannot be protected, resulting in inhibition of cell replication. The lengths of the telomeres are normally maintained by an enzyme called *telomerase*. Telomerase extends one of the DNA strands at the end of the chromosome by using a RNA template that is an integral part of the enzyme itself, producing a highly repeated DNA sequence that extends the nucleotide pairs at each chromosome end. Telomerase activity is expressed in germ cells and is present in low levels in stem cells, but is usually absent in most adult cells. Therefore, as cells age, their telomeres become shorter and they lose their ability to replicate and replace damaged or senescent cells. Moreover, oxidative stress induces single-stranded damage to telomeric DNA and this defect cannot be repaired in telomeres. In theory, such mechanisms could also provide a safeguard against uncontrolled cell proliferation of abnormal cells. It has been shown that telomerase is reactivated and telomeres are not shortened in immortal cancer cells, suggesting that telomere elongation may be important in tumor formation.

Genetic Influences

There is ongoing interest in genes that determine longevity. Longevity genes have been found in fruit flies and roundworms, organisms that have attracted considerable attention from scientists because of their short life span and their well-characterized genomes. One example is the mutation of the INDY (I'm Not Dead Yet) gene in the fruit fly, which can double its life.[35] Scientists have also found genetic clues to the aging process in the tiny roundworm, *Caenorhabditis elegans*. By altering one of its genes called *daf-2*, which codes for a protein that is similar to insulin and IGF-1 receptors found in humans, researchers can substantially extend the longevity of these worms.[1,35] Pathways related to the daf-2 gene, for example, may be responsible for relationships between caloric restriction and prolonged life span in rodents and other animals. Whether human counterparts of genes found in these laboratory organisms exist and whether they have similar effects remain an ongoing area of inquiry.

However, many genes that are associated with human life span are not intrinsically "longevity genes," per se. For example, because mutations in the tumor-suppressor genes BRAC-1 and BRAC-2 increase mortality associated with breast and ovarian cancer, they are rare among long-lived women.[40] Conversely, genes that reduce the risk of atherosclerosis may be more common in long-lived individuals. Genetic studies of biologic aging have explored the involvement of allelic variants in genes encoding apolipoproteins, in particular, that of apolipoprotein E (apoE). The presence of apoE4 is associated with an increased incidence of cardiovascular diseases and neurodegenerative diseases, thereby shortening life span by way of disease processes.[37,42]

Accumulation of Environmental and Genetic Damage

In addition to the importance of timing and a genetic clock, cellular life span may be determined by a balance between cellular damage resulting from metabolic events occurring within the cell and molecular responses that repair the damage. The damage eventually accumulates to a level sufficient to result in the physiologic decline associated with aging. The most prominent example of the damage theory is the somatic mutation theory of aging, which states that the longevity and function of cells in various tissues of the body are determined by the double-stranded DNA molecule and its specific repair enzymes. DNA undergoes continuous change in response to both exogenous agents and intrinsic processes. It has been suggested that aging results from conditions that produce mutations in DNA or deficits in DNA repair mechanisms.

The oxidative free radical explanation of aging is an error theory in which aging is thought to result partially from oxidative metabolism and the effects of free radical damage. The major by-products of oxidative metabolism include superoxides that react with DNA, ribonucleic acid, proteins, and lipids, leading to cellular damage and aging. Blood glucose is another suspect in cellular deterioration. In a process called *nonenzymatic glycation*, glucose molecules attach to proteins, setting into motion a chain of chemical reactions that ends with proteins binding together or cross-linking, thus altering their structure and function. Investigators hypothesize that glycation and oxidation are interdependent, since free radicals and cross-links seem to accelerate the formation of one another. Cross-links, also known as *advanced glycation end products (AGEs),* tend to stiffen tissues and cause some of the deterioration associated with aging.[2,35] For example, AGEs may help trap low-density cholesterol in arterial walls and thus contribute to atherosclerosis. They also have been linked to cataract formation, reduced kidney function, and neurologic disorders such as Alzheimer disease.

Syndromes of Premature Aging

The syndromes of premature aging, or *progeria*, represent a range of phenotypes seen in usual aging, but with much earlier ages of onset and more rapid rates of progression.[1] Hutchinson-Gilford progeria syndrome is a rare fatal genetic disorder characterized by accelerated aging in children.[43] The disorder is caused by a mutation in the LMNA gene, which codes for a precursor of lamin A—a scaffolding protein that lines the nucleus. The mutant gene leads to abnormal nuclear structure and altered gene regulation and DNA replication. Although they are born looking healthy, children with the disorder begin to display many characteristics of accelerated aging at around 18 to 24 months of age. Progeria signs include growth failure, loss of body fat and hair, aged-looking skin, cataracts, and coronary artery disease and stroke (Fig. 2-11). Death occurs at an early age of atherosclerotic heart disease (average age 13 years).

FIGURE 2-11. A 5-year-girl with progeria. (From National Human Genome Research Institute, National Institutes of Health.)

Other progeroid syndromes include Werner syndrome, also known as adult progeria, which does not have an onset until the late teens, with a life span into the 40s and 50s.[1] The gene responsible for the disorder has been localized to chromosome 8 and appears to code for an enzyme involved in unwinding DNA, a process that is necessary for DNA repair and replication.

In summary, cell injury can be caused by a number of agents, including physical agents, chemicals, biologic agents, and nutritional factors. Among the physical agents that generate cell injury are mechanical forces that produce tissue trauma, extremes of temperature, electricity, radiation, and nutritional disorders. Chemical agents can cause cell injury through several mechanisms: they can block enzymatic pathways, cause coagulation of tissues, or disrupt the osmotic or ionic balance of the cell. Biologic agents differ from other injurious agents in that they are able to replicate and continue to produce injury. Among the nutritional factors that contribute to cell injury are excesses and deficiencies of nutrients, vitamins, and minerals.

Injurious agents exert their effects largely through generation of free radicals, production of cell hypoxia, or unregulated intracellular calcium levels. Partially reduced oxygen species called free radicals are important mediators of cell injury in many pathologic conditions. They are an important cause of cell injury in hypoxia and after exposure to radiation and certain chemical agents. Lack of oxygen underlies the pathogenesis of cell injury in hypoxia and ischemia. Hypoxia can result from inadequate oxygen in the air, cardiorespiratory disease, anemia, or the inability of the cells to use oxygen. Increased intracellular calcium activates a number of enzymes with potentially damaging effects.

Injurious agents may produce sublethal and reversible cellular damage or may lead to irreversible cell injury and death. Cell death can involve two mechanisms: apoptosis or necrosis. Apoptosis involves controlled cell destruction and is the means by which the body removes and replaces cells that have been produced in excess, developed improperly, have genetic damage, or are worn out. Necrosis refers to cell death that is characterized by cell swelling, rupture of the cell membrane, and inflammation.

A number of body functions decline with age, including muscle strength, cardiac reserve, vital capacity, nerve conduction time, and glomerular filtration rate. At the cellular level, oxidative phosphorylation by the mitochondria is reduced, as is the synthesis of nucleic acids and transcription factors, cell receptors, and structural and enzymatic proteins. The theories of cellular aging include those that propose the changes are genetically programmed and those that maintain that the changes result from an accumulation of random events or environmental influences that damage DNA. The syndromes of premature aging (progeria) represent a range of phenotypes seen in usual aging, but with much earlier ages of onset and more rapid rates of progression.

REVIEW EXERCISES

1. A 30-year-old man sustained a fracture of his leg 2 months ago. The leg has been encased in a cast and he has just had the cast removed. He is amazed at the degree to which the muscles in his leg have shrunk.

A. Explain.

2. A 45-year-old woman has been receiving radiation therapy for breast cancer.

A. Explain the effects of ionizing radiation in eradicating the tumor cells.
B. Why is the radiation treatment given in small divided, or fractionated, doses rather than as a single large dose?
C. Partway through the treatment schedule, the woman notices that her skin over the irradiated area has become reddened and irritated. What is the reason for this?

3. People who have had a heart attack may experience additional damage once blood flow has been restored, a phenomenon referred to as *reperfusion injury.*

A. What is the proposed mechanism underlying reperfusion injury?
B. What factors might influence this mechanism?

4. Every day blood cells in our body become senescent and die without producing signs of inflammation; yet, massive injury or destruction of tissue, such as occurs with a heart attack, produces significant signs of inflammation.

A. Explain.

REFERENCES

1. Strayer D.S., Rubin E. (2008). Cell injury. In Rubin R., Strayer C.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1–35). Philadelphia: Lippincott Williams & Wilkins.
2. Kumar V., Abbas A.K., Fauusto N., et al. (2010). *Robbins basic pathology* (8th ed., pp. 3–42). Philadelphia: Saunders Elsevier.
3. Heszele M.F.C., Price S.R. (2004). Insulin-like growth factor 1: The yin and yang of muscle atrophy. *Endocrinology* 145, 4803–4805.
4. Heineke J., Molkentin J.D. (2006). Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nature Reviews: Molecular Cell Biology* 7, 589–600.
5. Hunter J.J., Chien K.R. (1999). Signaling pathways in cardiac hypertrophy and failure. *New England Journal of Medicine* 341, 1276–1283.
6. Anastassios C., Koumbourlis M.D. (2002). Electrical injuries. *Critical Care Medicine* 30(Suppl), S424–S430.
7. Strayer D.S., Rubin E. (2008). Environmental and nutritional pathology. In Rubin R., Strayer C.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 253–264). Philadelphia: Lippincott Williams & Wilkins.

8. Centers for Disease Control. (2005). *Preventing lead poisoning in young children: A statement by the Centers for Disease Control and Prevention*. Atlanta: U.S. Department of Health and Human Services, Public Health Service.
9. Markowitz M. (2007). Lead poisoning. In Behrman R.E., Kliegman R.M., Jenson H.B., et al., (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2913–2917). Philadelphia: Saunders Elsevier.
10. Health Canada. (2008). *Lead information package—Some commonly asked questions about lead and human health*. [Online]. Available: http://www.hc-sc/ewh-semt/contaminants/lead-plomb/exposure. Accessed October 6, 2008.
11. Canfield R.L., Henderson C.R. Jr., Cory-Slechta D.A., et al. (2003). Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. *New England Journal of Medicine* 348, 1517–1526.
12. Clarkson T.W., Magos L., Myers G.J. (2003). The toxicity of mercury—Current exposures and clinical manifestations. *New England Journal of Medicine* 349, 1731–1737.
13. McCord J.M. (2000). The evolution of free radicals and oxidative stress. *American Journal of Medicine* 108, 652–659.
14. Kerr M.E., Bender C.M., Monti E.J. (1996). An introduction to oxygen free radicals. *Heart and Lung* 25, 200–209.
15. Chuyanyu C.L., Jackson R.M. (2002). Reactive species mechanisms of cellular hypoxia-reoxygenation injury. *American Journal of Physiology: Cell Physiology* 282, C227–C241.
16. Van Houten B., Woshner V., Santos J.H. (2006). Role of mitochondrial DNA in toxic responses to oxidative stress. *DNA Repair* 5, 145–152.
17. Finkel T. (2003). Oxidant signals and oxidative stress. *Current Opinion in Cell Biology* 15, 247–254.
18. Brenneistein P., Steinbrenner H., Seis H. (2005). Selenium, oxidative stress, and health aspects. *Molecular Aspects of Medicine* 26, 256–267.
19. Comhair S.A., Erzuum S.C. (2005). The regulation and role of extracellular glutathione peroxidase. *Antioxidants & Redox Signaling* 7, 72–79.
20. Johnson F., Giulivi C. (2005). Superoxide dismutases and their impact upon human health. *Molecular Aspects of Medicine* 26, 340–352.
21. Klaunig J.E., Kamendulis L.M. (2004). The role of oxidative stress in carcinogenesis. *Annual Review of Pharmacology and Toxicology* 44, 239–267.
22. Fenster B.E., Tsao P.S., Rockson S.G. (2003). Endothelial dysfunction: Clinical strategies for treating oxidant stress. *American Heart Journal* 146, 218–226.
23. Martin I., Grotewiel M.S. (2006). Oxidative damage and age-related functional declines. *Mechanisms of Aging and Development* 127, 411–423.
24. Vogt M.T., Farber E. (1968). On the molecular pathology of ischemic renal cell death: Reversible and irreversible cellular and mitochondrial metabolic alterations. *American Journal of Pathology* 53, 1–26.
25. Marx J. (2004). How cells endure low oxygen. *Science* 303, 1454–1456.
26. Skikumar P., Dong Z., Mikhailov V., et al. (1999). Apoptosis: Definitions, mechanisms, and relevance to disease. *American Journal of Medicine* 107, 490–505.
27. Vermeulen K., Van Bockstaele D.R., Berneman Z.N. (2005). Apoptosis: Mechanisms and relevance in cancer. *Annals of Hematology* 84, 627–639.
28. Cruise M.W., Lukens J.R., Nguyen A.P., et al. (2006). Fas ligand is responsible for CXCR3 chemokine induction in CD4+ T cell-dependent liver damage. *Journal of Immunology* 176, 6235–6244.
29. Alberts B., Johnson A., Lewis L., et al. (2008). *Molecular biology of the cell* (5th ed., pp. 1115–1129). New York: Garland Press.
30. Malhi H., Gores G.J., Lemasters J.J. (2006). Apoptosis and necrosis in the liver: A tale of two deaths? *Hepatology* 43(2 Suppl 1), S31–S44.
31. Dorner T., Lipsky P.E. (2006). Signalling pathways in B cells: Implications for autoimmunity. *Current Topics in Microbiology & Immunology* 305, 213–240.
32. Proskuryakov S.Y., Konoplyannikov A.G., Gabai V.L. (2003). Necrosis: A specific form of programmed cell death. *Experimental Cell Research* 283, 1–16.
33. Kasper D.L., Madoff L.C. (2005). Gas gangrene, and other clostridial infections. In Kasper D.L., Braunwald E., Fauci A., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 845–849). New York: McGraw-Hill.
34. Weinert B.T., Timiras P.S. (2003). Invited review: Theories of aging. *Journal of Applied Physiology* 95, 1706–1716.
35. National Institute of Aging. (2006). *Aging under the microscope: A biological quest*. [Online]. Available: http://www.nia.nih.gov/HealthInformation/Publications/AgingUndertheMicroscope/. Accessed October 6, 2008.
36. Hayflick L. (2007). Biological aging is no longer an unsolved problem. *Annals of New York Academy Sciences* 1100, 1–13.
37. Troen B.R. (2003). The biology of aging. *Mount Sinai Journal of Medicine* 70, 3–22.
38. Kim S. (2003). Molecular biology of aging. *Archives of Surgery* 138, 1051–1054.
39. Magalhães J.P., Faragher G.A. (2008). Cell divisions and mammalian aging: Integrative biology insights from genes that regulate longevity. *BioEssays* 30, 567–576.
40. Browner W.S., Kahn A.J., Ziv E., et al. (2004). The genetics of human longevity. *American Journal of Medicine* 117, 851–860.
41. Hayflick L., Moorehead P.S. (1965). The limited in vitro lifetime of human diploid cell strains. *Experimental Cell Research* 37, 614–636.
42. Vijg J., Suh Y. (2005). Genetics of longevity and aging. *Annual Reviews of Medicine* 56, 193–212.
43. Warner H.H. (2008). Research on Hutchinson-Gilford progeria syndrome. *Journal of Gerantology* 63A(3), 775–786.

General Features of Inflammation
Cells of Inflammation
Endothelial Cells
Platelets
Leukocytes
Acute Inflammation
Vascular and Cellular Stages
Vascular Stage
Cellular Stage
Inflammatory Mediators
Plasma-Derived Mediators
Cell-Derived Mediators
Local Manifestations
Resolution
Chronic Inflammation
Causes of Chronic Inflammation
Granulomatous Inflammation
Systemic Manifestations of Inflammation
Acute-Phase Response
Acute-Phase Proteins
White Blood Cell Response
Systemic Inflammatory Response
Fever
Body Temperature Regulation
Fever and the Febrile Response
Fever in Children
Fever in the Elderly

Chapter 3

Inflammation, the Inflammatory Response, and Fever

In Chapter 2, the causes of cell injury were discussed. At the tissue level, these same stimuli can invoke a response called *inflammation*. Inflammation is a complex response intended to minimize the effects of injury or infection, remove the damaged tissue, and generate new tissue. It accomplishes this by diluting, destroying, or otherwise neutralizing the harmful agents. Although first described over 2000 years ago, the inflammatory response has evoked renewed interest during the past several decades. As a result, a number of diseases are now known be linked to the inflammatory response. For example, the role of the inflammatory response in producing the incapacitating effects of bronchial asthma and the crippling effects of rheumatoid arthritis has been well established. There is also increasing evidence that the inflammatory response may play a role in the pathogenesis of a number of other diseases, such as atherosclerosis, diabetes mellitus, and Alzheimer disease.

The discussion in this chapter is divided into four sections: (1) the general features of inflammation, (2) acute inflammation, (3) chronic inflammation, and (4) systemic manifestations of inflammation, including fever. The innate and adaptive immune responses that are closely intertwined with the inflammatory response are discussed in Chapter 15.

General Features of Inflammation

Inflammation is the reaction of vascularized tissues to cell injury or death. It is characterized by the elaboration of inflammatory mediators and the movement of fluid and leukocytes from the vascular system into the extravascular tissues.[1–4] Inflammatory conditions are commonly named by adding the suffix *-itis* to the affected organ or system. For example, *appendicitis* refers to inflammation of the appendix, *pericarditis* to inflammation of the pericardium, and *neuritis* to inflammation of a nerve.

The Inflammatory Response

- Inflammation represents the response of body tissue to immune reactions, injury, or ischemic damage.
- The classic response to inflammation includes redness, swelling, heat, pain or discomfort, and loss of function.
- The manifestations of an acute inflammatory response can be attributed to the immediate vascular changes that occur (vasodilation and increased capillary permeability), the influx of inflammatory cells such as neutrophils, and, in some cases, the widespread effects of inflammatory mediators, which produce fever and other systemic signs and symptoms.
- The manifestations of chronic inflammation are due to infiltration with macrophages, lymphocytes, and fibroblasts, leading to persistent inflammation, fibroblast proliferation, and scar formation.

Inflammation can be acute or chronic.[1,2] *Acute inflammation* is the adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury, and is of relatively short duration, lasting from a few minutes to several days. It is characterized by the exudation of fluid and plasma proteins and emigration of leukocytes, predominantly neutrophils. *Chronic inflammation* is of a longer duration, lasting for days to years, and is associated with the proliferation of blood vessels, tissue necrosis, and fibrosis (scarring). Acute and chronic inflammation may coexist, with episodes of acute inflammation being superimposed on chronic inflammation.

Cells of Inflammation

Many cells and tissue components are involved in the inflammatory process, including the endothelial cells that line blood vessels, circulating platelets and leukocytes, connective tissue cells (mast cells, fibroblasts, tissue macrophages), and components of the extracellular matrix[1–3] (Fig. 3-1). The principal leukocytes in acute inflammation are neutrophils, whereas macrophages, lymphocytes and plasma cells, eosinophils, and mast cells predominate in chronic inflammation.

Endothelial Cells

Endothelial cells comprise the single-cell-thick epithelial lining of blood vessels.[1,5] They produce antiplatelet and antithrombotic agents that maintain vessel patency, as well as vasodilators and vasoconstrictors that regulate blood flow. Endothelial cells are also key players in the inflammatory response. As such, they provide a selective permeability barrier to exogenous (microbial) and endogenous inflammatory stimuli; regulate leukocyte extravasation by expression of adhesion molecules and receptors; contribute to the regulation and modulation of immune responses through synthesis and release of inflammatory mediators; and regulate immune cell proliferation through secretion of hematopoietic colony-stimulating factors (CSFs). Endothelial cells also participate in the repair process that

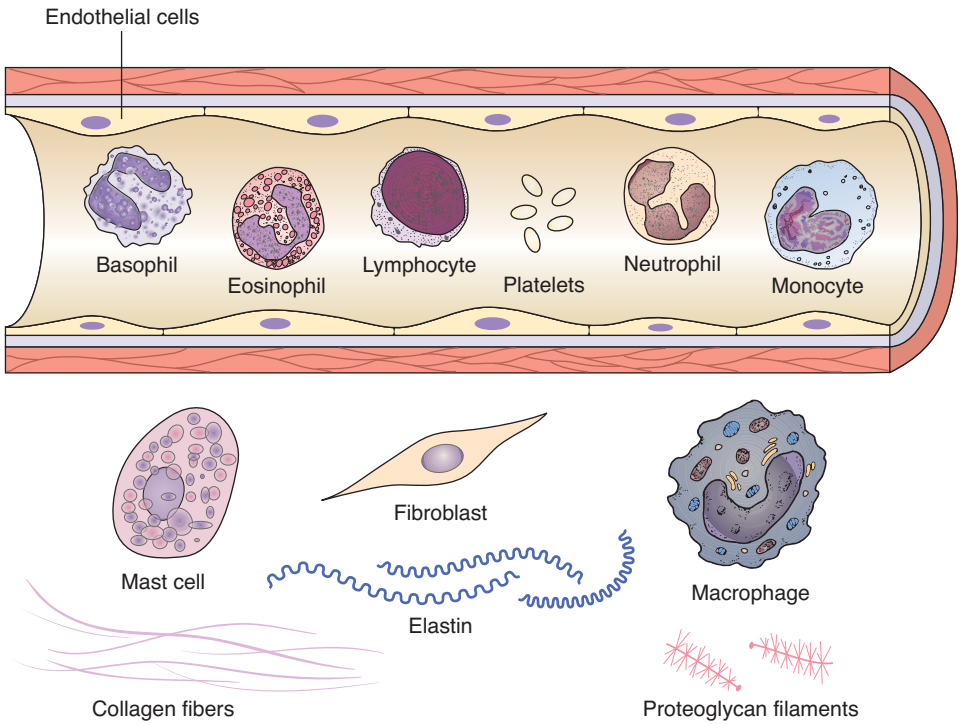


FIGURE 3-1. Cells involved in the inflammatory process.

accompanies inflammation through the production of growth factors that stimulate angiogenesis (formation of new blood vessels) and extracellular matrix synthesis.

Platelets

Platelets or thrombocytes are small membrane-bound disks circulating in the blood that play an active role in normal hemostasis (see Chapter 12). Activated platelets also release a number of potent inflammatory mediators, thereby increasing vascular permeability and altering the chemotactic, adhesive, and proteolytic properties of the endothelial cells.[6,7] When a platelet undergoes activation, over 300 proteins are released. While only a relatively small proportion of these have been identified, it appears that a significant number are inflammatory mediators.[6] The association between the platelet and inflammatory diseases is highlighted by the number of inflammatory disease processes (e.g., atherosclerosis, migraine headaches, systemic lupus erythematosus) shown to be associated with platelet activation.[6]

Leukocytes

Leukocytes or white blood cells are the major cellular components of the inflammatory response. They include the granulocytes (neutrophils, eosinophils, and basophils), which contain specific cytoplasmic granules and a multilobed nucleus, and the agranulocytes (monocytes/macrophages and lymphocytes), which lack cytoplasmic granules and have a single nucleus.

Neutrophils. Neutrophils are the most numerous leukocytes in the circulating blood, accounting for 60% to 70% of all white blood cells. These leukocytes have nuclei that are divided into three to five lobes; therefore, they often are referred to *polymorphonuclear neutrophils (PMNs)*. Because of their ability to form pseudopods used in ameboid movement, neutrophils are highly mobile and are therefore the first cells to appear at the site of acute inflammation, usually arriving within 90 minutes of injury (Fig. 3-2A). Neutrophils are scavenger cells capable of engulfing bacteria and other cellular debris through phagocytosis. Their cytoplasmic granules, which resist staining and remain a neutral color, contain enzymes and other antibacterial substances that are used in destroying and degrading engulfed microbes and dead tissue.[3,8,9] Neutrophils also have oxygen-dependent metabolic pathways that generate toxic oxygen (e.g., hydrogen peroxide) and nitrogen (e.g., nitric oxide) products that aid in the destruction of engulfed pathogens. Neutrophils have a short life span. They die by apoptosis and disappear within 24 to 48 hours after entering the site of inflammation.

Eosinophils. Eosinophils account for 2% to 3% of circulating leukocytes and are recruited to tissues similar to neutrophils. Their appearance at the site of inflammation occurs 2 to 3 hours after the neutrophils. This is, in part, because of their slower mobility and comparatively slower reaction to chemotactic stimuli.

The granules of eosinophils, which stain pink with the acid dye eosin, contain a protein that is highly toxic to large parasitic worms that cannot be phagocytized.

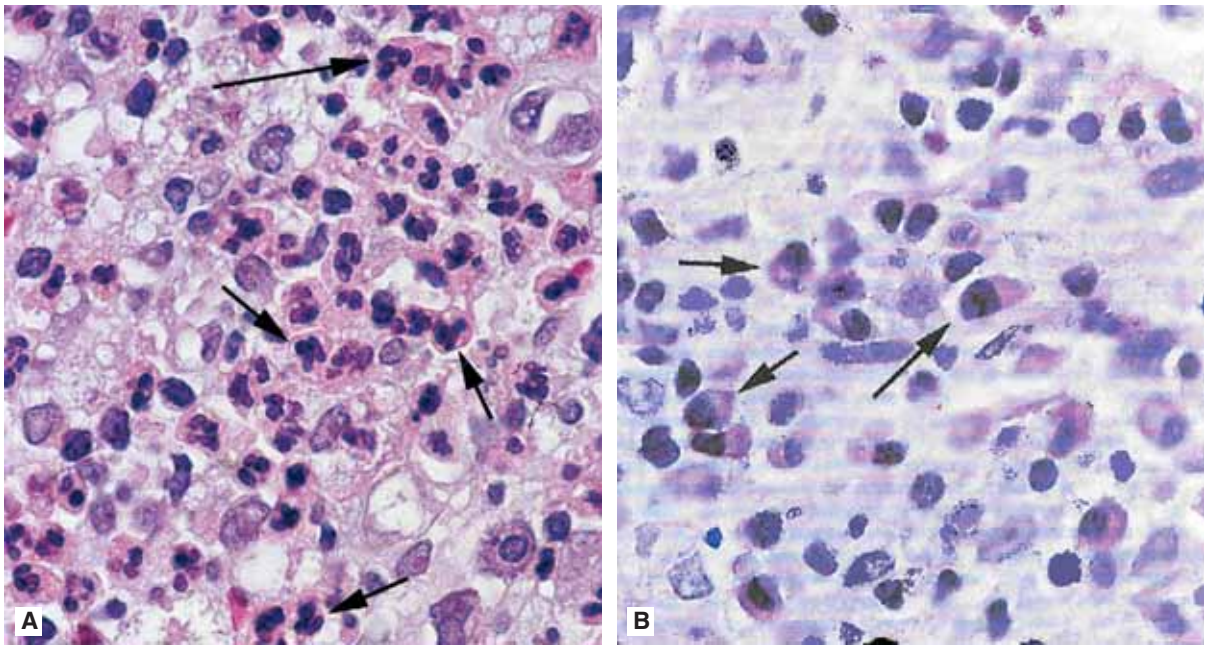


FIGURE 3-2. Inflammatory cells of acute and chronic inflammation. **(A)** Acute inflammation with densely packed polymorphonuclear neutrophils with multilobed nucleus (*arrows*). **(B)** Chronic inflammation with lymphocytes, plasma cells (*arrows*), and a few macrophages. (From Murphy H.S. [2008]. Inflammation. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 39]. Philadelphia: Lippincott Williams & Wilkins.)

Eosinophils also play an important role in allergic reactions by controlling the release of specific chemical mediators. They interact with basophils and are prominent in allergic reactions such as hay fever and bronchial asthma. Eosinophils have a longer life span than neutrophils and therefore present in chronic inflammation.

Basophils and Mast Cells. Basophils are granulocytes with granules that stain blue with a basic dye. Although they account for less than 1% of the circulating leukocytes, they are important participants in inflammatory reactions and are most prominent in allergic reactions mediated by immunoglobulin E (IgE). Binding of IgE triggers release of histamine and vasoactive agents from the basophil granules. Basophils are precursors of mast cells.

Mast cells derive from the same hematopoietic stem cells as basophils but do not develop until they leave the circulation and lodge in tissue sites. They are particularly prevalent along mucosal surfaces of the lung, gastrointestinal tract, and dermis of the skin.[2,10] This distribution places the mast cell in a sentinel position between environmental antigens and the host for a variety of acute and chronic inflammatory conditions.[2] Activation of mast cells results in release of the preformed contents of their granules (e.g., histamine, proteases, and cytokines such as tumor necrosis factor-α [TNF-α] and interleukin-16 [IL-16]), synthesis of lipid mediators derived from cell membrane precursors (arachidonic acid metabolites, such as prostaglandins, and platelet-activating factor), and stimulation of cytokine and chemokine synthesis by other inflammatory cells such as monocytes and macrophages.

Monocyte/Macrophages. *Monocytes* constitute 3% to 8% of the white blood cell count. They have a single kidney-shaped nucleus and are the largest of the circulating leukocytes. The half-life of circulating monocytes is about a day, after which they begin to migrate to the site of injury and undergo transformation into larger macrophages, which have a longer half-life and greater phagocytic ability than do blood monocytes. Circulating monocytes have been linked to a number of inflammatory disorders, particularly atherosclerosis, in which monocytes are transformed into macrophages that accumulate in atherosclerotic plaques and turn into lipid-laden foam cells (see Chapter 18).

Monocyte/macrophages produce potent vasoactive mediators including prostaglandins and leukotrienes, platelet-activating factor (PAF), inflammatory cytokines, and growth factors that promote regeneration of tissues.[8,9] As their name implies, macrophages are capable of phagocytosis and are active in bacterial killing. They engulf larger and greater quantities of foreign material than the neutrophils. The circulating life span of the macrophage is three to four times longer than that of the granulocytes. These longer-lived phagocytes help to destroy the causative agent, aid in the signaling processes of immunity, serve to resolve the inflammatory process, and contribute to initiation of the healing processes. Macrophages are especially important in maintaining the chronic inflammatory process.

Lymphocytes and Plasma Cells. Lymphocytes are the smallest of the leukocytes and have a thin rim of cytoplasm surrounded by a deeply staining nucleus (Fig. 3-2B). They participate in immune-mediated inflammation caused by infectious agents as well as non–immune-mediated inflammation associated with cell injury and death. Both T and B lymphocytes (T and B cells) migrate into inflammatory sites using some of the same adhesion molecules and chemokines that recruit neutrophils and other leukocytes (discussed in Chapter 15). Lymphocytes and macrophages interact in a bidirectional way, and these interactions play an important role in chronic inflammation Macrophages display antigen to T cells, express membrane molecules called costimulators, and produce cytokines that stimulate T-cell responses.[2] Activated T cells, in turn, produce cytokines that activate macrophages, increasing antigen presentation and cytokine production. The result is a cycle of cellular responses that fuel and sustain chronic inflammation.

Plasma cells develop from activated B lymphocytes and produce antibodies directed against persistent antigens in the inflammatory site and against altered tissue components. In some intense chronic inflammatory reactions, the accumulation of lymphocytes and plasma cells may assume the appearance of lymphoid organs, such as lymph nodes.[2] This pattern of lymphocyte accumulation is often seen in the inflamed synovium of persons with long-standing rheumatoid arthritis.

Cell Adhesion Molecules and Leukocyte Recruitment. Several families of cell adhesion molecules, including selectins, integrins, and the immunoglobulin superfamily, are involved in leukocyte recruitment and trafficking (see Chapter 1).[8,11,12] The *selectins* are a family of three closely related proteins (E-selectin, L-selectin, P-selectin) that differ in their cellular distribution but all function in adhesion of leukocytes to endothelial cells. The *integrin* superfamily consists of 30 structurally similar proteins that promote cell-to-cell and cell–to–extracellular matrix interactions. The name *integrin* derives from the hypothesis that they *integrate* the signals of extracellular ligands with cytoskeleton-dependent motility, shape change, and phagocytic responses of immune cells. *Adhesion* molecules of the immunoglobulin superfamily include intercellular adhesion and vascular adhesion molecules, all of which interact with integrins on leukocytes to mediate their recruitment.

The importance of the leukocyte adhesion molecules is demonstrated in persons with an inherited disorder called *leukocyte adhesion deficiency (LAD) type I*, in which deficiency of a member of the integrin superfamily leads to severe leukocytosis and recurrent infections. A similar deficiency is seen in individuals with impaired expression of a member of the selectin superfamily and has been labeled *LAD type 2*.[8] There is also evidence that excessive expression of cell adhesion molecules or their receptors contributes to the pathogenesis of some chronic inflammatory diseases such as rheumatoid arthritis.[11]

In summary, inflammation is the reaction of vascularized tissues to injury. It is characterized by the elaboration of chemical mediators and the movement of fluid and leukocytes from the vascular system into the extravascular tissues. Inflammation can be divided into two types: *acute inflammation,* which is of short duration and characterized by the exudation of fluid and plasma proteins, and *chronic inflammation,* which is associated with the proliferation of blood vessels, tissue necrosis, and fibrosis (scarring). Many cells and tissue components are involved in inflammation. These cells include the endothelial cells that line blood vessels, circulating platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils, lymphocytes), connective tissue cells (mast cells, tissue macrophages, resident lymphocytes), and components of the extracellular matrix.

Acute Inflammation

Acute inflammation is the early (almost immediate) reaction of local tissues and their blood vessels to injury. It typically occurs before the adaptive immune response becomes established (see Chapter 15) and is aimed primarily at removing the injurious agent and limiting the extent of tissue damage. Acute inflammation can be triggered by a variety of stimuli, including infections, immune reactions, blunt and penetrating trauma, physical or chemical agents (e.g., burns, frostbite, irradiation, caustic chemicals), and tissue necrosis from any cause.

The classic description of inflammation has been handed down through the ages. In the first century AD, the Roman physician Celsus described the local reaction of injury in terms that are now known as the *cardinal signs* of inflammation.[1] These signs are *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). In the second century AD, the Greek physician Galen added a fifth cardinal sign, *functio laesa* (loss of function). In addition to the cardinal signs that appear at the site of injury, systemic manifestations (e.g., fever) may occur as chemical mediators (e.g., cytokines) produced at the site of inflammation gain entrance to the circulatory system. The constellation of systemic manifestations that may occur during acute inflammation is known as the *acute-phase response*.

Vascular and Cellular Stages

Acute inflammation has two stages: the vascular stage, which is characterized by increased blood flow (vasodilation) and structural changes (increased vascular permeability) that allow plasma proteins to leave the circulation, and the cellular stage, which involves the emigration of leukocytes (mainly neutrophils) from the microcirculation and their accumulation at the site of injury or infection.

Vascular Stage

The vascular changes that occur with inflammation involve the arterioles, capillaries, and venules of the microcirculation. These changes begin almost immediately after injury and are characterized by vasodilation and changes in blood flow followed by increased vascular permeability and leakage of protein-rich fluid into the extravascular tissues.[1,2]

Vasodilation, which is one of the earliest manifestations of inflammation, follows a transient constriction of the arterioles, lasting a few seconds. Vasodilation first involves the arterioles and then results in opening of capillary beds in the area. As a result, the area becomes congested, causing the redness (erythema) and warmth associated with acute inflammation. Vasodilation is induced by the action of several mediators, most notably histamine and nitric oxide.

Vasodilation is quickly followed by increased permeability of the microvasculature, with the outpouring of a protein-rich fluid (exudate) into the extravascular spaces. The loss of fluid results in an increased concentration of blood constituents (red blood cells, leukocytes, platelets, and clotting factors), stagnation of flow, and clotting of blood at the site of injury. This aids in localizing the spread of infectious microorganisms. The loss of plasma proteins reduces the intracapillary osmotic pressure and increases the osmotic pressure of the interstitial fluid, causing fluid to move from the vascular compartment into the tissues and produce the swelling, pain, and impaired function that are the cardinal signs of acute inflammation. The exudation of fluid into the tissue spaces also serves to dilute the offending agent.

The increased permeability characteristic of acute inflammation results from formation of endothelial gaps in the venules of the microcirculation. Binding of the chemical mediators to endothelial receptors causes contraction of endothelial cells and separation of intercellular junctions. This is the most common mechanism of vascular leakage and is elicited by histamine, bradykinin, leukotrienes, and many other classes of chemical mediators.

Depending on the severity of injury, the vascular changes that occur with inflammation follow one of three patterns of responses.[2] The first pattern is an *immediate transient response,* which occurs with minor injury. It develops rapidly after injury and is usually reversible and of short duration (15 to 30 minutes). Typically, this type of leakage affects venules 20 to 60 μm in diameter, leaving capillaries and arterioles unaffected.[2] Although the precise mechanism for restriction of this effect to the venules is unknown, it may reflect the greater density of receptors in the endothelium of the venules. It has also been suggested that the later leukocyte events of inflammation (i.e., adhesion and emigration) also occur predominantly in the venules of most organs.

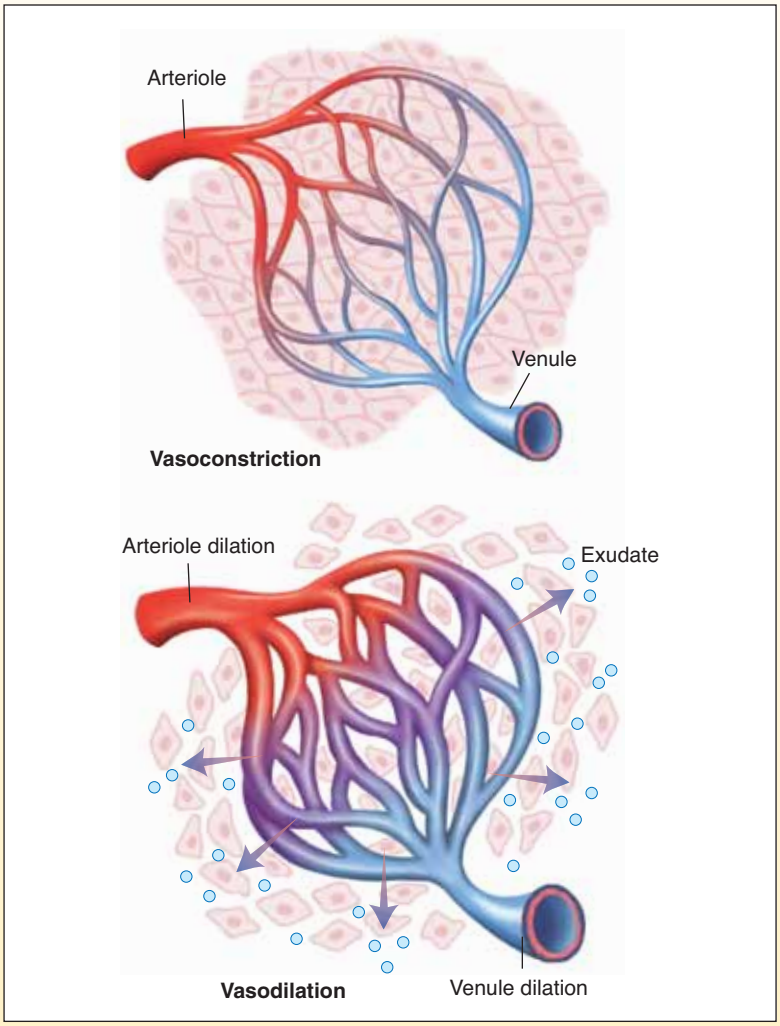
(*text continues on page 58*)

UNDERSTANDING → Acute Inflammation

Acute inflammation is the immediate and early response to an injurious agent. The response, which serves to control and eliminate altered cells, microorganisms, and antigens, occurs in two phases: (1) the vascular phase, which leads to an increase in blood flow and changes in the small blood vessels of the microcirculation; and (2) the cellular phase, which leads to the migration of leukocytes from the circulation and their activation to eliminate the injurious agent. The primary function of the inflammatory response is to limit the injurious effect of the pathologic agent and remove the injured tissue components, thereby allowing tissue repair to take place.

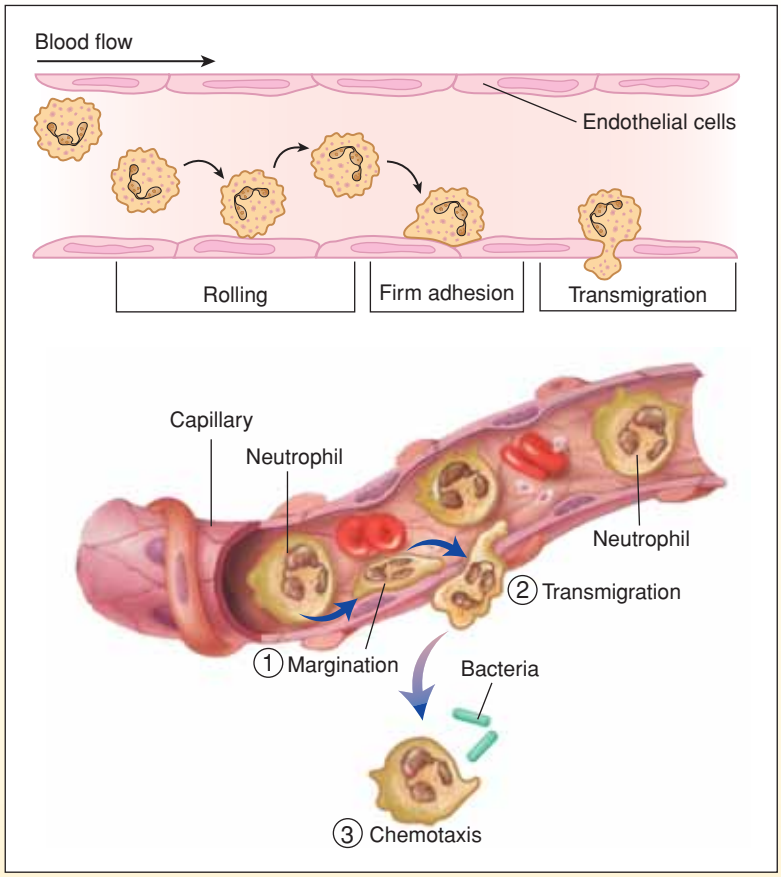
1

Vascular Phase. The vascular phase of acute inflammation is characterized by changes in the small blood vessels at the site of injury. It begins with momentary vasoconstriction followed rapidly by vasodilation. Vasodilation involves the arterioles and venules with a resultant increase in capillary blood flow, causing heat and redness, which are two of the cardinal signs of inflammation. This is accompanied by an increase in vascular permeability with outpouring of protein-rich fluid (exudate) into the extravascular spaces. The loss of proteins reduces the capillary osmotic pressure and increases the interstitial osmotic pressure. This, coupled with an increase in capillary pressure, causes a marked outflow of fluid and its accumulation in the tissue spaces, producing the swelling, pain, and impaired function that represent the other cardinal signs of acute inflammation. As fluid moves out of the vessels, stagnation of flow and clotting of blood occur. This aids in localizing the spread of infectious microorganisms.



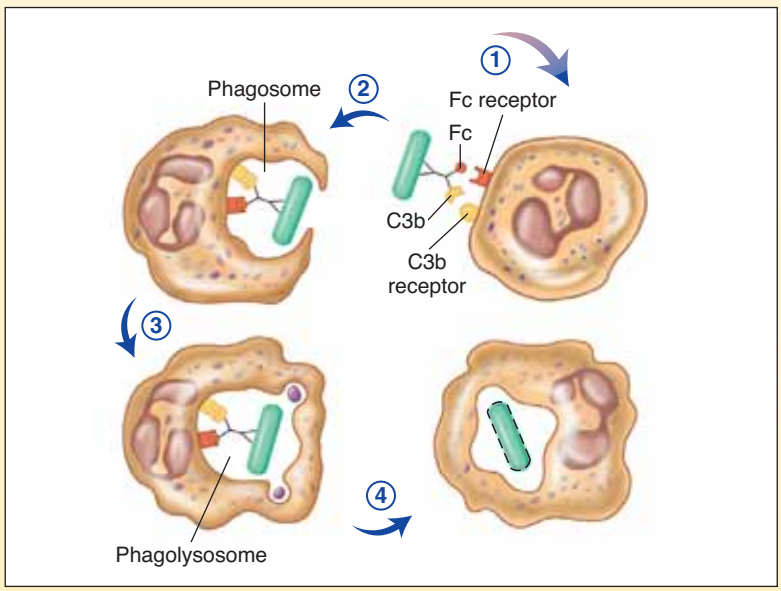
2

Cellular Phase: Leukocyte Margination, Adhesion, and Transmigration. The cellular phase of acute inflammation involves the delivery of leukocytes, mainly neutrophils, to the site of injury so they can perform their normal functions of host defense. The delivery and activation of leukocytes can be divided into the following steps: adhesion and margination, transmigration, and chemotaxis. The recruitment of leukocytes to the precapillary venules, where they exit the circulation, is facilitated by the slowing of blood flow and margination along the vessel surface. Leukocyte adhesion and transmigration from the vascular space into the extravascular tissue is facilitated by complementary adhesion molecules (e.g., selectins, integrins) on the leukocyte and endothelial surfaces. After extravasation, leukocytes migrate in the tissues toward the site of injury by chemotaxis, or locomotion oriented along a chemical gradient.



3

Leukocyte Activation and Phagocytosis. Once at the sight of injury, the products generated by tissue injury trigger a number of leukocyte responses, including phagocytosis and cell killing. Opsonization of microbes (1) by complement factor C3b and antibody facilitates recognition by neutrophil C3b and the antibody Fc receptor. Receptor activation (2) triggers intracellular signaling and actin assembly in the neutrophil, leading to formation of pseudopods that enclose the microbe within a phagosome. The phagosome (3) then fuses with an intracellular lysosome to form a phagolysosome into which lysosomal enzymes and oxygen radicals (4) are released to kill and degrade the microbe.



The second pattern is *an immediate sustained response,* which occurs with more serious types of injury and continues for several days. It affects all levels of the microcirculation (arterioles, capillaries, and venules) and is usually due to direct damage of the endothelium by injurious stimuli, such as burns or the products of bacterial infections.[2] Neutrophils that adhere to the endothelium may also injure endothelial cells.

The third pattern is a *delayed hemodynamic response,* in which the increased permeability begins after a delay of 2 to 12 hours, lasts for several hours or even days, and involves venules as well as capillaries.[2] A delayed response often accompanies injuries due to radiation, such as sunburn. The mechanism of the leakage is unknown, but it may result from the direct effect of the injurious agent, leading to delayed endothelial cell damage.

Cellular Stage

The cellular stage of acute inflammation is marked by changes in the endothelial cells lining the vasculature and movement of phagocytic leukocytes into the area of injury or infection. Although attention has been focused on the recruitment of leukocytes from the blood, a rapid response also requires the release of chemical mediators from tissue cells (mast cells and macrophages) that are prepositioned in the tissues. The sequence of events in the cellular response to inflammation includes leukocyte (1) margination and adhesion, (2) transmigration, (3) chemotaxis, and (4) activation and phagocytosis.[1–3]

During the early stages of the inflammatory response, cross-talk between blood leukocytes and the vascular endothelium defines a definite inflammatory event and ensures secure adhesion and arrest of the leukocytes along the endothelium.[9] As a consequence, the leukocytes slow their migration, adhere tightly to the endothelium, and begin to move along the periphery of the blood vessels. This process of leukocyte accumulation is called *margination*. The subsequent release of cell communication molecules called *cytokines* causes the endothelial cells lining the vessels to express cell adhesion molecules that bind to carbohydrates on the leukocytes. This interaction, which is called *tethering,* slows their flow and causes the leukocytes to move along the endothelial cell surface with a rolling movement, finally coming to rest and adhering strongly to intercellular adhesion molecules on the endothelium.[1–3] The adhesion causes the endothelial cells to separate, allowing the leukocytes to extend pseudopodia and *transmigrate* through the vessel wall and then, under the influence of chemotactic factors, migrate into the tissue spaces.

Chemotaxis is a dynamic and energy-directed process of cell migration.[1] Once leukocytes exit the capillary, they wander through the tissue guided by a gradient of secreted chemoattractants, such as chemokines, bacterial and cellular debris, and fragments generated from activation of the complement system (see Chapter 15). Chemokines, an important subgroup of chemotactic cytokines, are small proteins that direct the trafficking of leukocytes during the early stages of inflammation or injury.[13] Several immune (e.g., macrophages) and nonimmune cells secrete these chemoattractants to ensure the directed movement of leukocytes to the site of infection.

During the next and final stage of the cellular response, neutrophils, monocytes, and tissue macrophages are activated to engulf and degrade the bacteria and cellular debris in a process called *phagocytosis*.[1,2,14] Phagocytosis involves three distinct steps: recognition and adherence, engulfment, and intracellular killing. It is initiated by recognition and binding of particles by specific receptors on the surface of phagocytic cells. This binding is essential for trapping the agent, triggering engulfment, and intracellular killing of microbes. Microbes can be bound directly to the membrane of phagocytic cells by several types of pattern recognition receptors (e.g., toll-like and mannose receptors) or indirectly by receptors that recognize microbes coated with carbohydrate-binding lectins, antibody, and/or complement (see innate immunity, Chapter 15). The enhanced binding of an antigen due to antibody or complement is called *opsonization*. Engulfment follows the recognition of an agent as foreign. During the process of engulfment, extensions of cytoplasm move around and eventually enclose the particle in a membrane-surrounded phagocytic vesicle or *phagosome*. Once in the cell cytoplasm, the phagosome merges with a cytoplasmic lysosome containing antibacterial molecules and enzymes that can kill and digest the microbe (see Chapter 1).

Intracellular killing of pathogens is accomplished through several mechanisms, including toxic oxygen and nitrogen products, lysozymes, proteases, and defensins. The metabolic burst pathways that generate toxic oxygen and nitrogen products (e.g., nitric oxide, hydrogen peroxide) require oxygen and metabolic enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthetase. Individuals who are born with genetic defects in some of these enzymes have immunodeficiency conditions that make them susceptible to repeated bacterial infection.

Inflammatory Mediators

Having described the events of acute inflammation, we can now turn to a discussion of the chemical mediators responsible for the events. Inflammatory mediators may be derived from the plasma or they may be produced locally by cells at the site of inflammation (Fig. 3-3). The *plasma-derived mediators*, which are synthesized in the liver, include the acute-phase proteins, coagulation factors (discussed in Chapter 12), and complement proteins (discussed in Chapter 15). These mediators are present in the plasma in a precursor form that must be activated by a series of proteolytic processes, to acquire their biologic properties. *Cell-derived mediators* are normally sequestered in intracellular granules that need to be secreted (e.g., histamine from mast cells) or newly synthesized (e.g., cytokines) in response to a stimulus. The major sources of these mediators are platelets, neutrophils, monocyte/macrophages, and mast cells, but most endothelial cells, smooth muscle cells, and fibroblasts can be induced to produce some of the mediators.

Mediators can act on one or a few target cells, have diverse targets, or have differing effects on different types

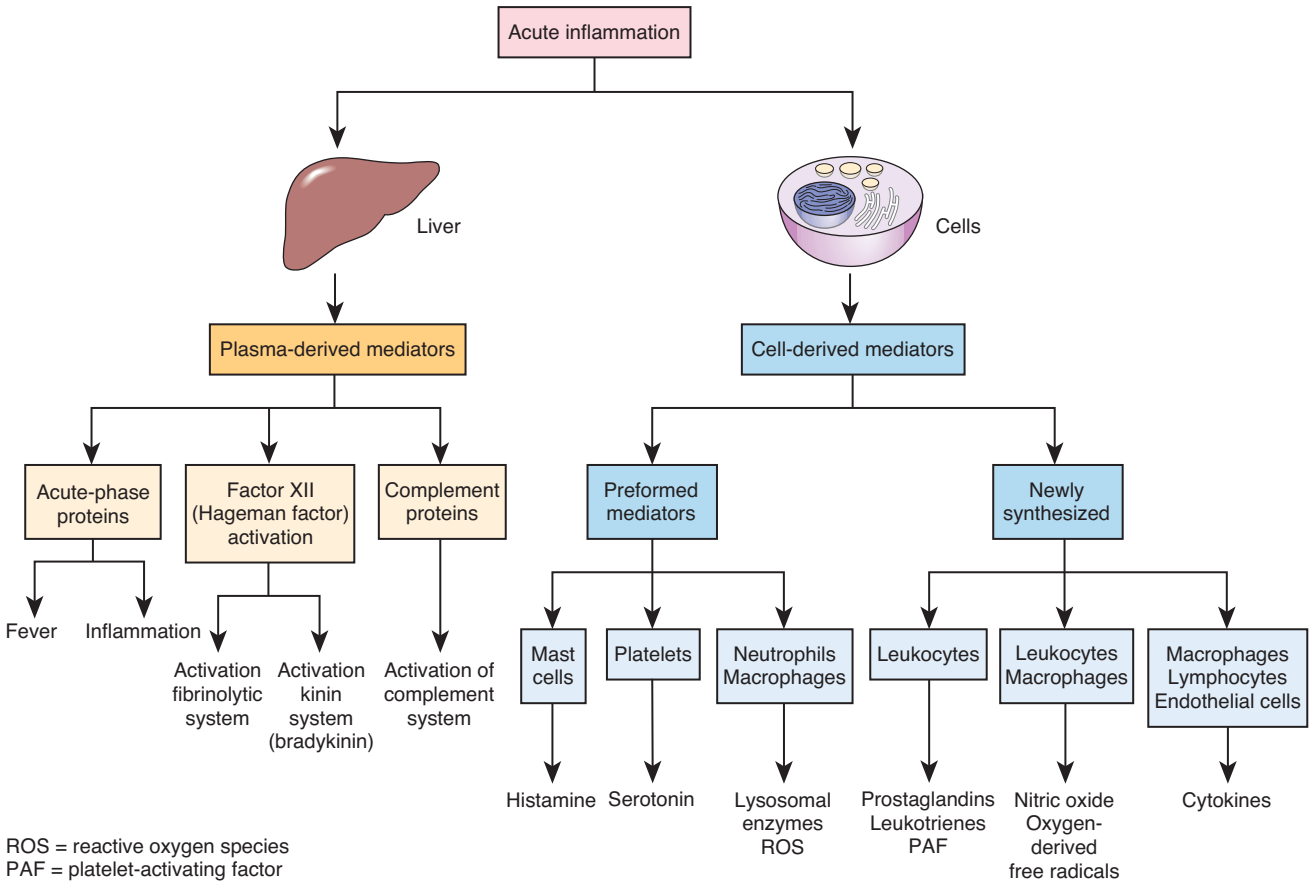


FIGURE 3-3. Plasma- and cell-derived mediators of acute inflammation.

of cells. Once activated and released from the cell, most mediators are short-lived. They may be transformed into inactive metabolites, inactivated by enzymes, or otherwise scavenged or degraded.

Plasma-Derived Mediators

The plasma is the source of three major mediators of inflammation, including kinins, products of the coagulation/fibrinolysis system, and proteins of the complement system. One kinin, bradykinin, causes increased capillary permeability and pain. The clotting system (see Chapter 12) contributes to the vascular phase of inflammation, mainly through fibrin products formed during the final steps of the clotting process. The complement system consists of a cascade of plasma proteins that plays an important role in both immunity and inflammation. Complement proteins contribute to the inflammatory response by (1) causing vasodilation and increasing vascular permeability; (2) promoting leukocyte activation, adhesion, and chemotaxis; and (3) augmenting phagocytosis (see Chapter 15).

Cell-Derived Mediators

The cell-derived mediators are released from cells that are present at sites of inflammation. Tissue macrophages, mast cells, endothelial cells, and platelets, as well as leukocytes that are recruited to the site from the blood, are all capable of producing the different mediators of inflammation (Fig. 3-3).

Histamine and Serotonin. Histamine and serotonin are classified as *vasoactive amines*, meaning they are derived from amino acids (histamine from histidine and serotonin from tryptamine) and act by producing changes in blood vessel tone. Both histamine and serotonin are stored as preformed molecules in mast cells and other cells and are among the first mediators to be released in acute inflammatory reactions.

Preformed histamine is widely distributed in tissues, the highest concentrations being found in mast cells adjacent to blood vessels.[1,2] It is also found in circulating platelets and basophils and is released in response to a variety of stimuli, including trauma and immune reactions involving binding of IgE to basophils and mast cells. Histamine produces dilation of arterioles and increases the permeability of venules. It acts at the level of the microcirculation by binding to histamine 1 (H_1) receptors on endothelial cells and is considered the principal mediator of the immediate transient phase of increased vascular permeability in the acute inflammatory response. Antihistamine drugs (H_1 receptor antagonists), which bind to the H_1 receptors, act to competitively antagonize many of the effects of the immediate inflammatory

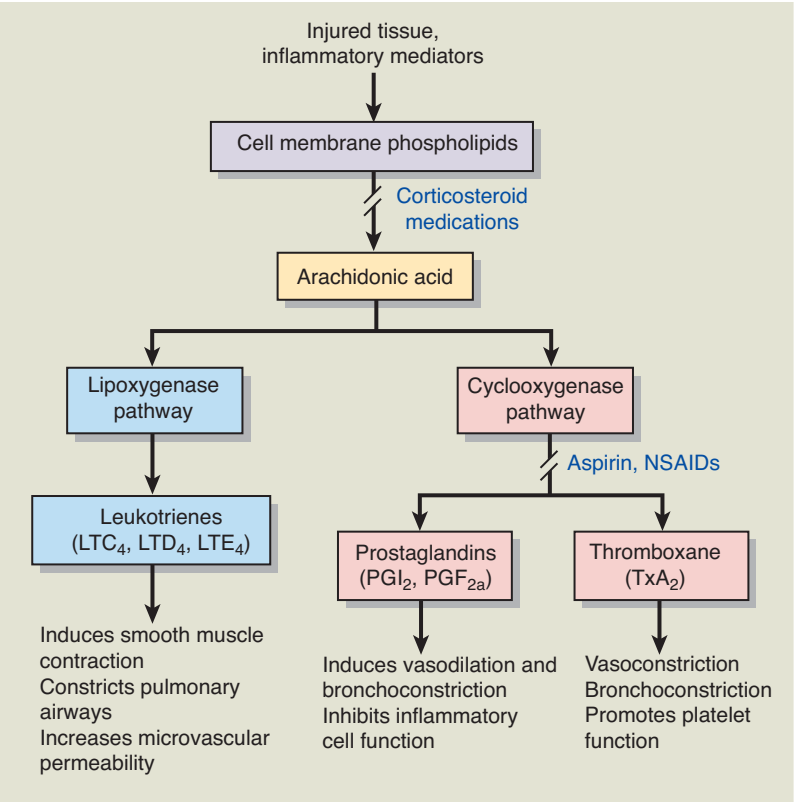


FIGURE 3-4. The cyclooxygenase and lipoxygenase pathways and sites where the corticosteroid and nonsteroidal anti-inflammatory drugs (NSAIDs) exert their action.

response. Serotonin (5-hydroxytryptamin) is also a preformed vasoactive mediator, with effects similar to histamine. It is found primarily within platelet granules and is released during platelet aggregation.

Arachidonic Acid Metabolites. Arachidonic acid is a 20-carbon unsaturated fatty acid found in the phospholipids of cell membranes. Release of arachidonic acid by phospholipases initiates a series of complex reactions that lead to the production of the *eicosanoid* family of inflammatory mediators (prostaglandins, leukotrienes, and related metabolites).[15] Eicosanoid synthesis follows one of two pathways: the cyclooxygenase pathway, which culminates in the synthesis of prostaglandins, and the lipoxygenase pathway, which culminates in the synthesis of the leukotrienes (Fig. 3-4). The corticosteroid drugs block the inflammatory effects of both pathways by inhibiting phosphodiesterase activity and thus preventing the release of arachidonic acid.[16]

Several prostaglandins are synthesized from arachidonic acid through the cyclooxygenase metabolic pathway.[15] The prostaglandins (e.g., PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2) induce inflammation and potentiate the effects of histamine and other inflammatory mediators. The prostaglandin thromboxane A_2 promotes platelet aggregation and vasoconstriction. Aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation by inactivating the first enzyme in the cyclooxygenase pathway for prostaglandin synthesis.

Like the prostaglandins, the leukotrienes are formed from arachidonic acid, but through the lipoxygenase pathway. Histamine and leukotrienes are complementary in action in that they have similar functions. Histamine is produced rapidly and transiently while the more potent leukotrienes are being synthesized. The leukotrienes also have been reported to affect the permeability of the postcapillary venules, the adhesion properties of endothelial cells, and the extravasation and chemotaxis of neutrophils, eosinophils, and monocytes. Leukotriene (LT) C_4, LTD_4, and LTE_4, collectively known as the *slow-reacting substance of anaphylaxis* (SRS-A), cause slow and sustained constriction of the bronchioles and are important inflammatory mediators in bronchial asthma and anaphylaxis.

Omega-3 Polyunsaturated Fatty Acids. There has been recent interest in dietary modification of the inflammatory response through the use of *omega-3 polyunsaturated fatty acids*, specifically *eicosapentaenoic acid* and *docosahexaenoic acid*, which are present in oily fish and fish oil.[17,18] α-*Linolenic acid*, which is present in flax seed, canola oil, green leafy vegetables, walnuts, and soybeans, is another source of omega-3 fatty acid. The omega-3 polyunsaturated fatty acids, which are considered antithrombotic and anti-inflammatory, are structurally different from the prothrombotic and proinflammatory omega-6 polyunsaturated fatty acids, which are present in most seeds, vegetable oils, and meats. Typically, the cell membranes of inflammatory cells contain high proportions of omega-6 arachidonic acid, which is the source of prostaglandin and leukotriene inflammatory mediators. Eating oily fish and other foods that are high

in omega-3 fatty acids results in partial replacement of omega-6 arachidonic acid in inflammatory cell membranes by eicosapentaenoic acid, a change that leads to decreased production of arachidonic acid–derived inflammatory mediators. This response alone is a potentially beneficial effect of omega-3 fatty acids. However, omega-3 fatty acids may have a number of other anti-inflammatory effects that occur downstream of altered eicosanoid production or might be independent of this function.

Platelet-Activating Factor. Originally named for its ability to cause platelet aggregation and granulation, PAF is another phospholipid-derived mediator with a broad spectrum of inflammatory effects. PAF is generated from the membrane phospholipids of virtually all activated inflammatory cells and affects a variety of cell types. In addition to activating platelets, PAF stimulates neutrophils, monocyte/macrophages, endothelial cells, and vascular smooth muscle. PAF-induced platelet aggregation and degranulation at the site of injury enhances serotonin release, thereby causing changes in vascular permeability. It also enhances leukocyte adhesion, chemotaxis, and leukocyte degranulation and stimulates the synthesis of other inflammatory mediators, especially the prostaglandins.

Cytokines and Chemokines. Cytokines are hormone-like, low-molecular-weight proteins produced by many cell types (principally activated macrophages and lymphocytes, but also endothelium, epithelium, and connective tissue types) that modulate the function of other cells.[1,2,8,19] Although well known for their role in immune responses, these proteins also play important roles in both acute and chronic inflammation.

TNF-α and IL-1 are two of the major cytokines that mediate inflammation. The major cellular source of TNF-α and IL-1 is activated mononuclear phagocytes (Fig. 3-5). IL-1 is also produced by many cell types other than macrophages, including neutrophils, endothelial cells, and epithelial cells (e.g., keratinocytes). The secretion of TNF-α and IL-1 can be stimulated by bacterial toxins, immune cells, injury, and a variety of inflammatory stimuli. TNF-α and IL-1 induce endothelial cells to express adhesion molecules and release cytokines, chemokines, and reactive oxygen species. TNF-α induces priming and aggregation of neutrophils, leading to augmented responses of these cells to other mediators. IL-1 and TNF-α are also mediators of the acute-phase responses associated with infection or injury. Features of these systemic responses include fever, hypotension and increased heart rate, anorexia, release of neutrophils into the circulation, and increased levels of corticosteroid hormones.

Chemotactic cytokines, or *chemokines*, are a family of small proteins that act primarily as chemoattractants that both recruit and direct the migration of inflammatory and immune cells[20] (see Chapter 15). Chemokines generate a chemotactic gradient by binding to proteoglycans on the surface of endothelial cells or in the extracellular matrix. As a result, high concentrations of

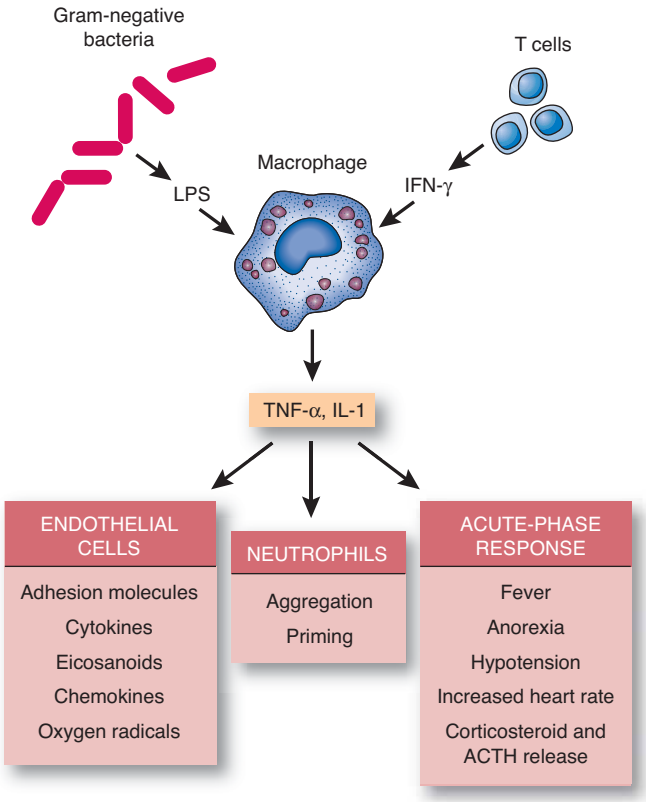


FIGURE 3-5. Central role of interleukin (IL)-1 and tumor necrosis factor (TNF)-α in inflammation. Lipopolysaccharide (LPS) and interferon (IFN)-γ activate macrophages to release inflammatory cytokines, principally IL-1 and TNF-α, responsible for directing both local and systemic inflammatory responses. ACTH, adrenocorticotrophic hormone. (From Murphy H.S. [2008]. Inflammation. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 50]. Philadelphia: Lippincott Williams & Wilkins.)

chemokines persist at sites of tissue injury or infection. Two classes of chemokines have been identified: inflammatory chemokines and homing chemokines. Inflammatory chemokines are produced in response to bacterial toxins and inflammatory cytokines (i.e., IL-1, TNF-α). These chemokines recruit leukocytes during an inflammatory response. Homing chemokines are constantly produced, with the genes that control their production being up-regulated during inflammatory reactions.

Nitric Oxide. Nitric oxide (NO), which is produced by a variety of cells, plays multiple roles in inflammation, including relaxation of vascular smooth muscle; antagonism of platelet adhesion, aggregation, and degranulation; and as regulator of leukocyte recruitment.[2] Blocking of NO production under normal conditions promotes leukocyte rolling and adhesion to postcapillary venules and delivery of exogenous NO reduces leukocyte recruitment. Thus, production of NO appears to be an endogenous compensatory mechanism that reduces the cellular phase of inflammation. Impaired production of NO by vascular endothelial cells is implicated in the inflammatory changes that occur with atherosclerosis (see Chapter 18). NO and

its derivatives also have antimicrobial actions and thus NO is also a host mediator against infection.

Oxygen-Derived Free Radicals. Oxygen free radicals may be released extracellularly from leukocytes after exposure to microbes, cytokines, and immune complexes, or during the phagocytic process that occurs during the cellular phase of the inflammatory process. The superoxide radical, hydrogen peroxide, and hydroxyl radical (discussed in Chapter 2) are the major species produced within the cell. These species can combine with NO to form other reactive nitrogen intermediates. Extracellular release of low levels of these potent mediators can increase the expression of cytokines and endothelial adhesion molecules, amplifying the cascade that elicits the inflammatory process.[2] At higher levels, these potent mediators can produce endothelial cell damage, with a resultant increase in vascular permeability; inactivate antiproteases, such as α_1-antitrypsin, which protects against lung damage in smokers; and produce injury to other cell types, including red blood cells.[2] Thus, the influence of oxygen-derived free radicals in any inflammatory process depends on a balance between the generation and inactivation of these metabolites.

Local Manifestations

The local manifestations of acute inflammation, which are determined by severity of the reaction, its specific cause, and the site of involvement, can range from mild swelling and redness to abscess formation or ulceration. As part of the normal defense reaction, inflammation can also injure adjacent tissues.[2] In some infections such as tuberculosis and certain viral infections, the host response can cause more damage than the microbe itself. As a normal attempt to clear damaged and dead tissues (e.g., after a myocardial infarction), the inflammatory response may prolong and exacerbate the injurious consequences of the infarction.

Characteristically, the acute inflammatory response involves the production of exudates. These exudates vary in terms of fluid type, plasma protein content, and presence or absence of cells. They can be serous, hemorrhagic, fibrinous, membranous, or purulent. Often the exudate is composed of a combination of these types. *Serous exudates* are watery fluids low in protein content that result from plasma entering the inflammatory site. *Hemorrhagic exudates* occur when there is severe tissue injury that causes damage to blood vessels or when there is significant leakage of red cells from the capillaries. *Fibrinous exudates* contain large amounts of fibrinogen and form a thick and sticky meshwork, much like the fibers of a blood clot. *Membranous* or *pseudomembranous exudates* develop on mucous membrane surfaces and are composed of necrotic cells enmeshed in a fibropurulent exudate.

A *purulent* or *suppurative exudate* contains pus, which is composed of degraded white blood cells, proteins, and tissue debris. The term *pyogenic* refers to "pus forming." Certain pyogenic microorganisms, such as *Staphylococcus*, are more likely to induce localized suppurative inflammation than others. An *abscess* is a localized area of inflammation containing a purulent exudate. Abscesses typically have a central necrotic core containing purulent exudates surrounded by a layer of neutrophils.[2] Fibroblasts may eventually enter the area and wall off the abscess. Because antimicrobial agents cannot penetrate the abscess wall, surgical incision and drainage may be required to effect a cure.

An *ulceration* refers to a site of inflammation where an epithelial surface (e.g., skin or gastrointestinal epithelium) has become necrotic and eroded, often with associated subepithelial inflammation. Ulceration may occur as the result of traumatic injury to the epithelial surface (e.g., peptic ulcer) or because of vascular compromise (e.g., foot ulcers associated with diabetes). In chronic lesions where there is repeated insult, the area surrounding the ulcer develops fibroblastic proliferation, scarring, and accumulation of chronic inflammatory cells.[2]

Resolution

Although the manifestations of acute inflammation are largely determined by the nature and intensity of injury, the tissue affected, and the person's ability to mount a response, the outcome generally results in one of three processes: resolution, progression to chronic inflammation, or substantial scarring and fibrosis.[2] Resolution involves the replacement of any irreversibly injured cells and return of tissues to their normal structure and function. It is seen with short-lived and minimal injuries and involves neutralization or degradation of inflammatory mediators, normalization of vascular permeability, and cessation of leukocyte infiltration. Progression to chronic inflammation may follow acute inflammation if the offending agent is not removed. Depending on the extent of injury, as well as the ability of the affected tissues to regenerate, chronic inflammation may be followed by restoration of normal structure and function. Scarring and fibrosis occurs when there is substantial tissue injury or when inflammation occurs in tissues that do not regenerate.

Although the mechanisms used in the resolution of acute inflammation have remained somewhat elusive, emerging evidence now suggests that an active, coordinated program of resolution begins in the first hours after an inflammatory response begins.[2,21,22] Studies suggest that after entering the site of acute inflammation, neutrophils promote a switch from the previously described proinflammatory eicosanoids (e.g., prostaglandins and leukotrienes) to other anti-inflammatory classes of eicosanoids, also generated from arachidonic acid. These eicosanoids initiate the termination sequence during which neutrophil recruitment ceases and programmed cell death by apoptosis commences. The apoptotic neutrophils then undergo phagocytosis by macrophages, leading to their clearance and release of anti-inflammatory and reparative cytokines. Although much new information regarding the resolution of inflammation has been obtained over the past few years, many issues require further characterization. New therapeutic targets are currently being investigated and potential proresolution properties of existing drugs studied. These discoveries may bring profound advances in therapies aimed at reducing the adverse effects of persistent inflammation.

In summary, acute inflammation is the local response to an injurious agent that serves to deliver leukocytes and plasma proteins to the site of injury. The classic signs of an acute inflammatory response are redness, swelling, local heat, pain, and loss of function. It involves a hemodynamic phase, during which blood flow and capillary permeability are increased, and a cellular phase, during which phagocytic white blood cells move into the area to engulf and degrade the inciting agent. The inflammatory response is orchestrated by chemical mediators such as cytokines and chemokines, histamine, prostaglandins, complement fragments, and reactive molecules that are liberated by leukocytes.

Acute inflammation may involve the production of exudates containing serous fluid (serous exudate), red blood cells (hemorrhagic exudate), fibrinogen (fibrinous exudate), or tissue debris and white blood cell breakdown products (purulent exudate). The outcome of acute inflammation generally results in one of three processes: resolution, progression to chronic inflammation, or substantial scarring and fibrosis. Current evidence suggests that the resolution of acute inflammation begins early in the process and is initiated by the neutrophils as they promote a switch from the generation of arachidonic acid–derived proinflammatory mediators to those that have an anti-inflammatory action.

Chronic Inflammation

In contrast to acute inflammation, which is usually self-limited and of short duration, chronic inflammation is self-perpetuating and may last for weeks, months, or even years. It may develop as a result of a recurrent or progressive acute inflammatory process or from low-grade, smoldering responses that fail to evoke an acute response. Instead of the vascular changes, edema, and predominantly neutrophilic infiltration seen in acute inflammation, chronic inflammation is characterized by infiltration with mononuclear cells (macrophages, lymphocytes, and plasma cells) and attempted connective tissue repair involving new vessel formation (angiogenesis) and fibrosis. Although it may follow acute inflammation, chronic inflammation often begins insidiously as a low-grade smoldering, often asymptomatic process. This type of process is the cause of tissue damage in some of the most common disabling diseases such as atherosclerosis, chronic lung disease, rheumatoid arthritis, and inflammatory bowel disease.

There is also evidence that recurrent and persistent inflammation may induce, promote, or influence susceptibility to cancer by causing deoxyribonucleic acid (DNA) damage, inciting tissue reparative proliferation, and/or creating an environment that is enriched with cytokines and growth factors that favor tumor development and growth (see Chapter 7).[23,24] Among the cancers associated with chronic infection and inflammation are cervical cancer (human papillomavirus [HPV]), cancer of the liver (hepatitis B and C), cancer of the stomach (*Helicobacter pylori*), and cancer of the gallbladder (chronic cholecystitis and cholelithiasis).

Causes of Chronic Inflammation

Agents that evoke chronic inflammation typically are low-grade, persistent infections or irritants that are unable to penetrate deeply or spread rapidly.[1,2] Among the causes of chronic inflammation are foreign bodies such as talc, silica, asbestos, and surgical suture materials. Many viruses provoke chronic inflammatory responses, as do certain bacteria, fungi, and larger parasites of moderate to low virulence. Examples are the tubercle bacillus and the actinomyces. The presence of injured tissue such as that surrounding a healing fracture also may incite chronic inflammation. Diseases that cause excessive and inappropriate activation of the immune system are increasingly being recognized as causes of chronic inflammation. Under certain conditions, immune reactions may develop against the person's own tissues, leading to autoimmune disease.

Obesity is a newly suspected cause of chronic inflammation.[25–27] During the last decade, white adipose tissue was recognized to be an active endocrine organ and a source of a number of proinflammatory mediators. Many of the mediators appear to play an important role in the pathogenesis of obesity-related diseases including accelerated atherosclerosis and diabetes mellitus. The link between obesity and inflammation dates back to the discovery that adipose tissue was a source of the proinflammatory cytokine TNF-α, and that adipose tissue TNF-α concentrations are correlated with insulin resistance both in persons with and without type 2 diabetes mellitus. It was later found that obesity is related not only to increased number and size of adipocytes, but also to infiltration of adipose tissue by macrophages that possess the ability to produce TNF-α, nitric oxide, and other inflammatory mediators. The mechanisms mediating the proinflammatory state associated with obesity are still unclear, but recent studies suggest that circulating free fatty acids may play a role.

Granulomatous Inflammation

A granulomatous lesion is a distinctive form of chronic inflammation.[1,2] A *granuloma* typically is a small, 1- to 2-mm lesion in which there is a massing of macrophages surrounded by lymphocytes. These modified macrophages resemble epithelial cells and sometimes are called *epithelioid cells*. Like other macrophages, these epithelioid cells are derived originally from blood monocytes. Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, sarcoidosis, deep fungal infections, and brucellosis. These types of agents have one thing in common: they are poorly digested and usually are not easily controlled by other inflammatory mechanisms. The epithelioid cells in granulomatous inflammation may clump in a mass or coalesce, forming a multinucleated giant cell that attempts to

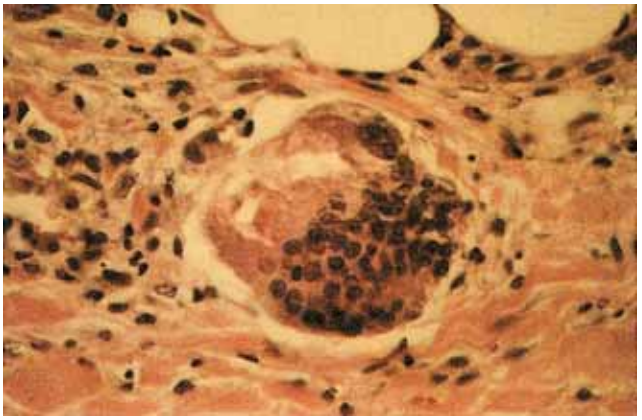


FIGURE 3-6. Foreign body giant cell. The numerous nuclei are randomly arranged in the cytoplasm. (From Rubin E., Farber L.L. [1999]. *Rubin's pathology: Clinicopathologic foundations of medicine* [3rd ed., p. 40]. Philadelphia: Lippincott-Raven.)

surround the foreign agent (Fig. 3-6). A dense membrane of connective tissue eventually encapsulates the lesion and isolates it. These cells are often referred to as foreign body giant cells.

In summary, chronic inflammation, which involves the presence of mononuclear cells (lymphocytes and macrophages) and is recognized for its persistence, is increasingly being recognized as a contributing factor in a number of disease conditions. It is associated with excessive and inappropriate activation of the immune system as occurs with autoimmune disorders; may contribute to the state of low-grade inflammation associated with conditions such as atherosclerosis and type 2 diabetes mellitus; and may induce, promote, or influence susceptibility to cancer by causing DNA damage, inciting tissue reparative proliferation, and/or creating an environment that is enriched with cytokines and growth factors that favor tumor development and growth.

A granulomatous lesion is a distinctive form of chronic inflammation characterized by aggregates of epithelioid macrophages that "wall off" the causal agent. Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, sarcoidosis, deep fungal infections, and brucellosis.

Systemic Manifestations of Inflammation

Under optimal conditions, the inflammatory response remains confined to a localized area. In some cases, however, local injury can result in prominent systemic manifestations as inflammatory mediators are released into the circulation. The most prominent systemic manifestations of inflammation include the acute-phase response, alterations in white blood cell count (leukocytosis or leukopenia), and fever. Localized acute and chronic inflammation may extend to the lymphatic system and lead to a reaction in the lymph nodes that drain the affected area. Painful palpable nodes are more commonly associated with inflammatory processes, whereas nonpainful lymph nodes are more characteristic of neoplasms.

Acute-Phase Response

Along with the cellular responses that occur during the inflammatory response, a constellation of systemic effects called the *acute-phase response* occurs.[1,2] The acute-phase response, which usually begins within hours or days of the onset of inflammation or infection, includes changes in the concentrations of plasma proteins, skeletal muscle catabolism, negative nitrogen balance, elevated erythrocyte sedimentation rate, and increased numbers of leukocytes. Other manifestations of the acute-phase response include fever, increased heart rate, anorexia, somnolence, and malaise.

Acute-Phase Proteins

During the acute-phase response, the liver dramatically increases the synthesis of acute-phase proteins such as fibrinogen, C-reactive protein (CRP), and serum amyloid A protein (SAA) that serve several different defense functions.[1,2] The synthesis of these proteins is stimulated by cytokines, especially TNF-α, IL-1 (for SAA), and IL-6 (for fibrinogen and CRP).

CRP was named because it precipitated with the C fraction (C polypeptide) of pneumococci. The function of CRP is thought to be protective, in that it binds to the surface of invading microorganisms and targets them for destruction by complement and phagocytosis. Although everyone maintains a low level of CRP, this level rises when there is an acute inflammatory response.[28] Recent interest has focused on the use of high-sensitivity CRP (hsCRP) serum measurements as a marker for increased risk of myocardial infarction in persons with coronary heart disease.[29,30] It is believed that inflammation involving atherosclerotic plaques in coronary arteries may predispose to thrombosis and myocardial infarction (see Chapter 18).

During the acute-phase response, SAA protein replaces apolipoprotein A, a component of high-density lipoprotein (HDL) particles (see Chapter 18). This presumably increases the transfer of HDLs from liver cells to macrophages, which can then utilize these particles for energy. The rise in fibrinogen causes red blood cells to form stacks (rouleaux) that settle or sediment more rapidly than individual erythrocytes. This is the basis for the accelerated erythrocyte sedimentation rate (ESR) that occurs in disease conditions characterized by the systemic inflammatory response.

White Blood Cell Response

Leukocytosis, or the increase in white blood cells, is a frequent sign of an inflammatory response, especially

those caused by bacterial infection. The white blood cell count commonly increases from a normal value of 4000 to 10,000 cells/μL to 15,000 to 20,000 cells/μL in acute inflammatory conditions. After being released from the bone marrow, circulating neutrophils have a life span of only about 10 hours and therefore must be constantly replaced if their numbers are to be adequate. With excessive demand for phagocytes, immature forms of neutrophils (bands) are released from the bone marrow. The phrase a "shift to the left" in a white blood cell differential count refers to the increase in immature neutrophils seen in severe infections.

Bacterial infections produce a relatively selective increase in neutrophils (neutrophilia), while parasitic and allergic responses induce eosinophilia. Viral infections tend to produce a decrease in neutrophils (neutropenia) and an increase in lymphocytes (lymphocytosis).[3] A decrease in white blood cells (leukopenia) may occur with persons with overwhelming infections or impaired ability to produce white blood cells.

Systemic Inflammatory Response

In severe bacterial infections (sepsis), the large quantities of microorganisms in the blood result in an uncontrolled inflammatory response with the production and release of enormous quantities of inflammatory cytokines (most notably IL-1 and TNF-α) and development of what is referred to as the *systemic inflammatory response syndrome* (see Chapter 20).[31] These cytokines cause generalized vasodilation, increased vascular permeability, intravascular fluid loss, myocardial depression, and circulatory shock.

Fever

Fever or an elevation in body temperature is one of the most prominent manifestations of the acute-phase response.[1,2] It is caused by a cytokine-induced upward displacement of the *set point* of the hypothalamic thermoregulatory center.[32–34]

Body Temperature Regulation

The temperature in the deep tissues of the body (core temperature) is normally maintained within a range of 36.0°C to 37.5°C (97.0°F to 99.5°F).[32,33] Within this range, there are individual differences and diurnal variations; internal core temperatures reach their highest point in late afternoon and evening and their lowest point in the early morning hours (Fig. 3-7). Virtually all biochemical processes in the body are affected by changes in temperature. Metabolic processes speed up or slow down depending on whether body temperature is rising or falling.

Body temperature, which reflects the difference between heat production and heat loss, is regulated by the *thermoregulatory center* in the hypothalamus. Body heat is generated in the tissues of the body, transferred to the skin surface by the blood, and then released into the environment surrounding the body. It is the temperature

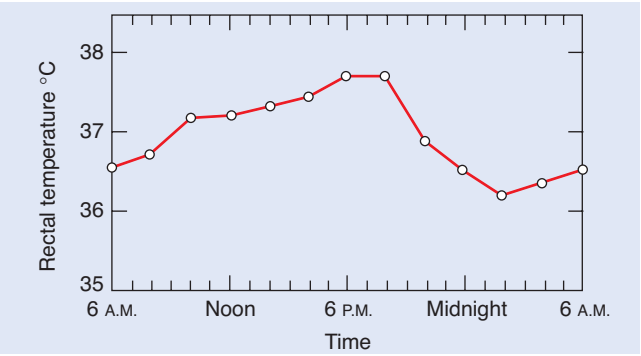


FIGURE 3-7. Normal diurnal variations in body temperature.

of the deep body tissues, or "core" of the body, rather than the surface temperature, that is regulated by the thermoregulatory center. The temperature of the body is regulated almost entirely by nervous system feedback mechanisms, with the thermoregulatory center integrating input from cold and warmth receptors located throughout the body. The *thermostatic set point* of the thermoregulatory center is the level at which body temperature is regulated so that core temperature is maintained within the normal range. When body temperature begins to rise above this set point, heat-dissipating behaviors are initiated, and when the temperature falls below the set point, heat production is increased. A core temperature greater than 41°C (105.8°F) or less than 34°C (93.2°F) usually indicates that the body's thermoregulatory ability is impaired (Fig. 3-8). Body responses that produce, conserve, and dissipate heat are described in Table 3-1. Spinal cord injuries that transect the cord at T6 or above can seriously impair temperature regulation because the hypothalamus no longer can control skin blood flow or sweating.

In addition to physiologic thermoregulatory mechanisms, humans engage in voluntary behaviors to help regulate body temperature. These behaviors include the selection of proper clothing and regulation of environmental temperature through heating systems and air conditioning. Body positions that hold the extremities close to the body (e.g., huddling) prevent heat loss and are commonly assumed in cold weather.

Mechanisms of Heat Production. Metabolism is the body's main source of heat production. The sympathetic neurotransmitters epinephrine and norepinephrine, which are released when an increase in body temperature is needed, act at the cellular level to shift body metabolism to heat production rather than energy generation. This may be one of the reasons fever tends to produce feelings of weakness and fatigue. Thyroid hormone increases cellular metabolism, but this response usually requires several weeks to reach maximal effectiveness.

Fine involuntary actions such as shivering and chattering of the teeth can produce a threefold to fivefold increase in body temperature. *Shivering* is initiated by impulses from the hypothalamus. The first muscle change that occurs with shivering is a general increase in muscle

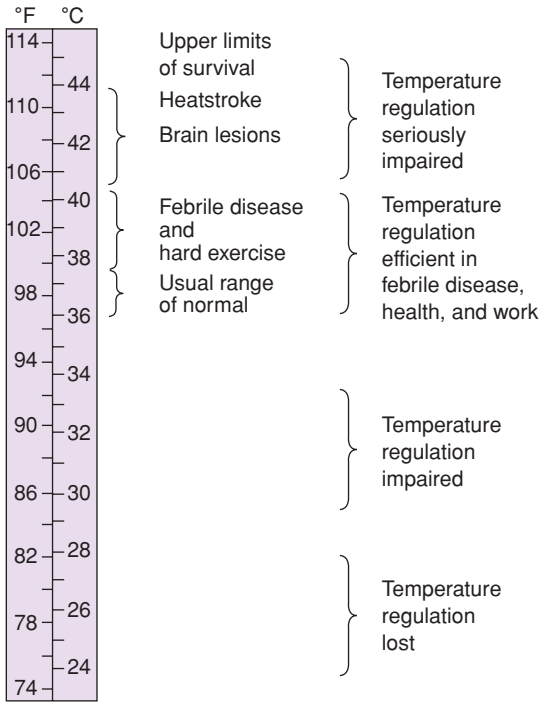


FIGURE 3-8. Body temperatures under different conditions. (From Dubois, E.F. [1948]. *Fever and the regulation of body temperature*. Springfield, IL: Charles C Thomas.)

tone, followed by an oscillating rhythmic tremor involving the spinal-level reflex that controls muscle tone. Because no external work is performed, all of the energy liberated by the metabolic processes from shivering is in the form of heat.

Physical exertion also increases body temperature. With strenuous exercise, more than three fourths of the increased metabolism resulting from muscle activity appears as heat within the body, and the remainder appears as external work.

Mechanisms of Heat Loss. Most of the body's heat is produced by the deeper core tissues (i.e., muscles and viscera) and then transferred in the blood to the body surface, where it is released into the environment. Contraction of the *pilomotor muscles* of the skin, which raises the skin hair and produces goose bumps, reduces the surface area available for heat loss.

There are numerous *arteriovenous (AV) shunts* under the skin surface that allow blood to move directly from the arterial to the venous system.[32] These AV shunts are much like the radiators in a heating system. When the shunts are open, body heat is freely dissipated to the skin and surrounding environment; when the shunts are closed, heat is retained in the body. The blood flow in the AV shunts is controlled almost exclusively by the sympathetic nervous system in response to changes in core temperature and environmental temperature. The transfer of heat to the body's surface is influenced by blood volume. In hot weather, the body compensates by increasing blood volume as a means of dissipating heat. Exposure to cold produces a cold diuresis and a reduction in blood volume as a means of controlling the transfer of heat to the body's surface.

Heat is lost from the body through radiation and conduction from the skin surface; through evaporation of sweat and insensible perspiration; through exhalation of air that has been warmed and humidified; and through heat lost in urine and feces. Of these mechanisms, only heat losses that occur at the skin surface are directly under hypothalamic control.

Radiation involves the transfer of heat through the air or a vacuum. Heat loss through radiation varies with the

TABLE 3-1 Heat Gain and Heat Loss Responses Used in Regulation of Body Temperature

Heat Gain		*Heat Loss*	
Body Response	**Mechanism of Action**	**Body Response**	**Mechanism of Action**
Vasoconstriction of the superficial blood vessels	Confines blood flow to the inner core of the body, with the skin and subcutaneous tissues acting as insulation to prevent loss of core heat	Dilatation of the superficial blood vessels	Delivers blood containing core heat to the periphery where it is dissipated through radiation, conduction, and convection
Contraction of the pilomotor muscles that surround the hairs on the skin	Reduces the heat loss surface of the skin	Sweating	Increases heat loss through evaporation
Assumption of the huddle position with the extremities held close to the body	Reduces the area for heat loss		
Shivering	Increases heat production by the muscles		
Increased production of epinephrine	Increases the heat production associated with metabolism		
Increased production of thyroid hormone	Is a long-term mechanism that increases metabolism and heat production		

temperature of the environment. Environmental temperature must be less than that of the body for heat loss to occur. About 60% of body heat loss typically occurs through radiation.[32] *Conduction* involves the direct transfer of heat from one molecule to another. Blood carries, or conducts, heat from the inner core of the body to the skin surface. Normally, only a small amount of body heat is lost through conduction to a cooler surface. Cooling blankets and mattresses that are used for reducing fever rely on conduction of heat from skin to the cooler surface of the mattress or blanket. Heat can also be conducted in the opposite direction—from the external environment to the body surface. For instance, body temperature may rise slightly after a hot bath.

Convection refers to heat transfer through the circulation of air currents. Normally, a layer of warm air tends to remain near the body's surface; convection causes continual removal of the warm layer and replacement with air from the surrounding environment. The wind-chill factor that often is included in the weather report combines the effect of convection caused by wind with the still-air temperature.

Evaporation involves the use of body heat to convert water on the skin to water vapor. Water that diffuses through the skin independent of sweating is called *insensible perspiration*. Insensible perspiration losses are greatest in a dry environment. Sweating occurs through the sweat glands and is controlled by the sympathetic nervous system. In contrast to other sympathetically mediated functions, sweating relies on acetylcholine as a neurotransmitter, rather than the catecholamines. This means that anticholinergic drugs, such as atropine, can interfere with heat loss by interrupting sweating.

Evaporative heat losses involve both insensible perspiration and sweating, with 0.58 calorie being lost for each gram of water that is evaporated.[32] As long as body temperature is greater than the atmospheric temperature, heat is lost through radiation. However, when the temperature of the surrounding environment becomes greater than skin temperature, evaporation is the only way the body can rid itself of heat. Any condition that prevents evaporative heat losses causes the body temperature to rise.

Fever and the Febrile Response

Fever, or pyrexia, describes an elevation in body temperature that is caused by a cytokine-induced upward displacement of the set point of the hypothalamic thermoregulatory center. Fever is resolved when the factor that caused the increase in the set point is removed. Fevers that are regulated by the hypothalamus usually do not rise above 41°C (105°F), suggesting a built-in thermostatic regulatory mechanism. Temperatures above that level are usually the result of superimposed activity, such as convulsions, hypermetabolic states, or direct impairment of the temperature control center.

Causes of Fever. Fever can be caused by a number of microorganisms and substances that are collectively called *pyrogens*[34–36] (Fig. 3-9). Many proteins, including lipopolysaccharide toxins released from bacterial cell membranes, can raise the set point of the hypothalamic thermostat. Noninfectious disorders, such as myocardial infarction and pulmonary emboli, also produce fever. In these conditions, the injured or abnormal cells incite the production of fever-producing pyrogens. Some malignant cells, such as those of leukemia and Hodgkin disease, also secrete *pyrogens*.

Some pyrogens act directly and immediately on the hypothalamic thermoregulatory center to increase its set point. Other pyrogens, often referred to as *exogenous pyrogens,* act indirectly and may require several hours to produce their effect.[33] Exogenous pyrogens induce host cells, such as blood leukocytes and tissue macrophages, to produce fever-producing mediators called *endogenous pyrogens* (e.g., IL-1). For example, the breakdown products of phagocytosed bacteria that are present in the blood lead to the release of endogenous pyrogens. The endogenous pyrogens are thought to increase the set point of the hypothalamic thermoregulatory center through the action of prostaglandin E_2.[33] In response to the sudden increase in set point, the hypothalamus initiates heat production behaviors (shivering and vasoconstriction) that increase the core body temperature to the new set point, and fever is established.

A fever that has its origin in the central nervous system is sometimes referred to as a *neurogenic fever.*[37] It usually is the result of damage to the hypothalamus caused by central nervous system trauma, intracerebral bleeding, or an increase in intracranial pressure. Neurogenic fevers are characterized by a high temperature that is resistant to antipyretic therapy and is not associated with sweating.

Purpose of Fever. The purpose of fever is not completely understood. However, from a purely practical

Fever

- Fever represents an increase in body temperature that results from a cytokine-induced increase in the set point of the thermostatic center in the hypothalamus.
- Fever is a nonspecific response that is mediated by endogenous pyrogens released from host cells in response to infectious or noninfectious disorders.
- The development of fever involves a prodrome, a chill during which the temperature rises until it reaches the new hypothalamic set point, a flush during which the skin vessels dilate and the temperature begins to fall, and a period of defervescence that is marked by sweating.
- Fever is resolved when the condition causing the increase in the set point of the thermostatic center in the hypothalamus is resolved.

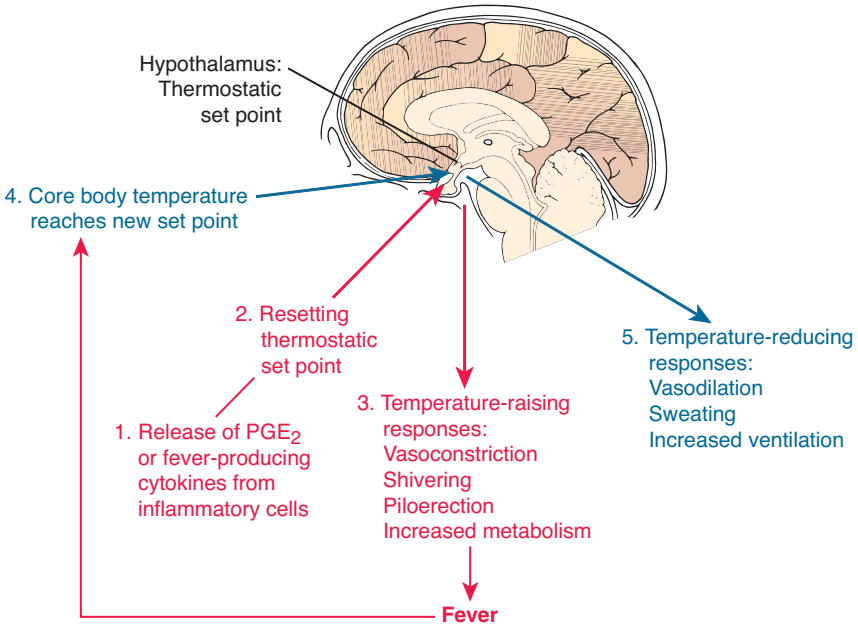


FIGURE 3-9. Mechanisms of fever. (*1*) Release of prostaglandin E_2 (PGE_2) or fever-producing cytokines from inflammatory cells, (*2*) resetting of the thermoregulatory set point in the hypothalamus to a higher level (prodrome), (*3*) generation of hypothalamic-mediated responses that raise body temperature (chill), (*4*) development of fever with elevation of body to new thermostatic set point, and (*5*) production of temperature-lowering responses (flush and defervescence) and return of body temperature to a lower level.

standpoint, fever is a valuable index to health status. For many, fever signals the presence of an infection and may legitimize the need for medical treatment. In ancient times, fever was thought to "cook" the poisons that caused the illness. With the availability of antipyretic drugs in the late 19th century, the belief that fever was useful began to wane, probably because most antipyretic drugs also had analgesic effects.

There is little research to support the belief that fever is harmful unless the temperature rises to extreme levels. It has been shown that small elevations in temperature, such as those that occur with fever, enhance immune function. There is increased motility and activity of the white blood cells, stimulation of interferon production, and activation of T cells.[38,39] Many of the microbial agents that cause infection grow best at normal body temperatures, and their growth is inhibited by temperatures in the fever range. For example, the rhinoviruses responsible for the common cold are cultured best at 33°C (91.4°F), which is close to the temperature in the nasopharynx. Temperature-sensitive mutants of the virus that cannot grow at temperatures greater than 37.5°C (99.5°F) produce fewer signs and symptoms.[40]

Fever Patterns. The patterns of temperature change in persons with fever vary and may provide information about the nature of the causative agent.[41,42] These patterns can be described as intermittent, remittent, sustained, or relapsing (Fig. 3-10). An *intermittent fever* is one in which temperature returns to normal at least once every 24 hours. Intermittent fevers are commonly associated with conditions such as gram-negative/-positive sepsis, abscesses, and acute bacterial endocarditis. In a *remittent fever,* the temperature does not return to normal and varies a few degrees in either direction. It is associated with viral upper respiratory tract, *Legionella,* and mycoplasma infections. In a *sustained* or *continuous* fever, the temperature remains above normal with minimal variations (usually less than 0.55°C or 1°F). Sustained fevers are seen in persons with drug fever. A *recurrent* or *relapsing fever* is one in which there is one or more episodes of fever, each as long as several days, with one or more days of normal temperature between episodes. Relapsing fevers may be caused by a variety of infectious diseases, including tuberculosis, fungal infections, Lyme disease, and malaria.

Critical to the analysis of a fever pattern is the relation of heart rate to the level of temperature elevation. Normally, a 1°C rise in temperature produces a 15-bpm (beats per minute) increase in heart rate (1°F, 10 bpm).[42] Most persons respond to an increase in temperature with an appropriate increase in heart rate. The observation that a rise in temperature is not accompanied by the anticipated change in heart rate can provide useful information about the cause of the fever. For example, a heart rate that is slower than would be anticipated can occur with Legionnaires disease and drug fever, and a heart rate that is more rapid than anticipated can be symptomatic of hyperthyroidism.

Manifestations. The physiologic behaviors that occur during the development of fever can be divided into four successive stages: a prodrome; a chill, during which the temperature rises; a flush; and defervescence (Fig. 3-9). During the *first* or *prodromal* period, there are nonspecific complaints, such as mild headache and fatigue, general malaise, and fleeting aches and pains. During the *second stage* or *chill,* there is the uncomfortable sensation of being chilled and the onset of generalized shaking, although the temperature is rising. Vasoconstriction and piloerection usually precede the onset of shivering. At this point the skin is pale and covered with goose flesh. There is a feeling of being cold and an urge to put on more clothing or covering and to curl up in a position that conserves

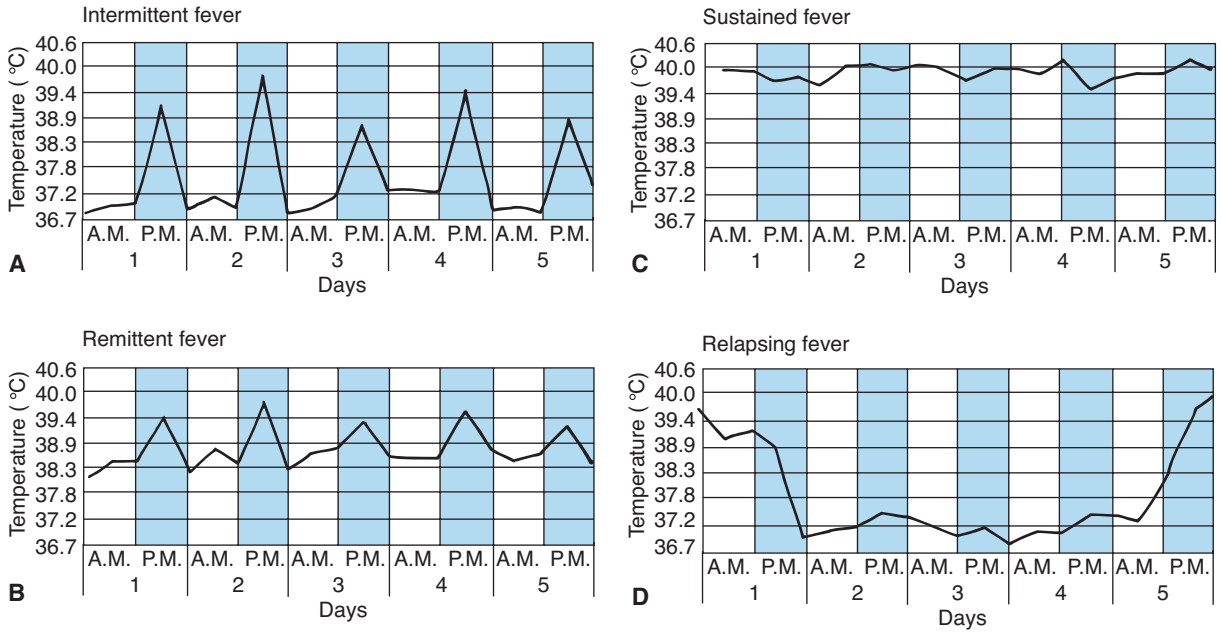


FIGURE 3-10. Schematic representation of fever patterns: **(A)** intermittent, **(B)** remittent, **(C)** sustained, and **(D)** recurrent or relapsing.

body heat. When the shivering has caused the body temperature to reach the new set point of the temperature control center, the shivering ceases, and a sensation of warmth develops. At this point, the *third stage* or *flush* begins, during which cutaneous vasodilatation occurs and the skin becomes warm and reddened. The *fourth,* or *defervescence,* stage of the febrile response is marked by the initiation of sweating. Not all persons proceed through the four stages of fever development. Sweating may be absent, and fever may develop gradually, with no indication of a chill or shivering.

Common manifestations of fever are anorexia, myalgia, arthralgia, and fatigue. These discomforts are worse when the temperature rises rapidly or exceeds 39.5°C (103.1°F). Respiration is increased, and the heart rate usually is elevated. Dehydration occurs because of sweating and the increased vapor losses caused by the rapid respiratory rate. The occurrence of chills commonly coincides with the introduction of pyrogen into the circulation. This is one of the reasons that blood cultures to identify the organism causing the fever are usually drawn during the first signs of a chill.

Many of the manifestations of fever are related to the increases in the metabolic rate, increased need for oxygen, and use of body proteins as an energy source. During fever, the body switches from using glucose (an excellent medium for bacterial growth) to metabolism based on protein and fat breakdown. With prolonged fever, there is increased breakdown of endogenous fat stores. If fat breakdown is rapid, metabolic acidosis may result (see Chapter 8).

Headache is a common accompaniment of fever and is thought to result from the vasodilatation of cerebral vessels occurring with fever. Delirium is possible when the temperature exceeds 40°C (104°F). In the elderly, confusion and delirium may follow moderate elevations in temperature. Because of the increasingly poor oxygen uptake by the aging lung, pulmonary function may prove to be a limiting factor in the hypermetabolism that accompanies fever in older persons. Confusion, incoordination, and agitation commonly reflect cerebral hypoxemia. Febrile seizures can occur in some children.[43] They usually occur with rapidly rising temperatures or at a threshold temperature that differs with each child.

Herpetic lesions, or fever blisters, develop in some persons during fever. They are caused by a separate infection by the type 1 herpes simplex virus that established latency in the regional ganglia and is reactivated by a rise in body temperature.

Management of Fever. Fever usually is a manifestation of a disease state, and as such, determining the cause of a fever is an important aspect of its treatment. Sometimes it is difficult to establish the cause of a fever. A prolonged fever for which the cause is difficult to ascertain is often referred to as *fever of unknown origin* (FUO). FUO is defined as a temperature elevation of 38.3°C (101°F) or higher that is present for 3 weeks or longer.[44] Among the causes of FUO are malignancies (i.e., lymphomas, metastases to the liver or central nervous system); infections such as human immunodeficiency virus or tuberculosis, or abscessed infections; and drug fever. Malignancies, particularly non-Hodgkin lymphoma, are important causes of FUO in the elderly. Cirrhosis of the liver is another cause of FUO.

The methods of fever treatment focus on modifications of the external environment intended to increase

heat transfer from the internal to the external environment, support of the hypermetabolic state that accompanies fever, protection of vulnerable body organs and systems, and treatment of the infection or condition causing the fever. Because fever is a disease symptom, its manifestation suggests the need for treatment of the primary cause.

Modification of the environment ensures that the environmental temperature facilitates heat transfer away from the body. Sponge baths with cool water or an alcohol solution can be used to increase evaporative heat losses. More profound cooling can be accomplished through the use of a cooling blanket or mattress, which facilitates the conduction of heat from the body into the coolant solution that circulates through the mattress. Care must be taken so that cooling methods do not produce vasoconstriction and shivering that decrease heat loss and increase heat production.

Adequate fluids and sufficient amounts of simple carbohydrates are needed to support the hypermetabolic state and prevent the tissue breakdown that is characteristic of fever. Additional fluids are needed for sweating and to balance the insensible water losses from the lungs that accompany an increase in respiratory rate. Fluids also are needed to maintain an adequate vascular volume for heat transport to the skin surface.

Antipyretic drugs, such as aspirin and acetaminophen, often are used to alleviate the discomforts of fever and protect vulnerable organs, such as the brain, from extreme elevations in body temperature. These drugs act by resetting the hypothalamic temperature control center to a lower level, presumably by blocking the activity of cyclooxygenase, an enzyme that is required for the conversion of arachidonic acid to prostaglandin E_2.

Fever in Children

Fever occurs frequently in infants and young children (i.e., ages 1 day to 3 years) and is a common reason for visits to the clinic or emergency department.[45–48] The differential diagnosis of fever is broad and includes both infectious and noninfectious causes, with the majority of febrile children having an underlying infection. The most common causes are minor or more serious infections of the respiratory system, gastrointestinal tract, urinary tract, or central nervous system. The epidemiology of serious bacterial disease has changed dramatically with the introduction of the *Haemophilus influenzae* and *Streptococcus pneumoniae* vaccines in developed countries.[46,47] *H. influenzae* type b has been nearly eliminated and the incidence of pneumococcal disease has declined substantially. Febrile children who are younger than 1 year of age and females between 1 and 2 years of age should be considered at risk for a urinary tract infection (see Chapter 24).[47]

While most children have identifiable causes for their fevers, many have fevers without localizing signs or symptoms. These fevers, which are usually of rapid onset and present for less than a week, are commonly referred to as *fever without source*. The American College of Emergency Physicians has developed clinical guidelines for use in the treatment of previously healthy infants and children ages 1 day to 3 years with fever without a source.[47,48] The guidelines define fever in this age group as a rectal temperature of at least 38°C (100.4°F). The reliability of other methods of temperature measurements (e.g., axillary, ear) is lower and must be considered when making decisions about the seriousness of the fever.[47] Bundling of infants may raise the skin temperature but not the rectal temperature.[46]

The approach to the young child who has fever without a source varies depending on the age of the child (neonate [0 to 28 days], young infant [1 to 3 months], and older infants and toddlers [3 to 36 months]).[46] Younger children have decreased immunologic function and are more commonly infected with virulent organisms. Neonates are particularly at high risk for serious bacterial infections that can cause bacteremia or meningitis. Also, neonates and young infants demonstrate limited signs of infection, often making it difficult to distinguish between serious bacterial infections that require immediate medical attention and other causes of an elevated temperature.

Fever without source in children younger than age 3 months requires careful history and physical examination.[45] The temperature-lowering response to antipyretic medications does not change the likelihood of a child having a serious bacterial infection and should not be used as an indicator of infection severity.[46,47] Neonates with signs of toxicity (and high risk) including lethargy, poor feeding, hypoventilation, poor tissue oxygenation, and cyanosis usually require hospitalization and treatment with antibiotics. Diagnostic tests such as white blood cell count, blood and urine cultures, chest radiographs, and lumbar puncture usually are done to determine the cause of fever. Infants with fever who are considered to be at low risk for bacterial infections often are managed on an outpatient basis provided the parents or caregivers are deemed reliable. Older children with fever without source also may be treated on an outpatient basis.

Fever in the Elderly

In the elderly, even slight elevations in temperature may indicate serious infection or disease. This is because the elderly often have a lower baseline temperature, and although they increase their temperature during an infection, it may fail to reach a level that is equated with significant fever.[49–51]

Elderly persons are reported to have a lower basal temperature (36.4°C [97.6°F] in one study) than younger persons.[52] It has been recommended that the definition of fever in the elderly be expanded to include an elevation of temperature of at least 1.1°C (2°F) above baseline values.[53] When fever is present in the elderly, it usually indicates the presence of serious infection, most often caused by bacteria.

The absence of fever may delay diagnosis and initiation of antimicrobial treatment. Unexplained changes in

functional capacity, worsening of mental status, weakness and fatigue, and weight loss are signs of infection in the elderly and should be viewed as possible signs of infection and sepsis when fever is absent. A thorough history and physical examination are critically important. The probable mechanisms for the blunted fever response include a disturbance in sensing of temperature by the thermoregulatory center in the hypothalamus, alterations in release of endogenous pyrogens, and the failure to elicit responses such as vasoconstriction of skin vessels, increased heat production, and shivering that increase body temperature during a febrile response.

Another factor that may delay recognition of fever in the elderly is the method of temperature measurement. Oral temperature remains the most commonly used method for measuring temperature in the elderly. It has been suggested that rectal and tympanic membrane methods are more effective in detecting fever in the elderly. This is because conditions such as mouth breathing, tongue tremors, and agitation often make it difficult to obtain accurate oral temperatures in the elderly.

In summary, the systemic manifestations of inflammation include the effects of the acute-phase response, such as fever and lethargy; increased ESR and levels of CRP and other acute-phase proteins; leukocytosis or, in some cases, leukopenia; and enlargement of the lymph nodes that drain the affected area. In severe bacterial infections (sepsis), the large quantities of microorganisms in the blood result in the production and release of enormous quantities of inflammatory cytokines and development of what is referred to as the *systemic inflammatory response syndrome*.

Fever, which is characterized by an elevation in body temperature, is one of the most prominent manifestations of the acute-phase response, especially if inflammation is caused by infection. Fever is produced in response to pyrogens that act by resetting of the hypothalamic thermoregulatory center. The reactions that occur during fever consist of four stages: a *prodromal period* with nonspecific complaints, such as mild headache and fatigue; a *chill,* during which the temperature rises; a *flush*, during which the skin becomes warm and flushed; and a *defervescence stage,* which is marked by the initiation of sweating. Many of the manifestations of fever are related to the increases in the metabolic rate, increased need for oxygen, and use of body proteins as an energy source. The approach to fever in children varies depending on the age of the child. Infants and young children have decreased immunologic function and are more commonly infected with virulent organisms. The elderly tend to have a lower baseline temperature, so serious infections may go unrecognized because of the perceived lack of a significant fever.

REVIEW EXERCISES

1. A 15-year-old boy presents with abdominal pain, a temperature of 38°C (100.5°F), and an elevated white blood cell count of 13,000/μL, with an increase in neutrophils. A tentative diagnosis of appendicitis is made.

A. Explain the significance of pain as it relates to the inflammatory response.
B. What is the cause of the fever and elevated white blood cell count?
C. What would be the preferred treatment for this boy?

2. Aspirin and other NSAIDs are often used to control the manifestations of chronic inflammatory disorders such as arthritis.

A. Explain their mechanism of action in terms of controlling the inflammatory response.

3. Persons with long-standing ulcerative colitis, an inflammatory bowel disease, have a higher risk of colorectal cancer than the general population.

A. Hypothesize on cancer-producing mechanisms of this chronic inflammatory disease.

4. A 3-year-old child is seen in a pediatric clinic with a temperature of 39°C (103°F). Her skin is warm and flushed, her pulse is 120 beats per minute, and her respirations are shallow and rapid at 32 breaths per minute. Her mother states that she has complained of a sore throat and has refused to drink or take medications to bring her fever down.

A. Explain the physiologic mechanisms of fever generation.
B. Are the warm and flushed skin, rapid heart rate, and respirations consistent with this level of fever?
C. After receiving an appropriate dose of acetaminophen, the child begins to sweat, and the temperature drops to 37.2°C. Explain the physiologic mechanisms responsible for the drop in temperature.

REFERENCES

1. Murphy H.S. (2008). Inflammation. In Rubin E., Strayer D. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 37–70). Philadelphia: Lippincott Williams & Wilkins.
2. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran basic pathology* (8th ed., pp. 43–77). Philadelphia: Saunders Elsevier.
3. Schmid-Schonbein G.W. (2006). Analysis of inflammation. *Annual Review of Biochemistry* 8, 93–131.
4. Medzhitov R. (2008). Origins and physiologic roles of inflammation. *Nature Insight Review* 454(24), 428–435.

5. Szekanecz Z., Koch A.E. (2004). Vascular endothelium and immune responses: Implications for inflammation and angiogenesis. *Rheumatology Clinics of North America* 30, 97–114.
6. Steinhubl S.R. (2007). Platelets as mediators of inflammation. *Hematology/Oncology Clinics of North America* 21, 115–121.
7. Gawaz M., Langer H., May A.E. (2005). Platelets in inflammation and atherogenesis. *Journal of Clinical Investigation* 115(12), 3378–3384.
8. Kindt T.J., Osborne B.A., Goldsby R.A. (2007). *Kuby immunology* (6th ed., pp. 327–349). New York: W.H. Freeman.
9. Nathan C. (2002). Points of control in inflammation. *Nature* 420, 848–852.
10. Bachelet I., Levi-Schaffer F., Mekori Y.A. (2006). Mast cells: Not only in allergy. *Immunology and Allergy Clinics of North America* 26, 407–425.
11. Frenette P.S., Wagner D.D. (1996). Adhesion molecules—Parts I and II. *New England Journal of Medicine* 334(23), 335(1), 1526–1529, 43–45.
12. Bochner B.S. (2004). Adhesion molecules as therapeutic targets. *Immunology Clinics of North America* 24, 615–630.
13. Stein D.M. Nombela-Arrieta C. (2005). Chemokine control of lymphocyte trafficking: A general review. *Immunology* 116, 1–12.
14. Underhill D.M., Ozinsky A. (2002). Phagocytosis of microbes. *Annual Review of Microbiology* 20, 825–852.
15. Simmons D.L., Botting R.M., Hla T. (2004). Cyclooxygenase isoenzymes: The biology of prostaglandin synthesis and inhibition. *Pharmacological Reviews* 56(3), 387–437.
16. Barnes P.J. (2006). How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *British Journal of Pharmacology* 14B, 245–254.
17. Covington M.B. (2004). Omega-3 fatty acids. *American Family Physician* 70(1), 133–140.
18. Harper C.R., Jacobson T.A. (2005). Usefulness of omega-3 fatty acids and prevention of coronary heart disease. *American Journal of Cardiology* 96, 1521–1529.
19. Gossain A., Gamelli R.L. (2005). A primer on cytokines. *Journal of Burn Care and Rehabilitation* 26, 7–12.
20. Charo I., Ransohoff R.M. (2006). The many roles of chemokines and chemokine receptors in inflammation. *New England Journal of Medicine* 354(6), 610–621.
21. Serhan C.N., Savill J. (2005). Resolution of inflammation: The beginning programs the end. *Nature Immunology* 6(12), 1191–1197.
22. Serham C.N., Brain S.D., Buckley C.D., et al. (2007). Resolution of inflammation: State of the art, definitions and terms. *FASEB Journal* 21, 325–332.
23. Schottenfeld D., Beebe-Dimmer J. (2006). Chronic inflammation: A common and important factor in the pathogenesis of neoplasia. *CA: A Cancer Journal for Clinicians* 56, 69–83.
24. Mantovani A., Paola A., Sica A., et al. (2008). Cancer-related inflammation. *Nature* 454(24), 436–444.
25. Nathan C. (2008). Epidemic inflammation: Pondering obesity. *Molecular Medicine* 7(8), 485–492.
26. Chaduk J., Wiececk A. (2006). Adipose tissue, inflammation and endothelial dysfunction. *Pharmacological Reports* 59(Suppl), 81–88.
27. Greenberg A.S., Obin M.S. (2006). Obesity and the role of adipose tissue in inflammation and metabolism. *American Journal of Clinical Nutrition* 83(Suppl), 461S–465S.
28. Ridker P.M. (2005). C-reactive protein, inflammation, and cardiovascular disease. *Current Issues in Cardiology* 32(3), 384–386.
29. Ridker P.M. (2001). High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in primary prevention of cardiovascular disease. *Circulation* 103, 1813–1818.
30. Pearson T.A., Mensah G.A., Alexander R.W., et al. (2003). Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107, 499–511.
31. Hotchiss R.S., Karl I.E. (2003). The pathophysiology and treatment of sepsis. *New England Journal of Medicine* 348(2), 138–150.
32. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 889–901). Philadelphia: Elsevier Saunders.
33. Wenger C.B. (2003). The regulation of body temperature. In Rhoades R.A., Tanner G.A. *Medical physiology* (2nd ed., pp. 527–550). Philadelphia: Lippincott Williams & Wilkins.
34. Roth J., Rummel C., Barth S.W., et al. (2006). Molecular aspects of fever and hyperthermia. *Neurologic Clinics of North America* 24, 421–439.
35. Blatteis C.M. (2006). Endotoxic fever: New concepts of its regulation suggest new approaches to its management. *Pharmacology & Therapeutics* 111, 194–223.
36. Holtclaw B.J. (2003). Thermoregulation. In Carrieri-Kohlman V., Lindsay A.M., West C.M. (Eds.), *Pathophysiological phenomena in nursing: Human responses to illness* (3rd ed., pp. 15–35). Philadelphia: Saunders.
37. Saper C.B., Breder C.D. (1994). The neurologic basis of fever. *New England Journal of Medicine* 330, 1880–1886.
38. Dinarello C.A., Gatti S., Bartfai T. (1999). Fever: Links with an ancient receptor. *Current Biology* 9, R147–R150.
39. Blatteis C.M., Li S., Li Z., et al. (2005). Cytokines, PGE_2, and endotoxic fever: A re-assessment. *Prostaglandins and Other Lipid Mediators* 76, 1–18.
40. Rodbard D. (1981). The role of regional temperature in the pathogenesis of disease. *New England Journal of Medicine* 305, 808–814.
41. Cunha B.A. (1996). The clinical significance of fever patterns. *Infectious Disease Clinics of North America* 10, 33–43.
42. McGee Z.A., Gorby G.L. (1987). The diagnostic value of fever patterns. *Hospital Practice* 22(10), 103–110.
43. Champi C., Gaffney-Yocum P.A. (1999). Managing febrile seizures in children. *Nurse Practitioner* 24(10), 28–30, 34–35.
44. Cunha B.A. (2007). Fever of unknown origin: Clinical overview of and classic and current concepts. *Infectious Disease Clinics of North America* 21, 867–915.
45. Powell K.R. (2004). Fever. In Behrman R.E., Kliegman R.M., Nelson H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 838–846). Philadelphia: Saunders.
46. Ishimine P. (2006). Fever without source in children 0 to 36 months of age. *Pediatric Clinics of North America* 53, 167–194.
47. ACEP Clinical Policy Committee and Clinical Policies Subcommittee on Pediatric Care. (2003). Clinical policy for children less than 3 years presenting to the emergency department with fever. *Annals of Emergency Medicine* 42(4), 530–545.
48. Baraff, L.J. (2003). Clinical policy for children less than 3 years presenting to the emergency department with fever [Editorial]. *Annals of Emergency Medicine* 42(4), 546–549.
49. Castle S.C., Norman D.C., Yeh M., et al. (1991). Fever response in elderly nursing home residents: Are the older truly colder? *Journal of the American Geriatric Society* 39(9), 853–857.
50. Woolery W.A., Franco, F.R. (2004). Fever of unknown origin: Keys to determining the etiology in older patients. *Geriatrics* 59(10), 41–45.
51. Norman D.C., Wong M.G., Yoshikawa T.T. (2007). Fever of unknown origin in older persons. *Infectious Disease Clinics of North America* 21, 937–945.
52. Castle S.C., Yeh M., Toledo S., et al. (1993). Lowering the temperature criterion improves detection of infections in nursing home residents. *Aging Immunology and Infectious Disea*se 4, 67–76.
53. Yoshikawa T.T., Norman D.C. (1998). Fever in the elderly. *Infectious Medici*ne 15, 704–706, 708.

Cell Proliferation and Tissue Regeneration
Cell Proliferation Versus Differentiation
The Cell Cycle
Proliferative Capacity of Tissues
Stem Cells
Influence of Growth Factors
Extracellular Matrix and Cell–Matrix Interactions
Healing by Connective Tissue Repair
Phases of Repair
Angiogenesis and Ingrowth of Granulation Tissue
Emigration of Fibroblasts and Deposition of Extracellular Matrix
Maturation and Remodeling of the Fibrous Tissue
Cutaneous Wound Healing
Healing by Primary and Secondary Intention
Phases of Healing
Factors That Affect Wound Healing
Nutritional Status
Blood Flow and Oxygen Delivery
Impaired Inflammatory and Immune Responses
Infection, Wound Separation, and Foreign Bodies
Wound Healing in the Elderly

Chapter 4

Cell Proliferation and Tissue Regeneration and Repair

Tissue repair, which overlaps the inflammatory process that was discussed in Chapter 3, refers to the restoration of tissue structure and function after an injury. Tissue repair can take the form of regeneration, in which injured parenchymal cells are replaced with cells of the same type, sometimes leaving no residual trace of previous injury, or it can take the form of replacement by connective (fibrous) tissue, which leads to scar formation or fibrosis in organs such as the liver or lung. For many types of common injuries, both regeneration and connective tissue replacement contribute to tissue repair. This chapter is divided into two parts: the first discusses cell proliferation and regeneration, the cell cycle, the role of stem cells, growth factors, and the extracellular matrix in tissue renewal. The second focuses on connective tissue repair, cutaneous wound healing, factors that affect wound healing, and the effect of aging on wound healing.

Cell Proliferation and Tissue Regeneration

Tissue repair involves the proliferation of various cells, and close interactions between cells and the extracellular matrix (ECM). Body organs and tissues are composed of two types of structures: parenchymal and stromal. The *parenchymal tissues* contain the functioning cells of an organ or body part. The *stromal tissues* consist of the supporting connective tissues, blood vessels, fibroblasts, nerve fibers, and extracellular matrix.

Cell Proliferation Versus Differentiation

Cell proliferation refers to the process of increasing cell numbers by mitotic division and *cell differentiation,* the process whereby a cell becomes more specialized in terms of structure and function.[1,2] Stem cells are undifferentiated cells that have the capacity to generate multiple cell

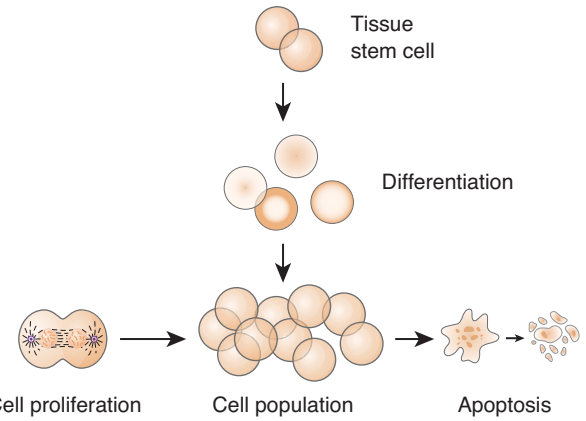


FIGURE 4-1. In normal tissues, the size of the cell population is determined by a balance of cell proliferation, death by apoptosis, and emergence of newly differentiated cells from stem cells.

types (to be discussed). In normal tissue the size of the cell population is determined by a balance of cell proliferation, death by apoptosis (see Chapter 2), and emergence of newly differentiated cells from stem cells[2] (Fig. 4-1). Several cell types proliferate during tissue repair including remnants of injured parenchymal tissue cells, vascular endothelial cells, and fibroblasts. The proliferation of these cell types is driven by proteins called *growth factors*. The production of growth factors and the ability of these cells to respond and expand in sufficient numbers are important determinants of the repair process.

All of the different cell types of the body originate from a single cell—the fertilized ovum. As the embryonic cells increase in number, they engage in a process called *differentiation* that facilitates the development of all the different cells and organs of the body. The process of differentiation is regulated by a combination of internal processes involving the expression of specific genes and external stimuli provided by neighboring cells, the ECM, and a variety of growth factors. The process of differentiation occurs in orderly steps, with each progressive step being exchanged for a loss of ability to develop different cell characteristics. As a cell becomes more highly specialized, the stimuli that are able to induce mitosis become more limited. Neurons, which are highly specialized cells, lose their ability to proliferate once development of the nervous system is complete. In other, less specialized tissues, such as the skin and mucosal lining of the gastrointestinal tract, a high degree of cell renewal continues throughout life. Even in these continuously renewing cell populations, the more specialized cells are unable to divide. These cell populations rely on *progenitor* or *parent cells* of the same lineage that have not yet differentiated to the extent that they have lost their ability to divide. Progenitor cells are sufficiently differentiated so that their daughter cells are limited to the same cell line, but they have not reached the point of differentiation that precludes the potential for active proliferation.

Cell Proliferation and Growth

- Tissue growth and repair involve cell proliferation, differentiation, and apoptosis.
- Cell proliferation is the process whereby tissues acquire new or replacement cells through mitotic cell division.
- Cell differentiation is the orderly process in which proliferating cells are transformed into different and more specialized cell types. It determines the microscopic characteristics of the cell, its functions, and its life span. Cells that are fully differentiated often have reduced rates of proliferation.
- Apoptosis is a form of programmed cell death that eliminates senescent and some types of injured cells (e.g., those with DNA damage or hydrogen peroxide–induced injury).

The Cell Cycle

In order to understand the normal physiologic (as in tissue repair) and pathologic (as in cancer) cell proliferation, it is important to learn about the cell cycle. Full regeneration or repair cannot occur without replacing cells lost through disease or injury through the cell cycle. The cell cycle is an orderly sequence of events that occur as a cell duplicates its genetic contents and divides. During the cell cycle, the duplicated chromosomes are appropriately aligned for distribution between two genetically identical daughter cells.

The cell cycle is divided into four distinct phases referred to as G_1, *S*, G_2, and *M*. Gap 1 (G_1) is the postmitotic phase during which deoxyribonucleic acid (DNA) synthesis ceases while ribonucleic acid (RNA) and protein synthesis and cell growth take place.[1–4] During the *S phase,* DNA synthesis occurs, giving rise to two separate sets of chromosomes, one for each daughter cell. G_2 is the premitotic phase and is similar to G_1 in that DNA synthesis ceases while RNA and protein synthesis continue. Collectively, G_1, S, and G_2 are referred to as *interphase*. The *M phase* is the phase of nuclear division, or mitosis, and cytokinesis. Continually dividing cells, such as the stratified squamous epithelium of the skin, continue to cycle from one mitotic division to the next. When environmental conditions are adverse, such as nutrient or growth factor unavailability, or cells become terminally differentiated (i.e., highly specialized), cells may exit the cell cycle, becoming mitotically quiescent and residing in a special resting state known as G_0. Cells in G_0 may reenter the cell cycle in response to extracellular nutrients, growth factors, hormones, and other signals such as blood loss or tissue injury that trigger cell renewal.[5] Highly specialized and terminally differentiated cells, such as neurons, may permanently stay in G_0.

Within the cell cycle are checkpoints where pauses or arrests can be made if the specific events in the phases of the cell cycle have not been completed. There are also opportunities for ensuring the accuracy of DNA replication. These DNA damage checkpoints allow for any defects to be edited and repaired, thereby ensuring that

each daughter cell receives a full complement of genetic information, identical to that of the parent cell.[1–3]

The *cyclins* are a family of proteins that control the entry and progression of cells through the cell cycle.[1–4] Cyclins bind to (thereby activating) proteins called *cyclin-dependent kinases* (CDKs). Kinases are enzymes that phosphorylate proteins. The CDKs phosphorylate specific target proteins and are expressed continuously during the cell cycle but in an inactive form, whereas the cyclins are synthesized during specific phases of the cell cycle and then degraded once their task is completed. Different arrangements of cyclins and CDKs are associated with each stage of the cell cycle. For example, cyclin B and CDK1 control the transition from G_2 to M. As the cell moves into G_2, cyclin B is synthesized and binds to CDK1. The cyclin B–CDK1 complex then directs the events leading to mitosis, including DNA replication and assembly of the mitotic spindle. Although each phase of the cell cycle is monitored carefully, the transition from G_2 to M is believed to be one of the most important checkpoints in the cell cycle. In addition to the synthesis and degradation of the cyclins, the cyclin–CDK complexes are regulated by the binding of CDK inhibitors. The CDK inhibitors are particularly important in regulating cell cycle checkpoints during which mistakes in DNA replication are repaired. The recent recognition that the cell cycle can be reactivated by removing CDK inhibitors in quiescent and nonproliferating cells has the potential implications for tissue repair and cell replacement therapy.[4]

Proliferative Capacity of Tissues

The capacity for regeneration varies with the tissue and cell type. Body tissues are divided into three types dependent on the ability of their parenchymal cells to undergo regeneration: (1) continuously dividing, (2) stable, and (3) permanent tissues.[1,2]

Continuously dividing or *labile* tissues are those in which the cells continue to divide and replicate throughout life, replacing cells that are continually being destroyed. They include the surface epithelial cells of the skin, oral cavity, vagina, and cervix; the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; the transitional epithelium of the urinary tract; and bone marrow cells. These tissues can readily regenerate after injury as long as a pool of stem cells is preserved. Bleeding, for example, stimulates the rapid proliferation of replacement cells by the blood-forming progenitor cells of the bone marrow.

Stable tissues contain cells that normally stop dividing when growth ceases. Cells in these tissues remain quiescent in the G_0 stage of the cell cycle. However, these cells are capable of undergoing regeneration when confronted with an appropriate stimulus and are thus capable of reconstituting the tissue of origin. Stable cells constitute the parenchyma of solid organs such as the liver and kidney. They also include smooth muscle cells, vascular endothelial cells, and fibroblasts, the proliferation of which is particularly important to wound healing. With the exception of the liver, stable cells have only limited replicative capacity.

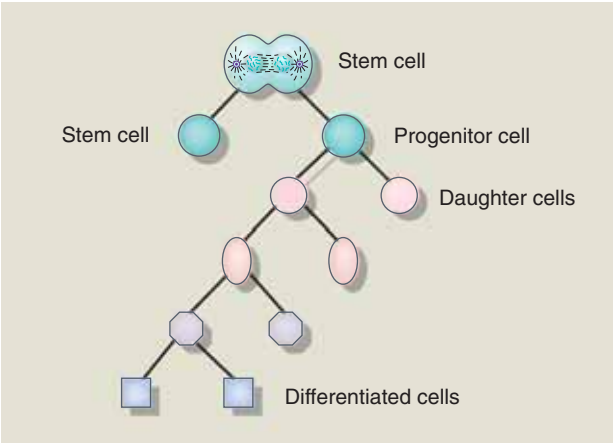


FIGURE 4-2. Mechanisms of stem cell-mediated cell replacement. Division of a stem cell with an unlimited potential for proliferation results in one daughter cell, which retains the characteristics of a stem cell, and a second daughter cell that differentiates into a progenitor or parent cell, with limited potential for differentiation and proliferation. As the daughter cells of the progenitor cell proliferate they become more differentiated, until they reach the stage where they are fully differentiated

The cells in *permanent* tissues do not proliferate. The cells in these tissues are considered to be terminally differentiated and do not undergo mitotic division in postnatal life. The permanent cells include nerve cells, skeletal muscle cells, and cardiac muscle cells. These cells do not normally regenerate; once destroyed, they are replaced with fibrous scar tissue that lacks the functional characteristics of the destroyed tissue.

Stem Cells

Another type of tissue cell, called a *stem cell,* remains incompletely differentiated throughout life.[1,2,5] In most continuously dividing tissues, the mature cells are terminally differentiated and short lived. As mature cells die the tissue is replenished by the differentiation of cells generated from stem cells. Stem cells are reserve cells that remain quiescent until there is a need for cell replenishment, in which case they divide, producing other stem cells and cells that can carry out the functions of the differentiated cell. When a stem cell divides, one daughter cell retains the stem cell characteristics, and the other daughter cell becomes a progenitor cell that proceeds through a process that leads to terminal differentiation (Fig. 4-2).

Stem cells are characterized by three important properties: self-renewal, asymmetric replication, and differential potential.[1,2] *Self-renewal* means that the stem cells can undergo numerous mitotic divisions while maintaining an undifferentiated state. *Asymmetric replication* means that after each cell division, some progeny of the stem cell enter a differentiation pathway, while others remain undifferentiated, retaining their self-renewal capacity. The progeny of each progenitor cell follows a more restricted genetic program, with the differentiating cells undergoing multiple mitotic divisions in the process of becoming a more mature cell type, and with each generation of cells

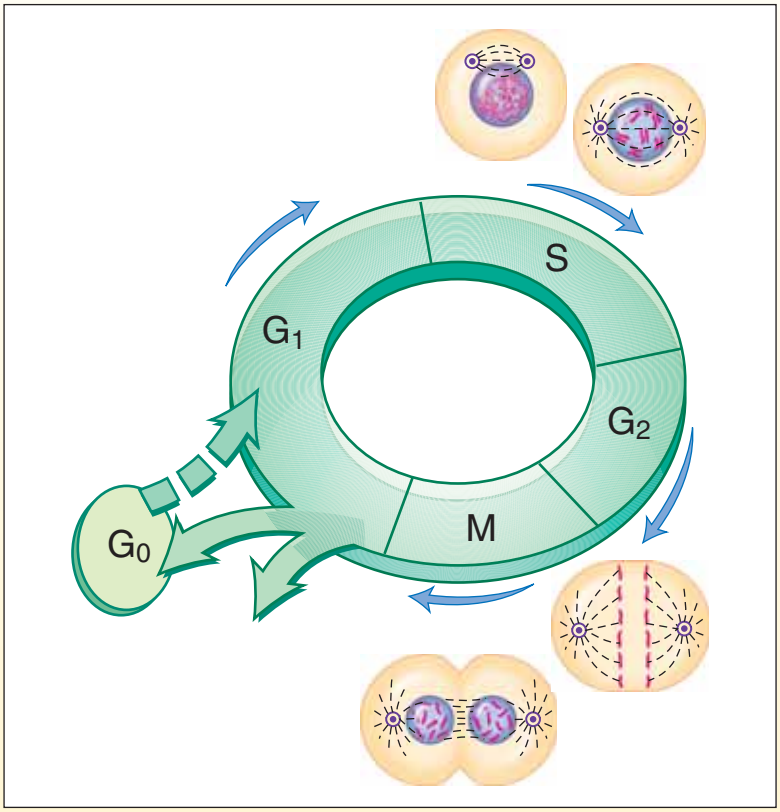
(*text continues on page 78*)

UNDERSTANDING → The Cell Cycle

A cell reproduces by performing an orderly sequence of events called the *cell cycle.* The cell cycle is divided into four phases of unequal duration that include the (1) synthesis (S) and mitosis (M) phases that are separated by (2) two gaps (G_1 and G_2). There is also (3) a dormant phase (G_0) during which the cell may leave the cell cycle. Movement through each of these phases is mediated at (4) specific checkpoints that are controlled by specific enzymes and proteins called *cyclins.*

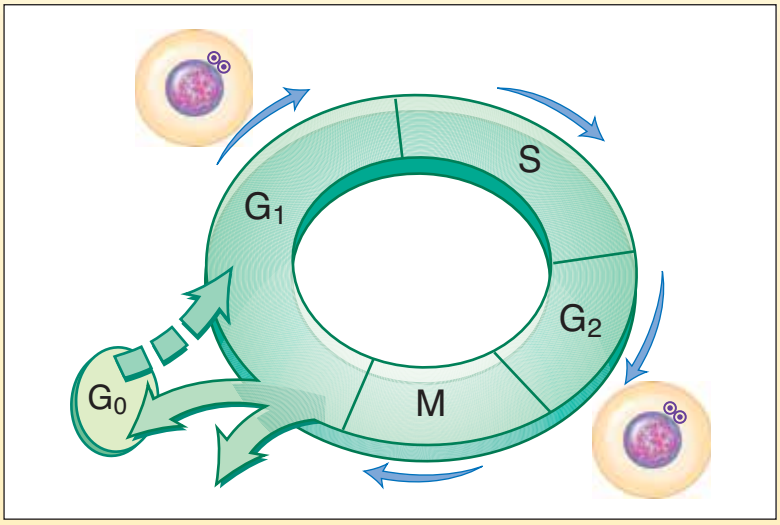
1

Synthesis and Mitosis. Synthesis (S) and mitosis (M) represent the two major phases of the cell cycle. The S phase, which takes about 10 to 12 hours, is the period of DNA synthesis and replication of the chromosomes. The M phase, which usually takes less than an hour, involves formation of the mitotic spindle and cell division with formation of two daughter cells.



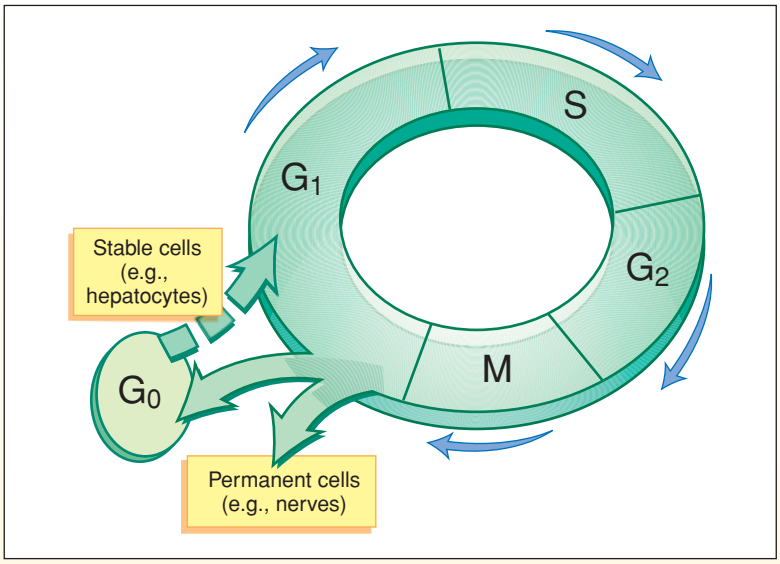
2

Gaps 1 and 2. Because most cells require time to grow and double their mass of proteins and organelles, extra gaps (G) are inserted into the cell cycle. G_1 is the stage during which the cell is starting to prepare for DNA replication and mitosis through protein synthesis and an increase in organelle and cytoskeletal elements. G_2 is the premitotic phase. During this phase, enzymes and other proteins needed for cell division are synthesized and moved to their proper sites.



3

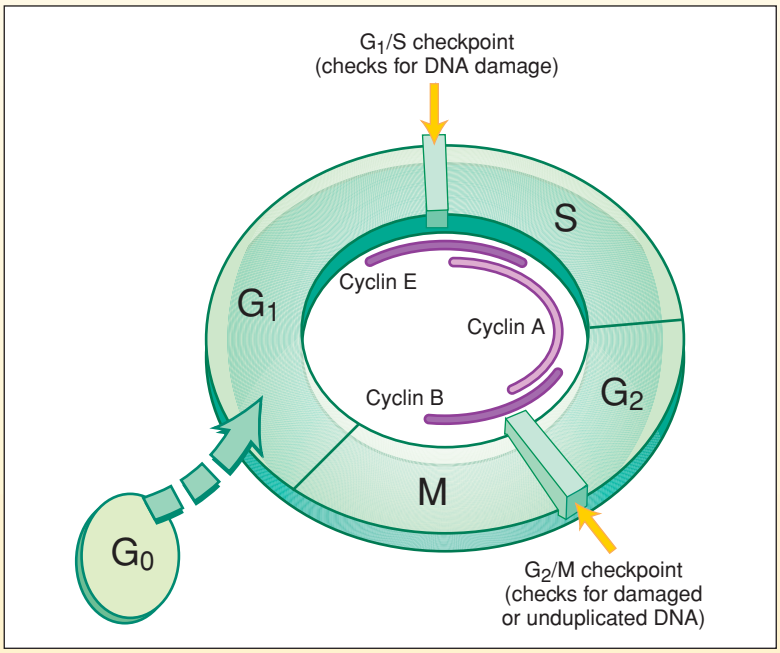
Gap 0. G_0 is the stage after mitosis during which a cell may leave the cell cycle and either remain in a state of inactivity or reenter the cell cycle at another time. Labile cells, such as blood cells and those that line the gastrointestinal tract, do not enter G_0 but continue cycling. Stable cells, such as hepatocytes, enter G_0 after mitosis but can reenter the cell cycle when stimulated by the loss of other cells. Permanent cells, such as neurons that become terminally differentiated after mitosis, leave the cell cycle and are no longer capable of cell renewal.



4

Checkpoints and Cyclins. In most cells there are several checkpoints in the cell cycle, at which time the cycle can be arrested if previous events have not been completed. For example, the G_1/S checkpoint monitors whether the DNA in the chromosomes is damaged by radiation or chemicals, and the G_2/M checkpoint prevents entry into mitosis if DNA replication is not complete.

The cyclins are a family of proteins that control entry and progression of cells through the cell cycle. They function by activating proteins called *cyclin-dependent kinases* (CDKs). Different combinations of cyclins and CDKs are associated with each stage of the cell cycle. In addition to the synthesis and degradation of the cyclins, the cyclin–CDK complexes are regulated by the binding of CDK inhibitors. The CDK inhibitors are particularly important in regulating cell cycle checkpoints during which mistakes in DNA replication are repaired.



becoming more specialized. In this way, a single stem cell can give rise to the many cells needed for normal tissue repair or blood cell production.

The term *potency* is used to define the differentiation potential of stem cells. *Totipotent stem cells* are those produced by a fertilized ovum. The first few cells produced after fertilization are totipotent and can differentiate into embryonic and extraembryonic cells. Totipotent stem cells give rise to *pluripotent stem cells* that can differentiate into the three germ layers of the embryo. *Multipotent stem cell*s are cells such as hematopoietic stem cells that give rise to a family of cells, including the red blood cells and all the various types of leukocytes. Finally, *unipotent stem cells* produce only one cell type but retain the property of self-renewal.

In recent years, it has become useful to categorize stem cells into two basic categories: embryonic and adult stem cells.[1,2,5] *Embryonic stem cells* are pluripotent cells derived from the inner cell mass of the blastocyst stage of the embryo. These pluripotent stem cells have the capacity to generate multiple cell lines. As mentioned earlier, unipotential stem cells are normally present in proliferative tissues and generate cell lineages specific to that tissue. It is now recognized, however, that stem cells with the capacity to generate multiple lineages are present in the bone marrow and several other tissues of adult individuals. These cells are called *adult stem cells* or *tissue stem cells*. Whether adult stem cells have the similar differentiation capacity as embryonic stem cells remains the subject of current debate and research.[2] Thus far, bone marrow stem cells have been shown to have very broad differentiation capabilities, being able to generate fat, cartilage, bone, endothelium, and muscle.

The new field of medicine called *regenerative medicine* has as its main goal the regeneration and restoration of damaged organs using embryonic and adult stem cells.[2,6,7] One of the most exciting prospects in this area is a type of stem cell therapy known as therapeutic cloning. Other potential therapeutic strategies that use stem cells involve the transplantation of stem cells into areas of injury, mobilization of stem cells from the bone marrow into injured tissues, and use of stem cell culture systems to produce large amounts of differentiated stem cells for transplantation into injured tissue.

Influence of Growth Factors

Cell proliferation can be triggered by chemical mediators including growth factors, hormones, and cytokines.[1,2,8,9] The term *growth factor* is generally applied to small hormonelike proteins that increase cell size and cell division.[2] In addition to cell proliferation, most growth factors have other effects. They assist in regulating the inflammatory process; serve as chemoattractants for neutrophils, monocytes (macrophages), fibroblasts, keratinocytes, and epithelial cells; stimulate angiogenesis; and contribute to the generation of the ECM. Some growth factors stimulate the proliferation of some cells and inhibit the cycling of other cells. In fact, a growth factor can have opposite effects on the same cell depending on its changing concentration during the healing process.

Many of the growth factors are produced by leukocytes recruited to the site of injury or activated at the site by the inflammatory process. Other growth factors are produced by parenchymal cells or stromal cells in response to injury or loss. Growth factors are named for their tissue of origin (e.g., platelet-derived growth factor [PDGF], fibroblast growth factor [FGF]), their biologic activity (e.g., transforming growth factor [TGF]), or the cells on which they act (e.g., vascular endothelial growth factor [VEGF]). The sources and functions of selected growth factors are described in Table 4-1.

The signaling pathways for the growth factors are similar to those of other cellular receptors that recognize extracellular ligands. The binding of a growth factor to its receptor triggers a series of events by which extracellular signals are transmitted into the cell, leading to the stimulation or inhibition of gene expression. These genes typically have several functions—they relieve blocks on cell cycle progression (thus promoting cell proliferation), they prevent apoptosis, and they enhance synthesis of cellular proteins in preparation for mitosis. Signaling may occur in the cell producing the growth factor (autocrine signaling), in cells in the immediate vicinity of the cell releasing the growth factor (paracrine signaling), or in distant target cells through growth factors that are released into the bloodstream (endocrine signaling). There is continued interest in developing growth factors as a means of increasing cell proliferation and enhancing wound healing as well as developing strategies to block growth factor signaling pathways that could be used to inhibit malignant cell proliferation in cancer.

Extracellular Matrix and Cell–Matrix Interactions

The understanding of tissue regeneration and repair has expanded over the past several decades to encompass the complex environment of the ECM. The ECM occurs in two basic forms: (1) the *basement membrane,* which surrounds epithelial, endothelial, and smooth muscle cells, and (2) the *interstitial matrix,* which is present in the spaces between cells in connective tissue and between the epithelium and supporting cells of blood vessels.

The ECM is secreted locally and assembles into a network of spaces surrounding tissue cells (see Chapter 1). There are three basic components of the ECM: fibrous structural proteins (e.g., collagen and elastin fibers), water-hydrated gels (e.g., proteoglycans and hyaluronic acid) that permit resilience and lubrication, and adhesive glycoproteins (e.g., fibronectin, laminin) that connect the matrix elements to one another and to cells[1–3,10] (Fig. 4-3). Integrins are a family of transmembrane glycoproteins that are the main cellular receptors for the ECM components such as fibronectin and laminin. They bind to many ECM components, initiating signaling cascades that affect cell proliferation and differentiation. Fibroblasts, which reside in close proximity to collagen fibers, are responsible for the synthesis of collagen, elastic, and reticular fibers, and complex carbohydrates in the ground substance.

TABLE 4-1 Growth Factors Involved in Tissue Regeneration and Wound Healing

Growth Factor	Source	Function
Epidermal growth factor (EGF)	Activated macrophages, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; simulates keratinocyte migration and granulation tissue formation
Transforming growth factor-α (TGF-α)	Activated macrophages, T lymphocytes, keratinocytes, and many other cells	Similar to EGF; stimulates replication of hepatocytes and many epithelial cells
Transforming growth factor-β (TGF-β)	Platelets, macrophages, T lymphocytes, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; stimulates angiogenesis and production of fibrous tissue; inhibits proteinase production and keratinocyte proliferation
Vascular endothelial cell growth factor (VEGF)	Mesenchymal cells	Increases vascular permeability; mitogenic for endothelial cells of blood vessels
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; stimulates production of proteinases, fibronectin, and hyaluronic acid; stimulates angiogenesis and wound remodeling
Fibroblast growth factor (FGF)	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts, and many other tissues	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates angiogenesis, wound contraction, and matrix deposition
Keratinocyte growth factor (KGF)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

The ECM provides turgor to soft tissue and rigidity to bone; it supplies the substratum for cell adhesion; it is involved in the regulation of growth, movement, and differentiation of the cells surrounding it; and it provides for the storage and presentation of regulatory molecules that control the repair process. The ECM also provides the scaffolding for tissue renewal. Although the cells in many tissues are capable of regeneration, injury does not always result in restoration of normal structure unless the ECM is intact. The integrity of the underlying basement membrane, in particular, is critical to the regeneration of tissue.

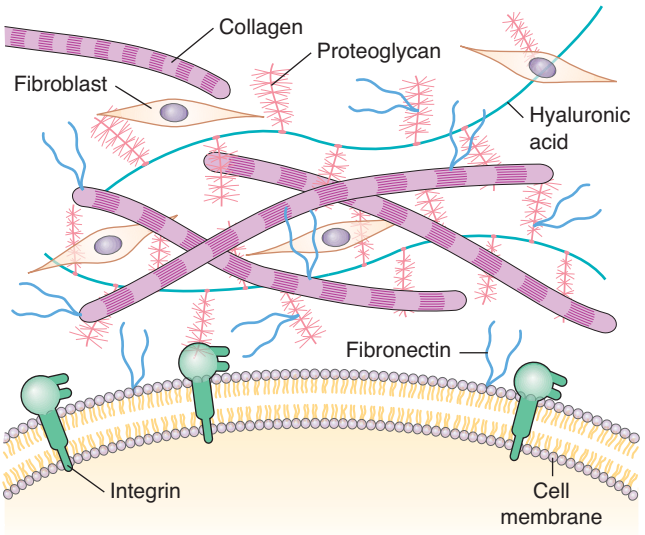


FIGURE 4-3. Components of the extracellular matrix and supporting connective tissue components involved in tissue repair.

When the basement membrane is disrupted, cells proliferate in a haphazard way, resulting in disorganized and nonfunctional tissues.

Critical to the process of wound healing is the transition from granulation tissue to scar tissue, which involves shifts in the composition of the ECM. In the transitional process, the ECM components are degraded by proteases (enzymes) that are secreted locally by a variety of cells (fibroblasts, macrophages, neutrophils, synovial cells, and epithelial cells). Some of the proteases, such as the collagenases, are highly specific, cleaving particular proteins at a small number of sites.[11] This allows for the structural integrity of the ECM to be retained while cell migration occurs. Because of their potential to produce havoc in tissues, the actions of the proteases are tightly controlled. They are typically elaborated in an inactive form that must first be activated by certain chemicals or proteases that are likely to be present at the site of injury, and they are rapidly inactivated by tissue inhibitors. Recent research has focused on the unregulated action of the proteases in disorders such as cartilage matrix breakdown in arthritis and neuroinflammation in multiple sclerosis.[11]

In summary, body organs and tissues are composed of two types of structures: parenchymal and the supporting connective tissues. The process of tissue repair involves the proliferation of functioning parenchymal cells of an organ or body part and the supporting connective tissues and extracellular matrix. Cell proliferation refers to the process of increasing cell numbers by mitotic division

and *cell differentiation*, the process whereby a cell becomes more specialized in terms of structure and function. The periodic biochemical and structural events occurring during cell proliferation are called the *cell cycle*. The entry into and the progression through the various stages of the cell cycle are tightly regulated by cyclins, CDKs, and CDK inhibitors.

Body cells are divided into types according to their ability to regenerate: labile cells, such as the epithelial cells of the skin and gastrointestinal tract, which continue to regenerate throughout life; stable cells, such as those in the liver, which normally do not divide but are capable of regeneration when confronted with an appropriate stimulus; and permanent or fixed cells, such as nerve cells, which are unable to regenerate. Continuously dividing labile tissues contain stem cells. Stem cells are undifferentiated cells that have the capacity to generate multiple cell types.

Tissue regeneration and repair is mediated by growth factors that increase cell size and cell division, stimulates cell migration and differentiation, and enhances the production of specialized ECM proteins by cells such as fibroblasts. In addition to growth factor activity, tissue repair also depends on interactions between the cells and ECM components. Among its many functions, the ECM aids in the regulation of cell proliferation, movement, and differentiation during wound repair by providing a foundation for cell adhesion and a reservoir for growth factors.

Tissue Repair and Wound Healing

- Injured tissues can be repaired by regeneration of the injured tissue cells with cells of the same tissue or parenchymal type, or by connective repair processes in which scar tissue is used to effect healing.
- Regeneration is limited to tissues with cells that are able to undergo mitosis.
- Connective tissue repair occurs by primary or secondary intention and involves the inflammatory phase, the proliferative phase, and the remodeling phase of the wound healing process.
- Wound healing is impaired by conditions that diminish blood flow and oxygen delivery, restrict nutrients and other materials needed for healing, and depress the inflammatory and immune responses; and by infection, wound separation, and the presence of foreign bodies.

Healing by Connective Tissue Repair

The primary objective of the healing process is to fill the gap created by tissue destruction and to restore the structural continuity of the injured part. *Tissue regeneration* refers to the restoration of injured tissue to its normal structure and function by proliferation of adjacent surviving cells. As discussed earlier in the chapter, cell renewal occurs continuously in labile tissues such as gastrointestinal epithelium and skin. Regeneration can also occur in parenchymal organs with stable cell populations but, with the exception of the liver, is usually a limited process. It should be pointed out that extensive regeneration can occur only if the residual tissue is structurally and functionally intact. If the tissue is damaged by infection or inflammation, regeneration is incomplete and is accompanied by scarring.

When regeneration cannot occur, healing by replacement with a connective (fibrous) tissue occurs, a process that terminates in *scar formation*. The term *fibrosis* is often used to describe the extensive deposition of collagen that occurs in organs such as the lungs, liver, or kidney as a result of chronic inflammation or injury.[2] If fibrosis occurs in any tissue space occupied by an inflammatory exudate, it is called *organization*.[1,2] It occurs in serous cavities such as the pericardium and peritoneal cavities. In the pericardium, fibroblasts secrete and organize collagen within fibrous strands, thereby binding the visceral and parietal pericardia together[1] (Fig. 4-4). Fibrous strands sometimes become organized within the peritoneal cavity following abdominal surgery or peritonitis. These strands of collagen, called *adhesions*, can trap loops of bowel and cause obstruction.[1]

Phases of Repair

Repair by connective tissue deposition can be divided into three phases: (1) angiogenesis and ingrowth of granulation tissue, (2) emigration of fibroblasts and deposition of extracellular matrix, and (3) maturation and reorganization of the fibrous tissue (remodeling).[1,2,12–14] It usually begins within 24 hours of injury and is evidenced by the migration of fibroblasts and the induction of fibroblast and endothelial cell proliferation.[2] By 3 to 5 days, a special type of tissue called *granulation tissue* is apparent.[2] The granulation tissue then progressively accumulates connective tissue, eventually resulting in the formation of a scar, which is then remodeled.

Angiogenesis and Ingrowth of Granulation Tissue

Granulation tissue is a glistening red, moist connective tissue that fills the injured area while necrotic debris is removed[1,2] (Fig. 4-5). It is composed of newly formed capillaries, proliferating fibroblasts, and residual inflammatory cells. The development of granulation tissue involves the growth of new capillaries (angiogenesis). Angiogenesis is a tightly regulated process that includes vasodilation in response to nitric oxide and increased permeability of preexisting vessels, migration of endothelial cells to the site of tissue injury, and proliferation of endothelial cells, followed by fusion and remodeling of the endothelial cells into capillary tubes.

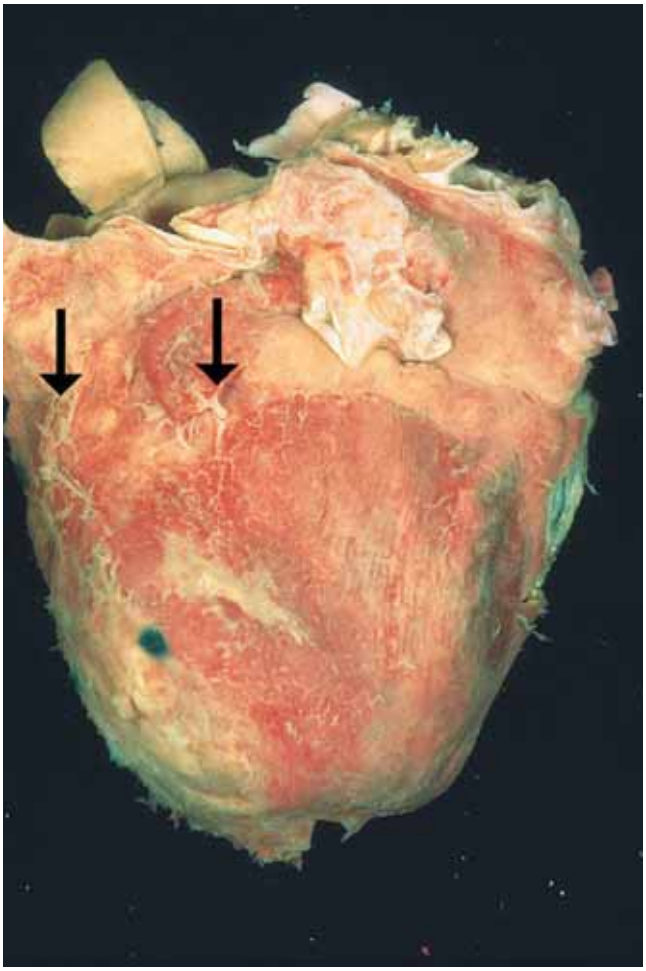


FIGURE 4-4. Organized strands of collagen (*arrows*) in constrictive pericarditis. (From Sephal G.C., Woodward S.C. [2008]. Rubin R., Strayer D.S. [Eds]. *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 81]. Philadelphia: Lippincott Williams & Wilkins.)

Several growth factors induce angiogenesis, but the most important are VEGF and basic FGF-2. In angiogenesis, VEGF stimulates both proliferation and motility of endothelial cells, thus initiating the process of capillary sprouting. FGF-2 participates in angiogenesis mainly by stimulating the proliferation of endothelial cells. New blood vessels during angiogenesis are leaky because of incompletely formed interendothelial cell junctions and because VEGF increases vascular permeability. This leakiness explains the edematous appearance of granulation tissue and accounts in part for the swelling that may persist in healing wounds long after the acute inflammation has subsided.

Emigration of Fibroblasts and Deposition of Extracellular Matrix

Scar formation builds on the granulation tissue framework of new vessels and loose ECM. The process occurs in two phases: emigration and proliferation of fibroblasts into the site of injury, and deposition of extracellular matrix by these cells. The recruitment and proliferation of fibroblasts is mediated by a number of growth factors including FGF-2 and TGF-β. These growth factors are released from endothelial cells and from inflammatory cells that are present at the site of injury.

As healing progresses, the number of proliferating fibroblasts and formation of new vessels decrease and there is increased synthesis and deposition of collagen. Collagen synthesis is important to the development of strength in the healing wound site. Ultimately, the granulation tissue scaffolding evolves into a scar composed of largely inactive spindle-shaped fibroblasts, dense collagen fibers, fragments of elastic tissue, and other ECM components. As the scar matures, vascular degeneration eventually transforms the highly vascular granulation tissue into a pale, largely avascular scar.

Maturation and Remodeling of the Fibrous Tissue

The transition from granulation to scar tissue involves shifts in the modification and remodeling of the ECM. The outcome of the repair process is, in part, a balance between previously discussed ECM synthesis and degradation. The rate of collagen synthesis diminishes until it

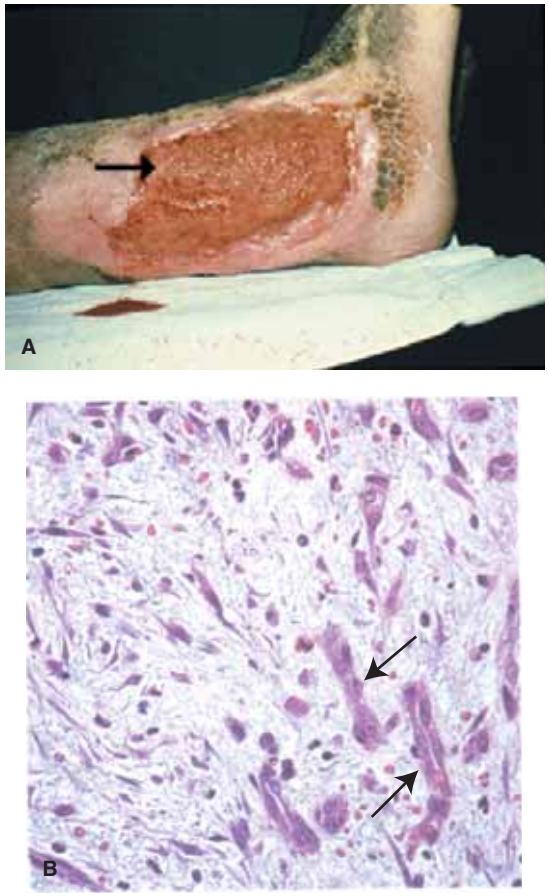


FIGURE 4-5. Granulation tissue. **(A)** A foot covered by granulation tissue. **(B)** A photomicrograph of granulation tissue shows the thin-walled vessels (*arrows*) embedded in a loose connective tissue matrix containing mesenchymal cells and occasional inflammatory cells. (From Sephal G.C., Woodward S.C. [2008]. Rubin R., Strayer D.S. [Eds]. *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 83]. Philadelphia: Lippincott Williams & Wilkins.)

reaches equilibrium with collagen degradation. The degradation of collagen and other ECM proteins is achieved through a family of metalloproteinases, which require zinc for their activity. The metalloproteinases are produced by a variety of cell types (fibroblasts, macrophages, synovial cells, and some epithelial cells), and their synthesis and secretion are regulated by growth factors, cytokines, and other agents. Their synthesis may be suppressed pharmacologically by corticosteroids. Because of their potential to raise havoc in tissues, the activity of the metalloproteinases is tightly controlled. They are typically released as inactive precursors that require activation. This is accomplished by certain chemicals or proteases likely to be present only at sites of injury.

Cutaneous Wound Healing

Thus far, the discussion in this chapter has focused on general aspects of tissue repair and wound healing. The following section specifically addresses healing of skin wounds (cutaneous wound healing). This is a process that involves both epithelial cell regeneration and formation of connective tissue scar formation and thus is illustrative of general principles that apply to all tissues.

Healing by Primary and Secondary Intention

Depending on the extent of tissue loss, wound closure and healing occur by primary or secondary intention (Fig. 4-6). A sutured surgical incision is an example of healing by *primary intention*. Larger wounds (e.g., burns and large surface wounds) that have a greater loss of tissue and contamination heal by *secondary intention*. Healing by secondary intention is slower than healing by primary intention and results in the formation of larger amounts of scar tissue. A wound that might otherwise have healed by primary intention may become infected and heal by secondary intention.

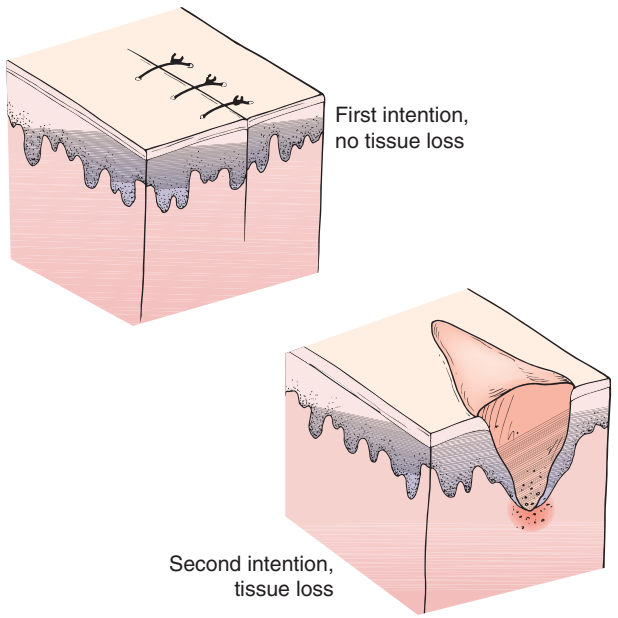


FIGURE 4-6. Healing by primary and secondary intention.

Phases of Healing

Cutaneous wound healing is commonly divided into three phases: (1) the inflammatory phase, (2) the proliferative phase, and (3) the maturational or remodeling phase.[1,2,15–18] The duration of the phases is fairly predictable in wounds healing by primary intention. In wounds healing by secondary intention, the process depends on the extent of injury and the healing environment.

Inflammatory Phase. The inflammatory phase of wound healing begins at the time of injury and is a critical period because it prepares the wound environment for healing. It includes hemostasis (see Chapter 12) and the vascular and cellular phases of inflammation. Hemostatic processes are activated immediately at the time of injury. There is constriction of injured blood vessels and initiation of blood clotting by way of platelet activation and aggregation. After a brief period of constriction, these same vessels dilate and capillaries increase their permeability, allowing plasma and blood components to leak into the injured area. In small surface wounds, the clot loses fluid and becomes a hard, desiccated scab that protects the area.

The cellular phase of inflammation follows and is evidenced by the migration of phagocytic white blood cells that digest and remove invading organisms, fibrin, extracellular debris, and other foreign matter. The neutrophils are the first cells to arrive and are usually gone by day 3 or 4. They ingest bacteria and cellular debris. Within 24 to 48 hours, macrophages, which are larger phagocytic cells, enter the wound area and remain for an extended period. These cells, arising from blood monocytes, are essential to the healing process. Their functions include phagocytosis and release of growth factors that stimulate epithelial cell growth, angiogenesis, and attraction of fibroblasts. When a large defect occurs in deeper tissues, neutrophils and macrophages are required to remove the debris and facilitate wound closure. Although a wound may heal in the absence of neutrophils, it cannot heal in the absence of macrophages.

Proliferative Phase. The proliferative phase of healing usually begins within 2 to 3 days of injury and may last as long as 3 weeks in wounds healing by primary intention. The primary processes during this time focus on the building of new tissue to fill the wound space. The key cell during this phase is the *fibroblast*. The fibroblast is a connective tissue cell that synthesizes and secretes collagen and other intercellular elements needed for wound healing. Fibroblasts also produce a family of growth factors that induce angiogenesis and endothelial cell proliferation and migration.

As early as 24 to 48 hours after injury, fibroblasts and vascular endothelial cells begin proliferating to form the granulation tissue that serves as the foundation for scar tissue development. This tissue is fragile and bleeds easily because of the numerous, newly developed capillary buds.

Wounds that heal by secondary intention have more necrotic debris and exudate that must be removed, and they involve larger amounts of granulation tissue. The newly formed blood vessels are leaky and allow plasma proteins and white blood cells to leak into the tissues.

The final component of the proliferative phase is epithelialization, which is the migration, proliferation, and differentiation of the epithelial cells at the wound edges to form a new surface layer that is similar to that destroyed by the injury. In wounds that heal by primary intention, these epidermal cells proliferate and seal the wound within 24 to 48 hours. Because epithelial cell migration requires a moist vascular wound surface and is impeded by a dry or necrotic wound surface, epithelialization is delayed in open wounds until a bed of granulation tissue has formed. When a scab has formed on the wound, the epithelial cells migrate between it and the underlying viable tissue; when a significant portion of the wound has been covered with epithelial tissue, the scab lifts off.

At times, excessive granulation tissue, sometimes referred to as *proud flesh*, may form and extend above the edges of the wound, preventing reepithelialization from taking place. Surgical removal or chemical cauterization of the defect allows healing to proceed.

As the proliferative phase progresses, there is continued accumulation of collagen and proliferation of fibroblasts. Collagen synthesis reaches a peak within 5 to 7 days and continues for several weeks, depending on wound size. By the second week, the white blood cells have largely left the area, the edema has diminished, and the wound begins to blanch as the small blood vessels become thrombosed and degenerate.

Remodeling Phase. The third phase of wound healing, the remodeling process, begins approximately 3 weeks after injury and can continue for 6 months or longer, depending on the extent of the wound. As the term implies, there is continued remodeling of scar tissue by simultaneous synthesis of collagen by fibroblasts and lysis by collagenase enzymes. As a result of these two processes, the architecture of the scar becomes reoriented to increase the tensile strength of the wound.

Most wounds do not regain the full tensile strength of unwounded skin after healing is completed. Carefully sutured wounds immediately after surgery have approximately 70% of the strength of unwounded skin, largely because of the placement of the sutures. This allows persons to move about freely after surgery without fear of wound separation. When the sutures are removed, usually at the end of the first week, wound strength is approximately 10%. It increases rapidly over the next 4 weeks and then slows, reaching a plateau of approximately 70% to 80% of the tensile strength of unwounded skin at the end of 3 months.[2] An injury that heals by secondary intention undergoes wound contraction during the proliferative and remodeling phases. As a result, the scar that forms is considerably smaller than the original wound. Cosmetically, this may be desirable because it reduces the size of the visible defect. However, contraction of scar tissue over joints and other body structures tends to limit movement and cause deformities. As a result of loss of elasticity, scar tissue that is stretched fails to return to its original length.

FIGURE 4-7. Keloid. A light-skinned black woman with keloid that developed after ear piercing. (From Sephel G.C., Woodward S.C. [2007]. Repair, regeneration, and fibrosis. In Rubin R., Strayer D.E. [Eds]. *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 97]. Philadelphia: Lippincott Williams & Wilkins.)

An abnormality in healing by scar tissue repair is *keloid* formation. Keloids are benign tumorlike masses caused by excess production of scar tissue (Fig. 4-7). They tend to develop in genetically predisposed individuals and are more common in African Americans, Asian Americans, Latin Americans, and other ethnic groups with darker pigmented skin.[19] The majority of keloids lead to considerable cosmetic defects, but can grow to sufficient size to become symptomatic by causing deformity or limiting joint mobility. Thus far the majority of keloid research has focused on growth factors and signaling pathways, but unfortunately, reliable preventative or treatment measures have yet to be established.

Factors That Affect Wound Healing

Many local and systemic factors influence wound healing. Although there are many factors that impair healing, science has found only a few ways to hasten the normal process of wound repair. Among the causes of impaired wound healing are malnutrition; impaired blood flow and oxygen delivery; impaired inflammatory and immune responses; infection, wound separation, and foreign bodies; and age effects.[20]

Nutritional Status

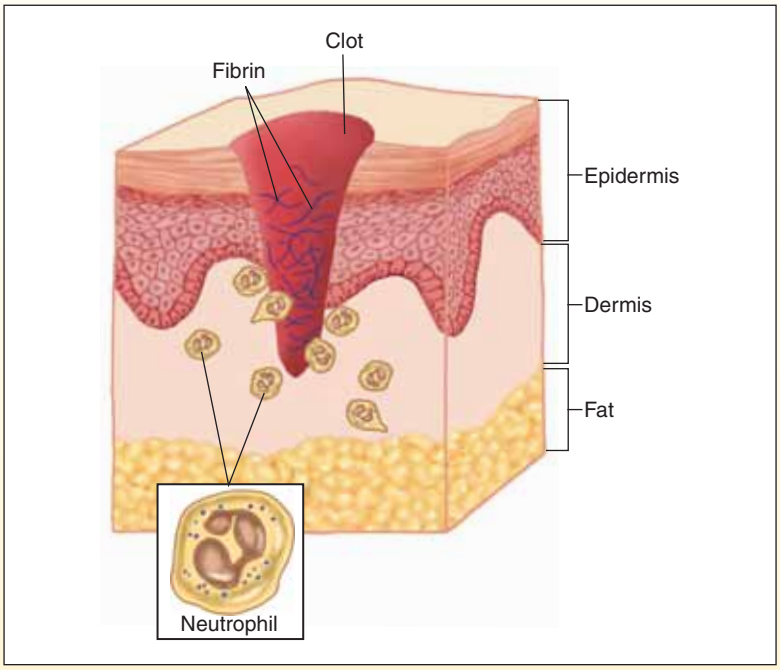
Successful wound healing depends in part on adequate stores of proteins, carbohydrates, fats, vitamins, and minerals. It is well recognized that malnutrition slows the healing process, causing wounds to heal inadequately or incompletely.[18,21,22] Protein deficiencies prolong the inflammatory phase of healing and impair fibroblast proliferation, collagen and protein matrix synthesis, angiogenesis, and wound remodeling. Carbohydrates are

UNDERSTANDING → Wound Healing

Wound healing involves the restoration of the integrity of injured tissue. The healing of skin wounds, which are commonly used to illustrate the general principles of wound healing, is generally divided into three phases: (1) the inflammatory phase, (2) the proliferative phase, and (3) the wound contraction and remodeling phase. Each of these phases is mediated through cytokines and growth factors.

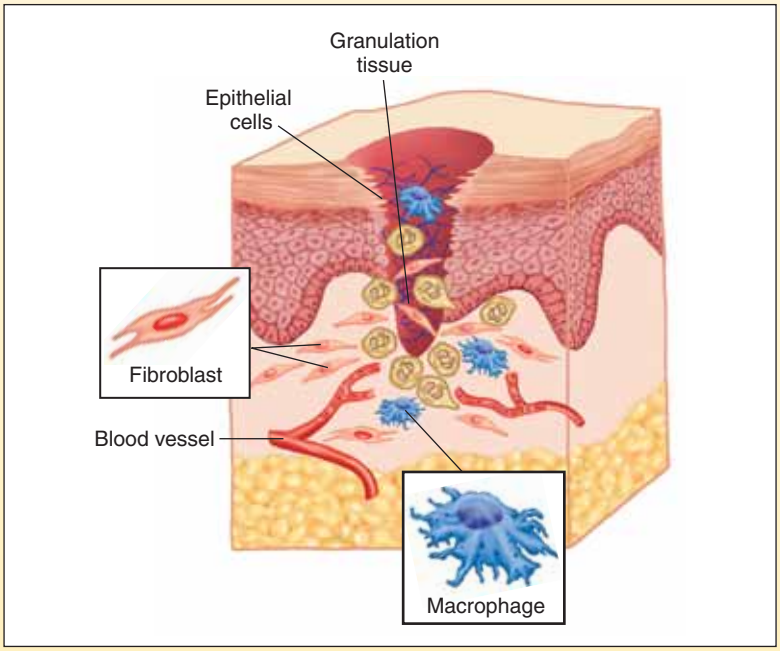
1

Inflammatory Phase. The inflammatory phase begins at the time of injury with the formation of a blood clot and the migration of phagocytic white blood cells into the wound site. The first cells to arrive, the neutrophils, ingest and remove bacteria and cellular debris. After 24 hours, the neutrophils are joined by macrophages, which continue to ingest cellular debris and play an essential role in the production of growth factors for the proliferative phase.



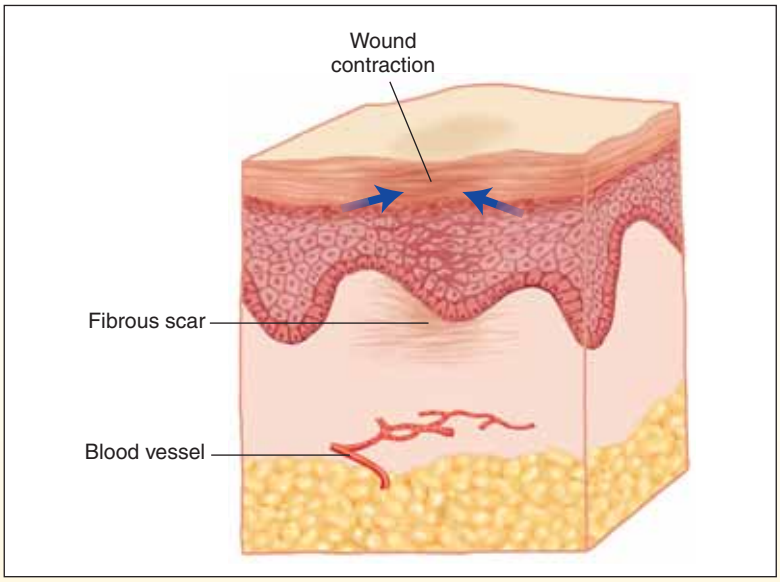
2

Proliferative Phase. The primary processes during this phase focus on the building of new tissue to fill the wound space. The key cell during this phase is the *fibroblast*, a connective tissue cell that synthesizes and secretes the collagen, proteoglycans, and glycoproteins needed for wound healing. Fibroblasts also produce a family of growth factors that induce angiogenesis (growth of new blood vessels) and endothelial cell proliferation and migration. The final component of the proliferative phase is epithelialization, during which epithelial cells at the wound edges proliferate to form a new surface layer that is similar to that which was destroyed by the injury.



3

Wound Contraction and Remodeling Phase. This phase begins approximately 3 weeks after injury with the development of the fibrous scar, and can continue for 6 months or longer, depending on the extent of the wound. During this phase, there is a decrease in vascularity and continued remodeling of scar tissue by simultaneous synthesis of collagen by fibroblasts and lysis by collagenase enzymes. As a result of these two processes, the architecture of the scar becomes reoriented to increase its tensile strength, and the scar shrinks so it is less visible.



needed as an energy source for white blood cells. Carbohydrates also have a protein-sparing effect and help to prevent the use of amino acids for fuel when they are needed for the healing process. Fats are essential constituents of cell membranes and are needed for the synthesis of new cells.

Although most vitamins are essential cofactors for the daily functions of the body, vitamins A and C play an essential role in the healing process. Vitamin C is needed for collagen synthesis. In vitamin C deficiency, improper sequencing of amino acids occurs, proper linking of amino acids does not take place, the by-products of collagen synthesis are not removed from the cell, new wounds do not heal properly, and old wounds may fall apart. Administration of vitamin C rapidly restores the healing process to normal. Vitamin A functions in stimulating and supporting epithelialization, capillary formation, and collagen synthesis. Vitamin A also has been shown to counteract the anti-inflammatory effects of corticosteroid drugs and can be used to reverse these effects in persons who are on chronic steroid therapy. The B vitamins are important cofactors in enzymatic reactions that contribute to the wound-healing process. All are water soluble, and with the exception of vitamin B_{12}, which is stored in the liver, almost all must be replaced daily. Vitamin K plays an indirect role in wound healing by preventing bleeding disorders that contribute to hematoma formation and subsequent infection.

The role of minerals in wound healing is less clearly defined. The macrominerals, including sodium, potassium, calcium, and phosphorus, as well as the microminerals such as copper and zinc, must be present for normal cell function. Zinc is a cofactor in a variety of enzyme systems responsible for cell proliferation. In animal studies, zinc has been found to aid in reepithelialization.

Blood Flow and Oxygen Delivery

Impaired healing due to poor blood flow and wound hypoxia may occur as a result of wound conditions (e.g., swelling) or preexisting health problems.[23,24] Arterial disease and venous pathology are well-documented causes of impaired wound healing. In situations of trauma, a decrease in blood volume may cause a reduction in blood flow to injured tissues.

For healing to occur, wounds must have adequate blood flow to supply the necessary nutrients and to remove the resulting waste, local toxins, bacteria, and other debris. Molecular oxygen is required for collagen synthesis and killing of bacteria by phagocytic white blood cells. It has been shown that even a temporary lack of oxygen can result in the formation of less stable collagen.[23] Wounds in ischemic tissue become infected more frequently than wounds in well-vascularized tissue. Neutrophils and macrophages require oxygen for destruction of microorganisms that have invaded the area. Although these cells can accomplish phagocytosis in a relatively anoxic environment, they cannot digest bacteria. Oxygen also contributes to signaling systems that support wound healing. Recent research suggests that almost all cells in the wound environment are fitted with specialized enzymes to convert oxygen to reactive oxygen species (ROS).[23] These ROS function as cellular messengers that support wound healing, stimulating cytokine action, angiogenesis, cell motility, and extracellular matrix formation.

The availability of respired oxygen to wound tissues depends on vascular supply, vasomotor tone, the partial pressure of oxygen (PO_2) in arterial blood, and the diffusion distance for oxygen (see Chapter 21). The central area of a wound has the lower oxygen level, with dermal wounds ranging from 0 to 10 mm Hg centrally to 60 mm Hg in the periphery, while the PO_2 of arterial blood is approximately 100 mm Hg.[23] Transcutaneous oxygen sensors are available for use in measuring wound oxygenation. From a therapeutic standpoint oxygen can be given systemically or administered locally using a topical device. Although topical oxygen therapy is not likely to diffuse into the deeper tissues, it does have the advantage of oxygenating superficial areas of the wound not supported by intact vasculature. Hyperbaric oxygen therapy delivers 100% oxygen at two to three times the normal atmospheric pressure at sea level.[25] The goal of hyperbaric oxygen therapy is to increase oxygen delivery to tissues by increasing the partial pressure of oxygen dissolved in the plasma. Hyperbaric oxygen is currently reserved for the treatment of problem wounds in which hypoxia and infection interfere with healing.

Impaired Inflammatory and Immune Responses

Inflammatory and immune mechanisms function in wound healing. Inflammation is essential to the first phase of wound healing, and immune mechanisms prevent infections that impair wound healing. Among the conditions that impair inflammation and immune function are disorders of phagocytic function, diabetes mellitus, and therapeutic administration of corticosteroid drugs.

Phagocytic disorders may be divided into extrinsic and intrinsic defects. Extrinsic disorders are those that impair attraction of phagocytic cells to the wound site, prevent engulfment of bacteria and foreign agents by the phagocytic cells (i.e., opsonization), or cause suppression of the total number of phagocytic cells (e.g., immunosuppressive agents). Intrinsic phagocytic disorders are the result of enzymatic deficiencies in the metabolic pathway for destroying the ingested bacteria by the phagocytic cell. The intrinsic phagocytic disorders include chronic granulomatous disease, an X-linked inherited disease in which there is a deficiency of myeloperoxidase and nicotinamide adenine dinucleotide peroxidase (NADPH)–dependent oxidase enzyme. Deficiencies of these compounds prevent generation of hydrogen superoxide and hydrogen peroxide needed for killing bacteria.

Wound healing is a problem in persons with diabetes mellitus, particularly those who have poorly controlled blood glucose levels.[26] Studies have shown delayed wound healing, poor collagen formation, and poor tensile strength in diabetic animals. Of particular importance is the effect of hyperglycemia on phagocytic function. Neutrophils, for example, have diminished chemotactic and phagocytic function, including engulfment and intracellular killing of bacteria, when exposed to altered glucose levels. Small blood vessel disease is also common among persons with diabetes, impairing the delivery of inflammatory cells, oxygen, and nutrients to the wound site.

The therapeutic administration of corticosteroid drugs decreases the inflammatory process and may delay the healing process. These hormones decrease capillary permeability during the early stages of inflammation, impair the phagocytic property of the leukocytes, and inhibit fibroblast proliferation and function.

Infection, Wound Separation, and Foreign Bodies

Wound contamination, wound separation, and foreign bodies delay wound healing. Infection impairs all dimensions of wound healing.[27] It prolongs the inflammatory phase, impairs the formation of granulation tissue, and inhibits proliferation of fibroblasts and deposition of collagen fibers. All wounds are contaminated at the time of injury. Although body defenses can handle the invasion of microorganisms at the time of wounding, badly contaminated wounds can overwhelm host defenses. Trauma and existing impairment of host defenses also can contribute to the development of wound infections.

Approximation of the wound edges (i.e., suturing of an incision type of wound) greatly enhances healing and prevents infection. Epithelialization of a wound with closely approximated edges occurs within 1 to 2 days. Large, gaping wounds tend to heal more slowly because it is often impossible to effect wound closure with this type of wound. Mechanical factors such as increased local pressure or torsion can cause wounds to pull apart, or *dehisce*. Foreign bodies tend to invite bacterial contamination and delay healing. Fragments of wood, steel, glass, and other compounds may have entered the wound at the site of injury and can be difficult to locate when the wound is treated. Sutures are also foreign bodies, and although needed for the closure of surgical wounds, they are an impediment to healing. This is why sutures are removed as soon as possible after surgery. Wound infections are of special concern in persons with implantation of foreign bodies such as orthopedic devices (e.g., pins, stabilization devices), cardiac pacemakers, and shunt catheters. These infections are difficult to treat and may require removal of the device.

Wound Healing in the Elderly

A number of structural and functional changes have been reported to occur in aging skin, including a decrease in dermal thickness, a decline in collagen content, and a loss of elasticity.[28,29] The observed changes in skin that occurs with aging are complicated by the effects of sun exposure. Since the effects of sun exposure are cumulative, older persons show more changes in skin structure.

Wound healing is thought to be progressively impaired with aging. The elderly have alterations in wound-healing phases including hemostasis and inflammation, cell proliferation, and resolution.[29] Keratinocytes, fibroblasts, and vascular endothelial cells display a reduced rate of proliferation. There is also a reported decrease in angiogenesis

and collagen synthesis, impaired wound contraction, and slower reepithelialization of open wounds. Although wound healing may be delayed, most wounds heal, even in the debilitated elderly patient undergoing major surgical procedures.

The elderly are more vulnerable to chronic wounds, chiefly pressure, diabetic, and ischemic ulcers, than younger persons, and these wounds heal more slowly. However, these wounds are more likely due to other disorders such as immobility, diabetes mellitus, or vascular disease, rather than aging.

In summary, the primary objective of the healing process is to fill the gap created by tissue destruction and to restore the structural continuity of the injured part. When regeneration cannot restore injured tissue to normal, healing by replacement with fibrous connective (scar) tissue replacement occurs. Repair by connective tissue deposition occurs in sequential phases that include angiogenesis and ingrowth of granulation tissue, emigration of fibroblasts and deposition of extracellular matrix, and maturation and reorganization of the fibrous tissue.

Cutaneous wound healing occurs by primary and secondary intention and is commonly divided into three phases: the inflammatory phase, the proliferative phase, and the maturational or remodeling phase. In wounds healing by primary intention, the duration of the phases is fairly predictable. In wounds healing by secondary intention, the process depends on the extent of injury and the healing environment. Wound healing can be impaired or complicated by factors such as malnutrition; restricted blood flow and oxygen delivery; diminished inflammatory and immune responses; aging; and infection, wound separation, and the presence of foreign bodies.

REVIEW EXERCISES

1. Following a heart attack, the area of heart muscle that has undergone necrosis because of a lack of blood supply undergoes healing by replacement with scar tissue.

A. Compare the functioning of the heart muscle that has been replaced by scar tissue with that of the normal surrounding heart muscle.

2. A 35-year-old man comes in with a large abscess on his leg. He tells you he injured his leg while doing repair work on his house and he thinks there might be a wood sliver in the infected area.

A. Explain the events that participate in formation of an abscess.

B. He is told that incision and drainage of the lesion will be needed so healing can take place. Explain.

C. He is reluctant to have the procedure done and asks whether an antibiotic would work as well. Explain why antibiotics alone are usually not effective in eliminating the microorganisms contained in an abscess.

REFERENCES

1. Sephel G.C., Woodward S.C. (2008). Repair, regeneration, and fibrosis. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 71–98). Philadelphia: Lippincott Williams & Wilkins.
2. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 79–110). Philadelphia: Saunders Elsevier.
3. Alberts B., Johnson A., Lewis J., et al. (2008). *Molecular biology of the cell* (5th ed., pp. 1053–1114, 1178–1195). New York: Garland Science.
4. Pajalunga D., Maxxola A., Franchitto A., et al. (2008). The logic of cell cycle exit and reentry. *Cellular and Molecular Life Sciences* 65, 8–15.
5. Vats A., Bielby R.C., Tolley N.S., et al. (2005). Stem cells. *Lancet* 366, 592–602.
6. Körbling M., Estrov Z. (2003). Adult stems for tissue repair—A new therapeutic strategy. *New England Journal of Medicine* 349, 570–582.
7. Metcalfe A.D., Ferguson M.W.J. (2008). Skin stem cells and progenitor cells: Using regeneration as a tissue-engineering strategy. *Cellular and Molecular Life Sciences* 65, 24–32.
8. Werner S., Grose R. (2003). Regulation of wound healing by growth factors and cytokines. *Physiological Reviews* 83, 835–870.
9. Cross K.J., Mustoe T.A. (2003). Growth factors in wound healing. *Surgical Clinics of North America* 83, 531–545.
10. Daley W.P., Peters S.B., Larsen M. (2008). Extracellular matrix dynamics in development and regenerative medicine. *Journal Cell Science* 21(3), 255–264.
11. Parks W.C. (1999). Metric metalloproteinases in repair. *Wound Repair and Regeneration* 7, 423–432.
12. Whitney J.D. (2005). Overview: Acute and chronic wounds. *Nursing Clinics of North America* 40, 191–205.
13. Wei L., Dasgeb B., Phillips T., et al. (2005). Wound-healing perspectives. *Dermatology Clinics* 23, 181–192.
14. Strecker-McGraw M.K., Jones T.R., Baer D.G. (2007). Soft tissue wounds and principles of healing. *Emergency Medical Clinics of North America* 25, 1–22.
15. Singer A.J., Clark R.A.F. (1999). Cutaneous wound healing. *New England Journal of Medicine* 341(10), 738–746.
16. Monaco J.L., Lawrence W.T. (2003). Acute wound healing: An overview. *Clinical Plastic Surgery* 30, 1–12.
17. Waldrop J., Doughty D. (2000). Wound-healing physiology. In Bryant R.A. (Ed.), *Acute and chronic wounds* (2nd ed., pp. 17–35). St. Louis: Mosby.
18. Harding K.G., Morris H.L., Patel K.G. (2002). Healing chronic wounds. *British Medical Journal* 324, 160–163.
19. Butler P.D., Longaker M.T., Yang G.P. (2008). Current progress in keloid research and treatment. *Journal American College of Surgeons* 206(6), 731–741.
20. Burns J.L., Mancoll J.S., Phillips L.G. (2003). Impairments of wound healing. *Clinical Plastic Surgery* 30, 47–56.
21. Williams J.Z., Barbul A. (2003). Nutrition and wound healing. *Surgical Clinics of North America* 83, 571–596.
22. Mechanick J.I. (2004). Practical aspects of nutrition support for wound-healing patients. *American Journal of Surgery* 188(Suppl), 52S–56S.

23. Gordillo G.M., Sen Chandan K. (2003). Revisiting the essential role of oxygen in wound healing. *American Journal of Surgery* 186, 259–263.
24. Tandara A.A., Mustoe T.A. (2004). Oxygen and wound healing—More than a nutrient. *World Journal of Surgery* 28, 294–300.
25. Zamboni W.A., Browder L.K., Martinez J. (2003). Hyperbaric oxygen and wound healing. *Clinics in Plastic Surgery* 30, 67–75.
26. Greenhalgh D.G. (2003). Wound healing and diabetes mellitus. *Clinics in Plastic Surgery* 30, 37–45.
27. Hunt T.K., Hopf H.W. (1977). Wound healing and wound infection. *Surgical Clinics of North America* 77, 587–605.
28. Thomas D.R. (2001). Age-related changes in wound healing. *Drugs & Aging* 18(8), 607–620.
29. Gosain A., Pipietro L.A. (2004). Aging and wound healing. *World Journal Surgery* 28, 321–326.

Genetic Control of Cell Function
DNA Structure and Function
Double Helix and Base Pairing
Packaging of DNA
Genetic Code
DNA Repair
Genetic Variability
Mitochondrial DNA
From Genes to Proteins
RNA Structure and Function
Transcription
Translation
Regulation of Gene Expression
Chromosomes
Cell Division
Chromosome Structure
Patterns of Inheritance
Definitions
Genetic Imprinting
Mendel Laws
Pedigree
Gene Technology
Gene Mapping
The Human Genome Project
Genetic Mapping Methods
Haplotype Mapping
Recombinant DNA Technology
Gene Isolation and Cloning
Pharmaceutical Applications
DNA Fingerprinting
Gene Therapy
RNA Interference Technology

Chapter 5

Genetic Control of Cell Function and Inheritance

Our genetic information is stored in the chemical structure of *deoxyribonucleic acid* (DNA), an extremely stable macromolecule. A person's genetic complement consists of large amounts of DNA that contains within its structure the information needed to direct the function of our cells, determine our appearance and how we respond to our environment, and serve as the unit of inheritance that is passed on from generation to generation. Genes also determine our disease susceptibility and how we react to drugs.

An understanding of the role that genetics plays in the pathogenesis of disease has expanded greatly over the past century. It is now apparent that many diseases, including cancer, diabetes, and cardiovascular diseases, have a genetic component. In the case of cancer, recent genetic advances have led to new methods for early detection and more effective treatment. Advances in immunogenetics have made compatible blood transfusion and organ transplants a reality, and recombinant DNA technology has provided the methods for producing human insulin, growth hormone, and clotting factors. Perhaps the most extensive use of gene technology involved the Human Genome Project, begun in 1990 and completed in 2003, in which the entire genetic complement (the genome) has been sequenced.

This chapter includes discussions of genetic control of cell function, chromosomes, patterns of inheritance, and gene technology.

Genetic Control of Cell Function

The genetic instructions for protein synthesis are encoded in the DNA contained in the cell nucleus. Because of its stable structure, the genetic information carried in DNA can survive the many stages of cell division involved in the day-to-day process of cell renewal and tissue growth. Its stable structure also allows the information to survive the many processes of reduction division involved in gamete (i.e., ovum and sperm) formation, the fertilization process, and the mitotic cell divisions involved in the formation of a new organism from the single-celled fertilized ovum called the *zygote*.

Function of DNA in Controlling Cell Function

- The information needed for the control of cell structure and function is embedded in the genetic information encoded in the stable DNA molecule.
- Although every cell in the body contains the same genetic information, each cell type uses only a portion of the information, depending on its structure and function.
- The production of the proteins that control cell function is accomplished by (1) the transcription of the DNA code for assembly of the protein onto messenger RNA, (2) the translation of the code from messenger RNA and assembly of the protein by ribosomal RNA in the cytoplasm, and (3) the delivery of the amino acids needed for protein synthesis to ribosomal RNA by transfer RNA.

Although genes have gotten a lot of attention, it is the proteins that the genes encode that make up the majority of cellular structures and contribute to their function. Proteins are responsible for the functional diversity of cells, they perform most biologic functions, and it is at their level that many regulatory processes take place, many disease processes occur, and most drug targets are found. The term *proteome* is a relatively new term, created to define the complete set of proteins encoded by a genome. *Proteomics*, the study of the proteome, uses highly sophisticated technologic methods to examine the molecular and biochemical events in a cell.

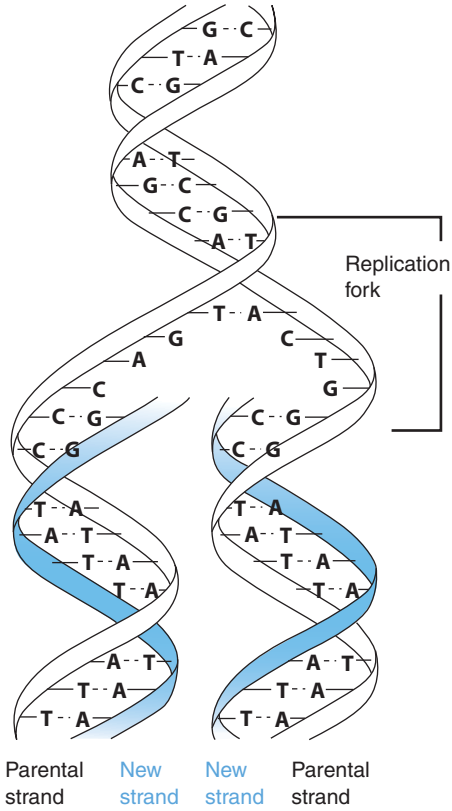


FIGURE 5-1. A replicating DNA helix. The parental strands separate at the replication fork. Each parental strand serves as a template for the synthesis of a new strand. The backbone of DNA consists of a sugar–phosphate backbone with paired pyrimidine bases (thymine [T] and cytosine [C] with their one nitrogen ring) and purine bases (adenine [A] and guanine [G] with their two nitrogen rings) projecting inward. (From Smith C. Marks, A.D., Lieberman M. [2005]. *Marks' basic medical biochemistry* [2nd ed., p. 222]. Philadelphia: Lippincott Williams & Wilkins.)

DNA Structure and Function

The DNA molecule that stores the genetic information in the nucleus is a long, double-stranded, helical structure. DNA is composed of *nucleotides*, which consist of phosphoric acid, a five-carbon sugar called *deoxyribose*, and one of four nitrogenous bases. These nitrogenous bases carry the genetic information and are divided into two groups: the *pyrimidine bases*, thymine (T) and cytosine (C), which have one nitrogen ring, and the *purine bases*, adenine (A) and guanine (G), which have two. The backbone of DNA consists of alternating groups of sugar and phosphoric acid, with the paired bases projecting inward from the sides of the sugar molecule.

Double Helix and Base Pairing

The native structure of DNA, as elucidated by James Watson and Frances Crick in 1953, is that of a spiral staircase, with the paired bases representing the steps (Fig. 5-1). A precise complementary pairing of purine and pyrimidine bases occurs in the double-stranded DNA molecule in which A is paired with T and G is paired with C. Each nucleotide in a pair is on one strand of the DNA molecule, with the bases on opposite DNA strands bound together by hydrogen bonds that are extremely stable under normal conditions. The double-stranded structure of DNA molecules allows them to replicate precisely by separation of the two strands, followed by synthesis of two new complementary strands. Similarly, the base complementary pairing allows for efficient and correct repair of damaged DNA molecules.

Several hundred to almost 1 million base pairs can represent a gene, the size being proportional to the protein product it encodes. Of the two DNA strands, only one is used in transcribing the information for the cell's protein-building machinery. The genetic information of one strand is meaningful and is used as a template for transcription; the complementary code of the other strand does not make sense and is ignored. Both strands, however, are involved in DNA duplication. Before cell division, the two strands of the helix separate and a complementary molecule is duplicated next to each original strand. Two strands become four strands. During cell division, the

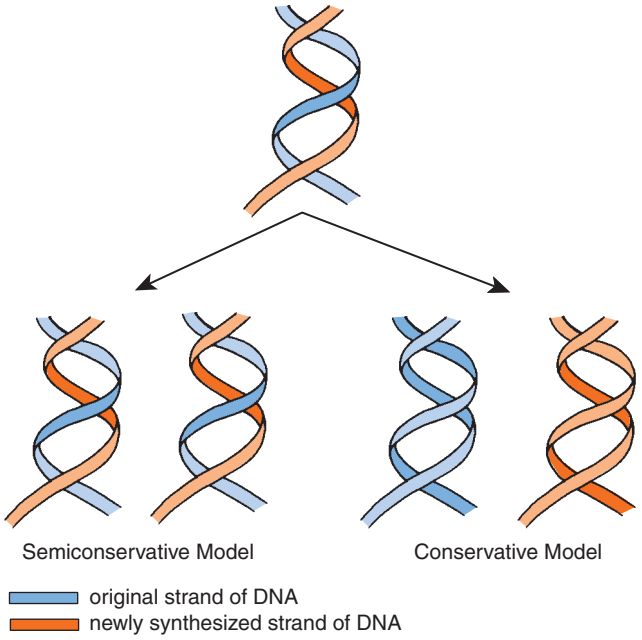


FIGURE 5-2. Semiconservative versus conservative models of DNA replication as proposed by Meselson and Stahl in 1958. In semiconservative DNA replication, the two original strands of DNA unwind and a complementary strand is formed along each original strand.

newly duplicated double-stranded molecules are separated and placed in each daughter cell by the mechanics of mitosis. As a result, each of the daughter cells again contains the meaningful strand and the complementary strand joined together as a double helix. In 1958, Meselson and Stahl characterized this replication of DNA as *semiconservative* replication, as opposed to *conservative* replication, in which the parental strands reassociate when the two strands are brought together (Fig. 5-2).

Although scientific discussion regarding the structure and functioning of a "gene" goes into explicit detail, it does not really address the question "what is a gene?" Many scientists are now in agreement that the proteins encoded by DNA know no boundaries. This means that nucleotides from one part of the genome can combine with nucleotides from other regions at extreme distances on the DNA molecule. It is also proposed that the function of some genes might be controlled by regulatory regions on other chromosomes. These and other current findings have put to rest the old hypothesis of "one gene–one protein."

Packaging of DNA

The genome or total genetic content is distributed in chromosomes. Each human somatic cell (cells other than the gametes [sperm and ovum]) has 23 pairs of different chromosomes, with one member of the pair derived from the individual's mother and the other from the father. One of the chromosome pairs consists of the sex chromosomes. Genes are arranged linearly along each chromosome. Each chromosome contains one continuous, linear DNA helix. The DNA in the longest chromosome is more than 7 cm in length. If the DNA of all 46 chromosomes were placed end to end, the total DNA would span a distance of about 2 m (more than 6 feet).

Because of their large size, the DNA double helices are packaged as a coiled structure known as *chromatin*. The DNA molecule of a chromosome exists in chromatin as a complex with a family of basic chromosomal proteins called *histones* and with a group of other less–well-characterized proteins that appear to be critical for ensuring normal chromosome behavior and appropriate gene expression. Some DNA-associated proteins form binding sites for repressor molecules and hormones that regulate genetic transcription; others may block genetic transcription by preventing access of nucleotides to the surface of the DNA molecule. The histones play a critical role in proper packaging of chromatin. They form a core, around which a segment of DNA double helix winds, like thread around a spool (Fig. 5-3). About 140 base pairs of DNA are associated with each histone core, making about two turns around the core. After a short "spacer" segment of DNA, the next core DNA complex forms, and so on, giving chromatin the appearance of beads on a string. Each complex of DNA with a histone core is called a *nucleosome,* which is the basic structural unit of chromatin. Each chromosome contains several hundred to over a million nucleosomes.

Although solving the structural problem of how to fit a huge amount of DNA into the nucleus, the chromatin fiber, when complexed with histones and packaged into various levels of compaction, makes the DNA inaccessible

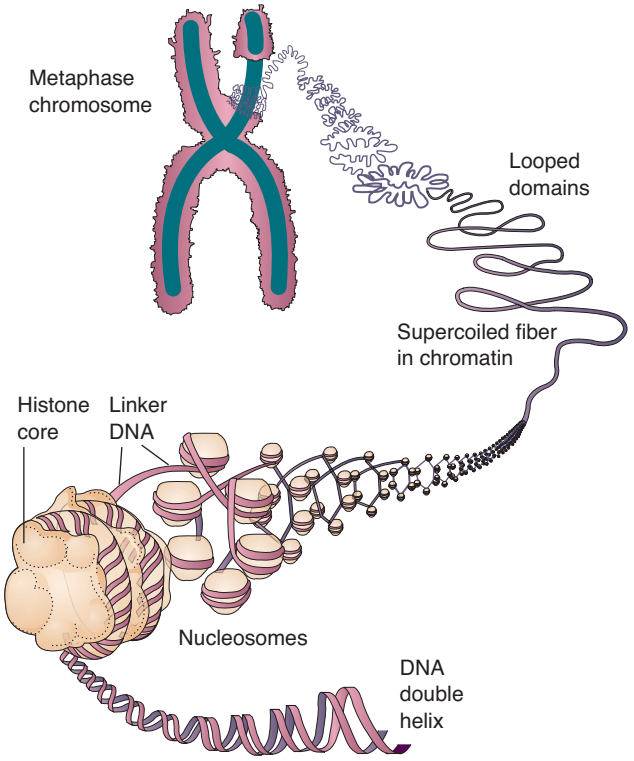


FIGURE 5-3. Increasing orders of DNA compaction in chromatin and mitotic chromosomes. (From Cormack D.H. [1993]. *Essential histology.* Philadelphia: J.B. Lippincott.)

during the processes of replication and gene expression. To accommodate these processes, chromatin must be induced to change its structure, a process called *chromatin remodeling*. Several chemical interactions are now known to affect this process. One of these involves the acetylation of a histone amino acid group that is linked to opening of the chromatin fiber and gene activation. Another important chemical modification involves the methylation of histone amino acids, which is correlated with gene inactivation.

Genetic Code

Four bases—guanine, adenine, cytosine, and thymine—make up the alphabet of the genetic code. A sequence of three of these bases forms the fundamental triplet code used in transmitting the genetic information needed for protein synthesis. This triplet code is called a *codon* (Table 5-1). The molecular link between these two related types of information (the DNA code of genes and the amino acid code of proteins) is ribonucleic acid (RNA), in which uracil (U) replaces thymine as one of the pyrimidine bases. An example is the nucleotide sequence GCU (guanine, cytosine, and uracil), which is the triplet RNA code for the amino acid alanine. The genetic code is a universal language used by most living cells (i.e., the code for the amino acid alanine is the same in a bacterium, a plant, and a human being). *Stop codes*, which signal the end of a protein molecule, are also present. Mathematically, the four bases can be arranged in 64 different combinations. Sixty-one of the triplets correspond to particular amino acids, and three are stop signals. Only 20 amino acids are used in protein synthesis in humans. Several triplets code for the same amino acid; therefore, the genetic code is said to be *redundant* or *degenerate*. For example, AUG is a part of the initiation or start signal as well as the codon for the amino acid methionine. Codons that specify the same amino acid are called *synonyms*. Synonyms usually have the same first two bases but differ in the third base.

DNA Repair

Rarely, accidental errors in duplication of DNA occur. These errors are called *mutations*. Mutations result from the substitution of one base pair for another, the loss or addition of one or more base pairs, or rearrangements of base pairs. Many of these mutations occur spontaneously, whereas others occur because of environmental agents, chemicals, and radiation. Mutations may arise in somatic cells or in germ cells. Only those DNA changes that occur in germ cells can be inherited.

Considering the millions of base pairs that must be duplicated in each cell division, it is not surprising that random changes in replication occur. Most of these defects are corrected by DNA repair mechanisms. Several repair mechanisms exist, and each depends on specific enzymes called *endonucleases* that recognize local distortions of the DNA helix, cleave the abnormal chain, and remove the distorted region. The gap is then filled when the correct deoxyribonucleotides, created by a DNA polymerase using the intact complementary strand as a template, are added to the cleaved DNA. The newly synthesized end of the segment is then joined to the remainder of the DNA strand by a DNA ligase. The normal regulation of these gene repair mechanisms is under the control of DNA repair genes. Loss of these gene functions renders the DNA susceptible to accumulation of

TABLE 5-1 Triplet Codes for Amino Acids

Amino Acid	RNA Codons					
Alanine	GCU	GCC	GCA	GCG		
Arginine	CGU	CGC	CGA	CGG	AGA	AGG
Asparagine	AAU	AAC				
Aspartic acid	GAU	GAC				
Cysteine	UGU	UGC				
Glutamic acid	GAA	GAG				
Glutamine	CAA	CAG				
Glycine	GGU	GGC	GGA	GGG		
Histidine	CAU	CAC				
Isoleucine	AUU	AUC	AUA			
Leucine	CUU	CUC	CUA	CUG	UUA	UUG
Lysine	AAA	AAG				
Methionine	AUG					
Phenylalanine	UUU	UUC				
Proline	CCU	CCC	CCA	CCG		
Serine	UCU	UCC	UCA	UCG	AGC	AGU
Threonine	ACU	ACC	ACA	ACG		
Tryptophan	UGG					
Tyrosine	UAU	UAC				
Valine	GUU	GUC	GUA	GUG		
Start (CI)	AUG					
Stop (CT)	UAA	UAG	UGA			

mutations; when these affect proto-oncogenes or tumor-suppressor genes, cancer may result (see Chapter 7).

Genetic Variability

As the Human Genome Project was progressing, it became evident that the human genome sequence is almost exactly (99.9%) the same in all people. It is the small variation (0.1%) in gene sequence (termed a *haplotype*) that is thought to account for the individual differences in physical traits, behaviors, and disease susceptibility. These variations are sometimes referred to as *polymorphisms* (from the existence of more than one morphologic or body form in a population). An international effort has been organized to develop a map (HapMap) of these variations with the intent of providing a link between genetic variations and common complex diseases such as cancer, heart disease, diabetes, and some forms of mental disease (discussed in the section under gene technology).

Mitochondrial DNA

In addition to nuclear DNA, part of the DNA of a cell resides in the mitochondria. Mitochondrial DNA (mtDNA) is inherited from the mother by her offspring (i.e., matrilineal inheritance). It is a double-stranded closed circle containing 37 genes, 24 of which are needed for mitochondrial DNA translation and 13 of which are needed for oxidative metabolism. Replication of mtDNA depends on enzymes encoded by nuclear DNA. Thus, the protein-synthesizing apparatus and molecular components for oxidative metabolism are jointly derived from nuclear and mitochondrial genes. Genetic disorders of mitochondrial DNA, although rare, commonly affect tissues such as those of the neuromuscular system that have a high requirement for oxidative metabolism (see Chapter 6).

From Genes to Proteins

Although DNA determines the type of biochemical product that is needed by the cell and directs its synthesis, it is RNA, through the process of transcription and translation, that is responsible for the actual assembly of the products.

RNA Structure and Function

RNA, like DNA, is a large molecule made up of a long string of nucleotides. However, it differs from DNA in three aspects of its structure. First, RNA is a single-stranded rather than a double-stranded molecule. Second, the sugar in each nucleotide of RNA is ribose instead of deoxyribose. Third, the pyrimidine base thymine in DNA is replaced by uracil in RNA.

Cells contain three types of RNA: messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). All three types of RNA are synthesized in the nucleus by RNA polymerase enzymes and then moved into the cytoplasm, where protein synthesis takes place. *Messenger RNA* carries the instructions for protein synthesis, obtained from the DNA molecule, into the cytoplasm. *Transfer RNA* reads the instructions and delivers the appropriate amino acids to the ribosome, where *ribosomal RNA* translates the instructions and provides the machinery needed for protein synthesis.

Messenger RNA. Messenger RNA is the template for protein synthesis. It is a long molecule containing several hundred to several thousand nucleotides. Each group of three nucleotides forms a codon that is exactly complementary to a nucleotide triplet of the DNA molecule. Messenger RNA is formed by a process called *transcription*. In this process, the weak hydrogen bonds of DNA are broken so that free RNA nucleotides can pair with their exposed DNA counterparts on the meaningful strand of the DNA molecule (see Fig. 5-1). As with the base pairing of the DNA strands, complementary RNA bases pair with the DNA bases.

Ribosomal RNA. The ribosome is the physical structure in the cytoplasm where protein synthesis takes place. Ribosomal RNA forms 60% of the ribosome, with the remainder of the ribosome composed of the structural proteins and enzymes needed for protein synthesis. As with the other types of RNA, rRNA is synthesized in the nucleus. Unlike the two other types of RNA, rRNA is produced in a specialized nuclear structure called the *nucleolus*. The formed rRNA combines with ribosomal proteins in the nucleus to produce the ribosome, which is then transported into the cytoplasm. On reaching the cytoplasm, most ribosomes become attached to the endoplasmic reticulum and begin the task of protein synthesis.

Transfer RNA. *Transfer RNA* is a clover-shaped molecule containing only 80 nucleotides, making it the smallest RNA molecule. Its function is to deliver the activated form of an amino acid to the protein that is being synthesized in the ribosomes. At least 20 different types of tRNA are known, each of which recognizes and binds to only one type of amino acid. Each tRNA molecule has two recognition sites: the first is complementary for the mRNA codon, the second for the amino acid itself. Each type of tRNA carries its own specific amino acid to the ribosomes, where protein synthesis is taking place; there it recognizes the appropriate codon on the mRNA and delivers the amino acid to the newly forming protein molecule.

Transcription

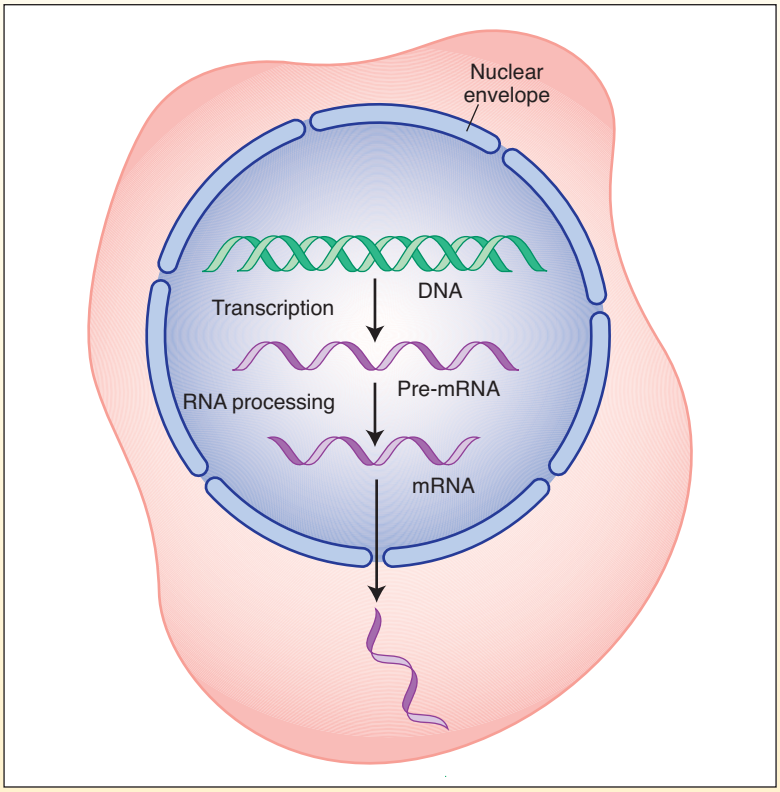
Transcription occurs in the cell nucleus and involves the synthesis of RNA from a DNA template (Fig. 5-4B). Genes are transcribed by enzymes called *RNA polymerases* that generate a single-stranded RNA identical in sequence (with the exception of U in place of T) to one of the strands of DNA. It is initiated by the assembly of a transcription complex composed of RNA polymerase and other associated factors. This complex binds to the double-stranded DNA at a specific site called the *promoter region*. Within the promoter region is the so-called

UNDERSTANDING → DNA-Directed Protein Synthesis

Deoxyribonucleic acid (DNA) directs the synthesis of the many thousands of proteins that are contained in the different cells of the body. Although some of the proteins are structural proteins, the majority are enzymes that catalyze the different chemical reactions in the cell. Because DNA is located in the cell's nucleus and protein synthesis takes place in the cytoplasm, a second type of nucleic acid—ribonucleic acid (RNA)—participates in the actual assembly of the proteins.There are three types of RNA: messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA) that participate in (1) the transcription of the DNA instructions for protein synthesis and (2) the translation of those instructions into the assembly of the polypeptides that make up the various proteins.

1

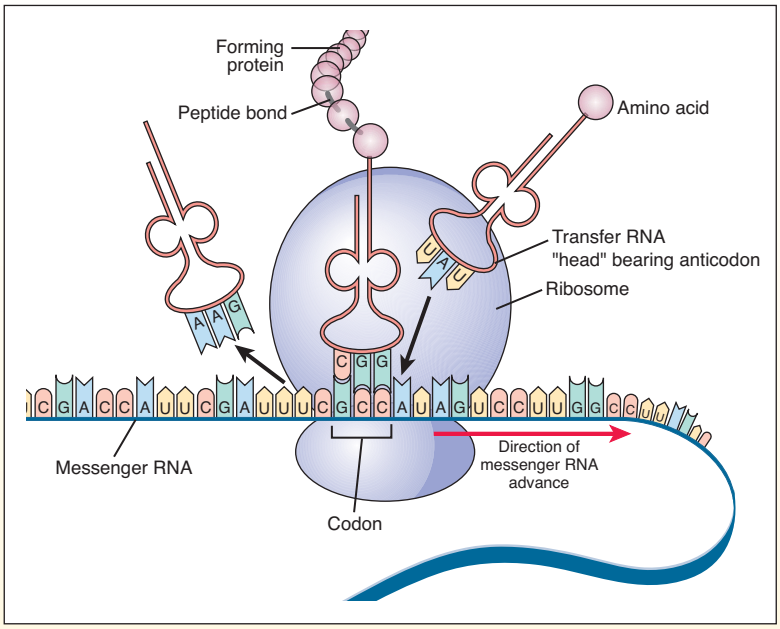
Transcription. Transcription involves copying the genetic code containing the instructions for protein synthesis from DNA to a complementary strand of mRNA. The genetic code is a triplet of four bases (adenine [A], thymine [T], guanine [G], and cytosine [C], with thymine in DNA being replaced with uracil [U] in RNA) that control the sequence of amino acids in a protein molecule that is being synthesized. (The triplet RNA code is called a *codon*.) Transcription is initiated by an enzyme called *RNA polymerase,* which binds to a promoter site on DNA. Many other proteins, including transcription factors, function to increase or decrease transcriptional activity of the genes. After mRNA has been transcribed, it detaches from DNA and is processed by cutting, removing, and splicing the internal RNA sequences to produce a variety of mRNA molecules from a single gene. Once mRNA has been processed, it diffuses through the nuclear pores into the cytoplasm, where it controls protein synthesis.



2

Translation. The process of translation involves taking the instructions transcribed from DNA to mRNA and transferring them to the rRNA of ribosomes located in the cytoplasm. When the mRNA carrying the instructions for a particular protein comes in contact with a ribosome, it binds to a small subunit of the rRNA. It then travels through the ribosome where the transcribed instructions are communicated to the tRNA, which delivers and transfers the correct amino acid to its proper position on the growing peptide chain. There are 20 types of tRNA, one for each of the 20 different types of amino acid. Each type of tRNA carries an anticodon complementary to the mRNA codon calling for the amino acid carried by the tRNA, and it is the recognition of the mRNA codon by the tRNA anticodon that ensures the proper sequence of amino acids in a synthesized protein.

In order to be functional, the newly synthesized protein must be folded into its functional form, modified further, and then routed to its final position in the cell.



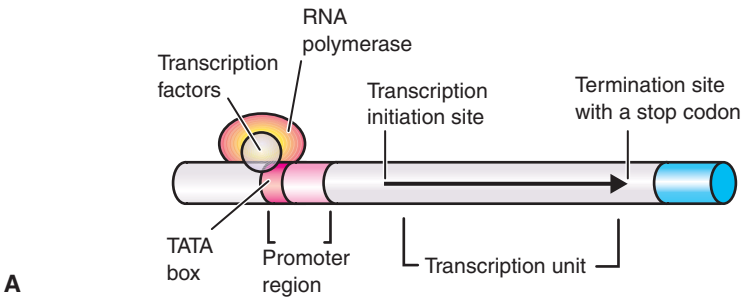
"TATA box" that contains the crucial thymine-adenine-thymine-adenine sequence that RNA polymerase recognizes and binds to, starting the replication process (Fig. 5-4A). The RNA polymerase continues to copy the meaningful DNA strand as it travels along the length of the gene, stopping only when it reaches a termination site with a stop codon. On reaching the stop signal, the RNA polymerase leaves the gene and releases the RNA strand. The RNA strand then is processed.

Processing involves the addition of certain nucleic acids at the ends of the RNA strand and cutting and splicing of certain internal sequences. Splicing often involves the removal of stretches of RNA (Fig. 5-5). Because of the splicing process, the final mRNA sequence is different from the original DNA template. The retained protein-coding regions of the mRNA sequences are called *exons* and the regions between exons are called *introns*. The functions of the introns are unknown. They are thought to be involved in the activation or deactivation of genes during various stages of development.

Splicing permits a cell to produce a variety of mRNA molecules from a single gene. By varying the splicing segments of the initial mRNA, different mRNA molecules are formed. For example, in a muscle cell, the original tropomyosin mRNA is spliced in as many as 10 different ways, yielding distinctly different protein products. This permits different proteins to be expressed from a single gene and reduces how much DNA must be contained in the genome.

Translation

The process of protein synthesis is called *translation* because the genetic code is translated into the production language needed for polypeptide assembly. Translation occurs in the cytoplasm of the cell using its mRNA template. Proteins are made from a standard set of amino acids, which are joined end to end to form the long polypeptide chains of protein molecules. Each polypeptide chain may have as many as 100 to more than 300



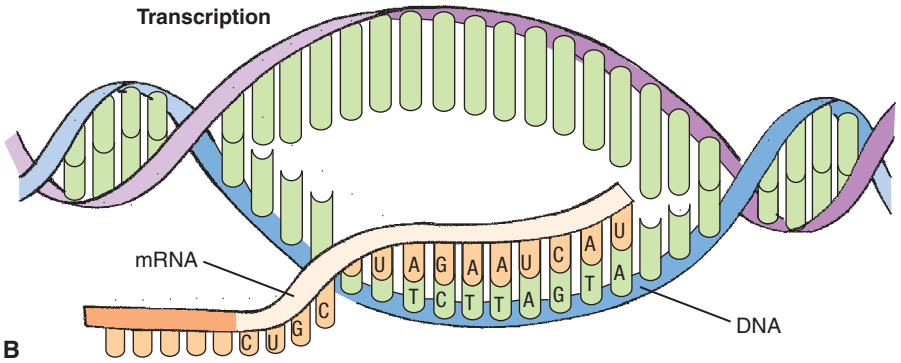


FIGURE 5-4. Transcription of messenger RNA (mRNA) from DNA double helix. **(A)** Transcription of mRNA involves attachment of RNA polymerase along with transcription factors to a specific nucleotide sequence, the TATA (thymine-adenosine-thymine-adenosine) region on the promoter region of the DNA. Transcription moves along the transcription unit and terminates at the stop codon. **(B)** Transcription creates a complementary copy mRNA from one of the DNA strands in the double helix.

amino acids in it. Besides rRNA, translation requires the coordinated actions of mRNA and tRNA. Each of the 20 different tRNA molecules transports its specific amino acid to the ribosome for incorporation into the developing protein molecule. Messenger RNA provides the information needed for placing the amino acids in their proper order for each specific type of protein. During protein synthesis, mRNA contacts and passes through the ribosome, during which it "reads" the directions for protein synthesis. As mRNA passes through the ribosome, tRNA delivers the appropriate amino acids for attachment to the growing polypeptide chain. The long mRNA molecule usually travels through and directs protein synthesis in more than one ribosome at a time. After the first part of the mRNA is read by the first ribosome, it moves onto a second and a third. As a result, ribosomes that are actively involved in protein synthesis are often found in clusters called *polyribosomes*.

The process of translation is not over when the genetic code has been used to create the sequence of amino acids that constitute a protein. To be useful to a cell, this new polypeptide chain must fold up into its unique three-dimensional conformation. The folding of many proteins is made more efficient by special classes of proteins called *molecular chaperones*. Typically, the function of a chaperone is to assist a newly synthesized polypeptide chain to attain a functional conformation as a new protein and then to assist the protein's arrival at the site in the cell where the protein carries out its function. Molecular chaperones also assist in preventing the misfolding of existing proteins. Disruption of chaperoning mechanisms causes intracellular molecules to become denatured and insoluble. These denatured proteins tend to stick to one another, precipitate, and form inclusion bodies. The development of inclusion bodies is a common pathologic process in Parkinson, Alzheimer, and Huntington diseases.

A newly synthesized polypeptide chain may also need to combine with one or more polypeptide chains from the same or an adjacent chromosome, bind small cofactors for its activity, or undergo appropriate enzyme modification. During the posttranslation process, two or more peptide chains may combine to form a single product. For example, two α-globin chains and two β-globin chains combine to form the $\alpha_2\beta_2$-hemoglobin molecule (see Chapter 13). The protein products may also be

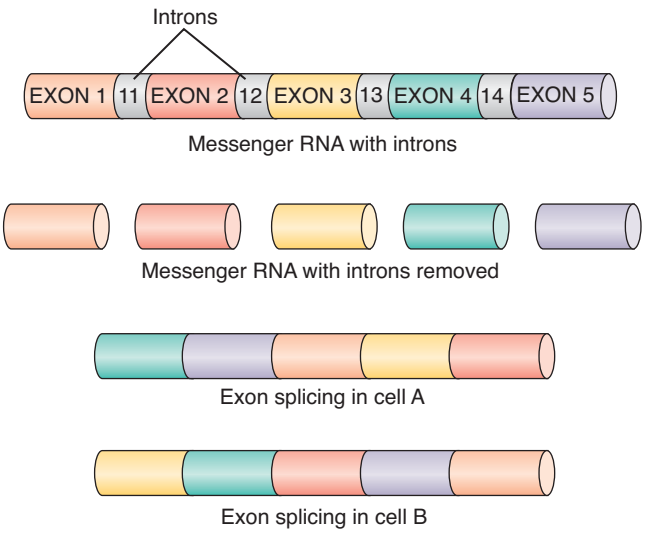


FIGURE 5-5. RNA processing. In different cells, an RNA strand may eventually produce different proteins depending on the sequencing of exons during gene splicing. This variation allows a gene to code for more than one protein. (Courtesy of Edward W. Carroll.)

modified chemically by the addition of various types of functional groups. For example, fatty acids may be added, providing hydrophobic regions for attachment to cell membranes. Other modifications may involve cleavage of the protein, either to remove a specific amino acid sequence or to split the molecule into smaller chains. As an example, the two chains that make up the circulating active insulin molecule, one containing 21 and the other 30 amino acids, were originally part of an 82-amino-acid proinsulin molecule.

Regulation of Gene Expression

Only about 2% of the genome encodes instructions for synthesis of proteins; the remainder consists of noncoding regions that serve to determine where, when, and in what quantity proteins are made. The degree to which a gene or particular group of genes is active is called *gene expression*. A phenomenon termed *induction* is an important process by which gene expression is increased. *Gene repression* is a process by which a regulatory gene acts to reduce or prevent gene expression. Activator and repressor sites commonly monitor levels of the synthesized product and regulate gene transcription through a negative feedback mechanism. Whenever product levels decrease, gene transcription is increased, and when product levels increase, gene transcription is repressed.

Although control of gene expression can occur in multiple steps, many regulatory events occur at the transcription level. The initiation and regulation of transcription require the collaboration of a battery of proteins, collectively termed *transcription factors*. Transcription factors are a class of proteins that bind to their own specific DNA region and function to increase or decrease transcriptional activity of the genes. The role of transcription factors in gene expression explains why neurons and liver cells have completely different structures and functions although all the nucleated cells in a person contain the same DNA and thus the same genetic information. Some, referred to as *general transcription factors*, are required for transcription of all structural genes. Others, termed *specific transcription factors*, have more specialized roles, activating genes only at specific stages of development. For example, the PAX family of transcription factors is involved in the development of such embryonic tissues as the eye and portions of the nervous system.

In summary, genes are the fundamental unit of information storage in the cell. They determine the types of proteins and enzymes made by the cell and therefore control inheritance and day-to-day cell function. Genetic information is stored in a stable macromolecule called *DNA*. Genes transmit information contained in the DNA molecule as a triplet code. The genetic code is determined by the arrangement of the nitrogenous bases of the four nucleotides (i.e., adenine, guanine, thymine [or uracil in RNA], and cytosine). Gene mutations represent accidental errors in duplication, rearrangement, or deletion of parts of the genetic code. Fortunately, most mutations are corrected by DNA repair mechanisms in the cell.

The transfer of stored information from DNA into production of cell products is accomplished through a second type of nucleotide called *RNA*. Messenger RNA transcribes the instructions for product synthesis from the DNA molecule and carries it into the cell's cytoplasm, where ribosomal RNA uses the information to direct protein synthesis. Transcription is initiated by RNA polymerase and other associated factors that bind to the double-stranded DNA at a specific site called the *promoter region*. Transfer RNA acts as a carrier system for delivering the appropriate amino acids to the ribosomes.

The degree to which a gene or particular group of genes is active is called *gene expression*. Gene expression involves a set of complex interrelationships among different levels of control including RNA transcription and posttranslational processing. The initiation and regulation of RNA transcription are controlled by *transcription factors* that bind to specific DNA regions and function to regulate gene expression of the many different types of cells in the body. Posttranslational processing involves the proper folding of the newly synthesized polypeptide chain into its unique three-dimensional conformation. Special classes of proteins called *molecular chaperones* make the folding of many proteins more efficient. Posttranslational processing may also involve the combination of polypeptide chains from the same or an adjacent chromosome, the binding of small cofactors, or enzyme modification.

Chromosomes

Most genetic information of a cell is organized, stored, and retrieved in small intracellular structures called *chromosomes*. Although the chromosomes are visible only in dividing cells, they retain their integrity between cell divisions. The chromosomes are arranged in pairs: one member of the pair is inherited from the father, the other from the mother. The maternal and paternal chromosomes of a pair are called *homologous chromosomes* (homologs). Each species has a characteristic number of chromosomes. In the human, 46 single or 23 pairs of chromosomes are present. Of the 23 pairs of human chromosomes, 22 are called *autosomes* and are alike in both males and females. Each of the 22 pairs of autosomes has the same appearance in all individuals, and each has been given a numeric designation for classification purposes (Fig. 5-6). The sex chromosomes, which make up the 23rd pair of chromosomes, determine the sex of a person. All males have an X and Y chromosome (i.e., an X chromosome from the mother and a Y chromosome from the father); all females have two X chromosomes (i.e., one from each parent). The much smaller Y chromosome contains the *male-specific region* (MSY) that determines sex. This region comprises more than 90% of the length of the Y chromosome.

Only one X chromosome in the female is active in controlling the expression of genetic traits; however,

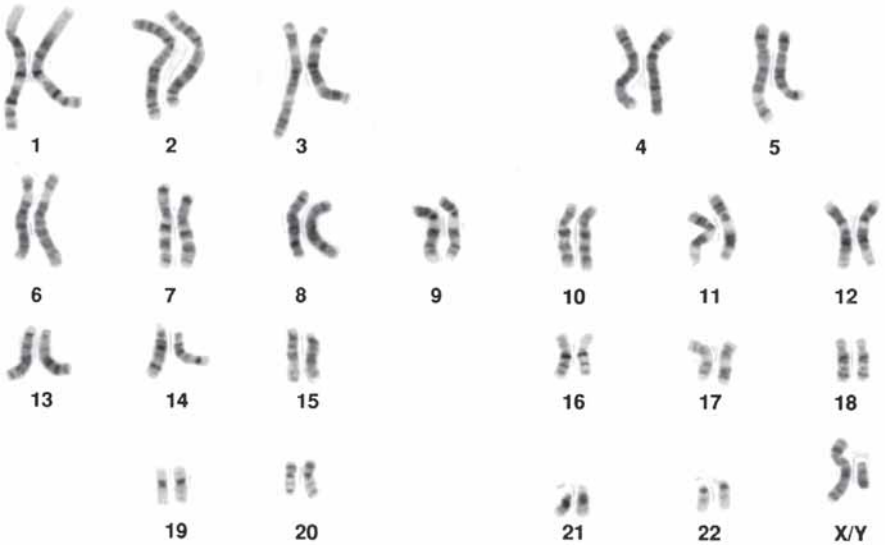


FIGURE 5-6. Karyotype of a normal male (xy). National Cancer Institute. [Available Online] http://visualsonline.cancer.gov.

both X chromosomes are activated during gametogenesis. In the female, the active X chromosome is invisible, but the inactive X chromosome can be visualized with appropriate nuclear staining. This inactive chromatin mass is seen as the *Barr body* in epithelial cells or as the drumstick body in the chromatin of neutrophils. The genetic sex of a child can be determined by microscopic study of cell or tissue samples. The total number of X chromosomes is equal to the number of Barr bodies plus one (i.e., an inactive plus an active X chromosome). For example, the cells of a normal female have one Barr body and therefore a total of two X chromosomes. A normal male has no Barr bodies. Males with Klinefelter syndrome (one Y, an inactive X, and an active X chromosome) exhibit one Barr body. In the female, whether the active X chromosome is derived from the mother or father is randomly determined within a few days after conception. This random selection is called the *Lyon principle*, after Mary Lyon, the British geneticist who described it.

Chromosome Structure

- The DNA that stores genetic material is organized into 23 pairs of chromosomes. There are 22 pairs of autosomes, which are alike for males and females, and one pair of sex chromosomes, with XX pairing in females and XY pairing in males.
- Cell division involves the duplication of the chromosomes. Duplication of chromosomes in somatic cell lines involves mitosis, in which each daughter cell receives a pair of 23 chromosomes. Meiosis is limited to replicating germ cells and results in formation of a single set of 23 chromosomes.

Cell Division

Cells reproduce by duplicating their chromosomes and dividing in two. There are two types of cell division: mitosis and meiosis. *Mitosis* is the cell cycle process in which nongerm cells are replicated. It provides a way for the body to replace cells that have a limited life span, such as skin and blood cells; increase tissue mass during periods of growth; and repair tissue, such as in wound healing.

Meiosis is limited to replicating germ cells and takes place only once in a cell line. It results in the formation of gametes or reproductive cells (i.e., ovum and sperm), each of which has only a single set of 23 chromosomes. Meiosis is typically divided into two distinct phases: meiosis I and meiosis II (Fig. 5-7). During meiotic division I, homologous chromosomes pair up, forming a synapsis or tetrad (two chromatids per chromosome). They are sometimes called *bivalents*. The X and Y chromosomes are not homologs and do not form bivalents. While in meiosis I, an interchange of chromatid segments can occur. This process is called *crossing over* (Fig. 5-8). Crossing over allows for new combinations of genes, increasing genetic variability. After cell division I, each of the two daughter cells contains one member of each homologous pair of chromosomes and a sex chromosome (23 double-stranded chromosomes). No DNA synthesis occurs before meiotic division II. During cell division II, the 23 double-stranded chromosomes (two chromatids) of each of the two daughter cells from meiosis I divide at their centromeres. Each subsequent daughter cell receives 23 single-stranded chromatids. Thus, a total of four daughter cells are formed by a meiotic division of one cell.

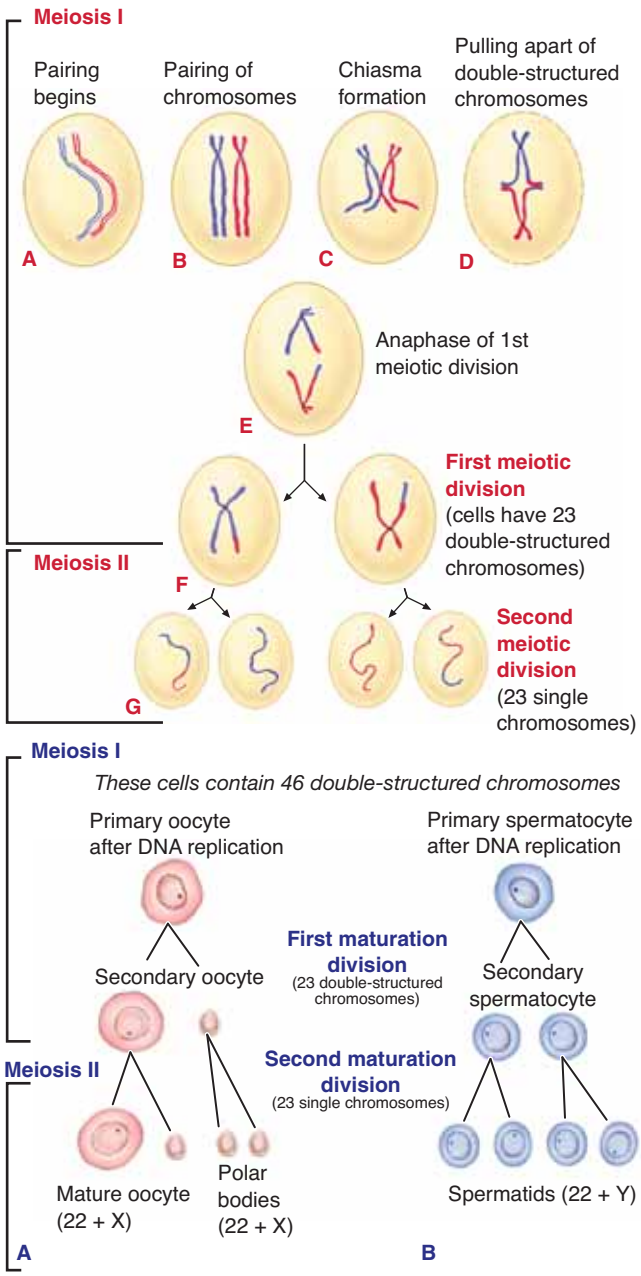


FIGURE 5-7. First and second meiotic divisions. (*Top*) Meiosis I, during which homologous chromosomes **(A)** approach each other and **(B)** pair; **(C)** intimately paired homologous chromosomes interchange chromatid fragments (crossing over) and **(D)** double-structured chromosomes pull apart. **(E)** Anaphase of first meiotic division. During meiosis II **(E, F),** the double-structured chromosomes pull apart at the centromere to form four single-stranded chromosomes (reduction division). (*Bottom*) Events occurring during meiosis I and II in female and male gametes. **(A)** The primitive female germ cell (oocyte) produces only one mature gamete, the mature oocyte. **(B)** The primitive male germ cell (primary spermatocyte) produces four spermatids, all of which develop into spermatozoa. (Adapted from Sadler R.W. [2003]. *Langman's medical embryology* [9th ed.]. Philadelphia: Lippincott Williams & Wilkins.)

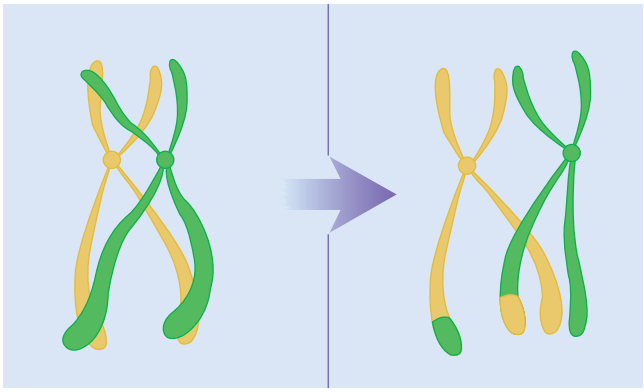


FIGURE 5-8. Crossing over of DNA at the time of meiosis.

Chromosome Structure

Cytogenetics is the study of the structure and numeric characteristics of the cell's chromosomes. Chromosome studies can be done on any tissue or cell that grows and divides in culture. Lymphocytes from venous blood are frequently used for this purpose. After the cells have been cultured, a drug called *colchicine* is used to arrest mitosis before the chromosomes separate. A chromosome spread is prepared by fixing and spreading the chromosomes on a slide. Subsequently, appropriate staining techniques show the chromosomal banding patterns so they can be identified. The chromosomes are photographed, and the photomicrographs of each of the chromosomes are cut out and arranged in pairs according to a standard classification system (see Fig. 5-6). The completed picture is called a *karyotype,* and the procedure for preparing the picture is called *karyotyping*. A uniform system of chromosome classification was originally formulated at the 1971 Paris Chromosome Conference and was later revised to describe the chromosomes as seen in preparations of more elongated mitotic stages.

While the chromosomes are aligned on the equatorial plate of the cell, each chromosome takes the form of chromatids to form an "X" or "wishbone" pattern. Human chromosomes are divided into three types according to the position of the centromere (Fig. 5-9). If the centromere is in the center and the arms are of approximately the same length, the chromosome is said to be *metacentric;* if it is not centered and the arms are of clearly different lengths, it is *submetacentric;* and if it is near one end, it is *acrocentric*. The short arm of the chromosome is designated as "p" for "petite," and the long arm is designated as "q" for no other reason than it is the next letter of the alphabet. The arms of the chromosome are indicated by the chromosome number followed by the p or q designation (e.g., 15p). Chromosomes 13, 14, 15, 21, and 22 have small masses of chromatin called *satellites* attached to their short arms by narrow stalks. At the ends of each chromosome are special DNA sequences called *telomeres*. Telomeres allow the end of the DNA molecule to be replicated completely.

The banding patterns of a chromosome are used in describing the position of a gene on a chromosome. Each

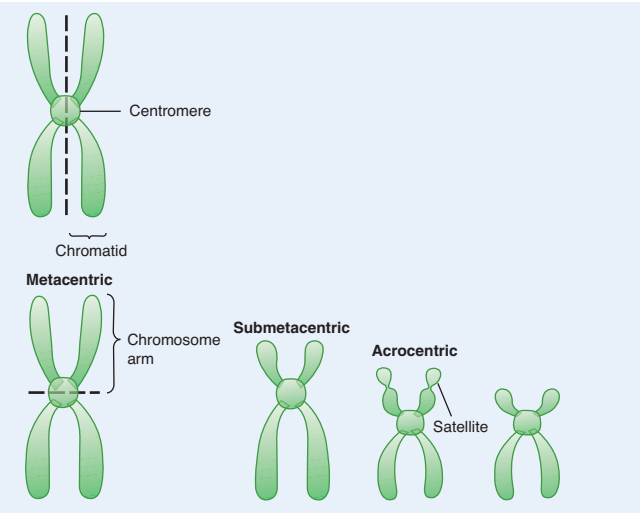


FIGURE 5-9. Three basic shapes and the component parts of human metaphase chromosomes. The relative size of the satellite on the acrocentric is exaggerated for visibility. (Adapted from Cormack D.H. [1993]. *Essential histology*. Philadelphia: J.B. Lippincott.)

In summary, the genetic information in a cell is organized, stored, and retrieved as small cellular structures called *chromosomes.* Forty-six chromosomes arranged in 23 pairs are present in the human being. Twenty-two of these pairs are autosomes. The 23rd pair is the sex chromosomes, which determine the sex of a person. Two types of cell division occur, meiosis and mitosis. Meiosis is limited to replicating germ cells and results in the formation of gametes or reproductive cells (ovum and sperm), each of which has only a single set of 23 chromosomes. Mitotic division occurs in somatic cells and results in the formation of 23 pairs of chromosomes. A karyotype is a photograph of a person's chromosomes. It is prepared by special laboratory techniques in which body cells are cultured, fixed, and then stained to display identifiable banding patterns. A photomicrograph is then made. Often the individual chromosomes are cut out and regrouped according to chromosome number.

arm of a chromosome is divided into regions, which are numbered from the centromere outward (e.g., 1, 2). The regions are further divided into bands, which are also numbered (Fig. 5-10). These numbers are used in designating the position of a gene on a chromosome. For example, Xp22 refers to band 2, region 2 of the short arm (p) of the X chromosome.

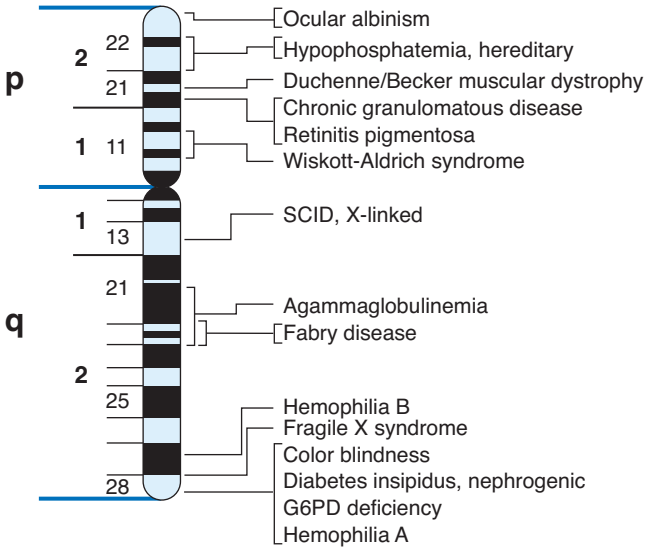


FIGURE 5-10. Localization of inherited diseases as represented on the banded karyotype of the X chromosome. Notice the nomenclature of arms (P, Q), regions (1, 2), and bands (e.g., 22 [region 2, band 2]). G6PD, glucose-6-phosphate dehydrogenase deficiency; SCID, severe combined immunodeficiency disease. (Modified from Rubin E., Gorstein F., Rubin R., et al. [2006]. *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 261]. Philadelphia: Lippincott Williams & Wilkins.)

Patterns of Inheritance

The characteristics inherited from a person's parents are inscribed in gene pairs found along the length of the chromosomes. Alternate forms of the same gene are possible (i.e., one inherited from the mother and the other from the father), and each may produce a different aspect of a trait.

Definitions

Genetics has its own set of definitions. The *genotype* of a person is the genetic information stored in the base sequence triplet code. The *phenotype* refers to the recognizable traits, physical or biochemical, associated with a specific genotype. Often, the genotype is not evident by available detection methods. More than one genotype may have the same phenotype. Some brown-eyed persons are carriers of the code for blue eyes, and other brown-eyed persons are not. Phenotypically, these two types of brown-eyed persons are the same, but genotypically they are different.

With regard to a genetic disorder, not all persons with a mutant gene are affected to the same extent. *Expressivity* refers to the manner in which the gene is expressed in the phenotype, which can range from mild to severe. *Penetrance* represents the ability of a gene to express its function. Seventy-five percent penetrance means 75% of persons of a particular genotype present with a recognizable phenotype. Syndactyly (webbed fingers or toes) and blue sclera are genetic mutations that often do not exhibit 100% penetrance.

The position of a gene on a chromosome is called its *locus,* and alternate forms of a gene at the same locus are called *alleles.* When only one pair of genes is involved in the transmission of information, the term *single-gene*

Transmission of Genetic Information

- The transmission of information from one generation to the next is vested in genetic material transferred from each parent at the time of conception.
- Alleles are the alternate forms of a gene (one from each parent), and the locus is the position that they occupy on the chromosome.
- The genotype of a person represents the sum total of the genetic information in the cells, and the phenotype the physical manifestations of that information.
- Penetrance is the percentage in a population with a particular genotype in which that genotype is phenotypically manifested, whereas expressivity is the manner in which the gene is expressed.
- Mendelian, or single-gene, patterns of inheritance include autosomal dominant and recessive traits that are transmitted from parents to their offspring in a predictable manner. Polygenic inheritance, which involves multiple genes, and multifactorial inheritance, which involves multiple genes as well as environmental factors, are less predictable.

trait is used. Single-gene traits follow the mendelian laws of inheritance (to be discussed).

Polygenic inheritance involves multiple genes at different loci, with each gene exerting a small additive effect in determining a trait. Most human traits are determined by multiple pairs of genes, many with alternate codes, accounting for some dissimilar forms that occur with certain genetic disorders. Polygenic traits are predictable, but with less reliability than single-gene traits. *Multifactorial* inheritance is similar to polygenic inheritance in that multiple alleles at different loci affect the outcome; the difference is that multifactorial inheritance includes environmental effects on the genes.

Many other gene–gene interactions are known. These include *epistasis*, in which one gene masks the phenotypic effects of another nonallelic gene; *multiple alleles*, in which more than one allele affects the same trait (e.g., ABO blood types); *complementary genes*, in which each gene is mutually dependent on the other; and *collaborative genes*, in which two different genes influencing the same trait interact to produce a phenotype neither gene alone could produce.

Genetic Imprinting

Besides autosomal and sex-linked genes and mitochondrial inheritance, it was found that certain genes exhibited a "parent of origin" type of transmission in which the parental genomes do not always contribute equally in the development of an individual (Fig. 5-11). The transmission of this phenomenon was given the name *genomic imprinting* by Helen Crouse in 1960. Although rare, it is estimated that approximately 100 genes exhibit genomic, or genetic, imprinting. Evidence suggests that a genetic

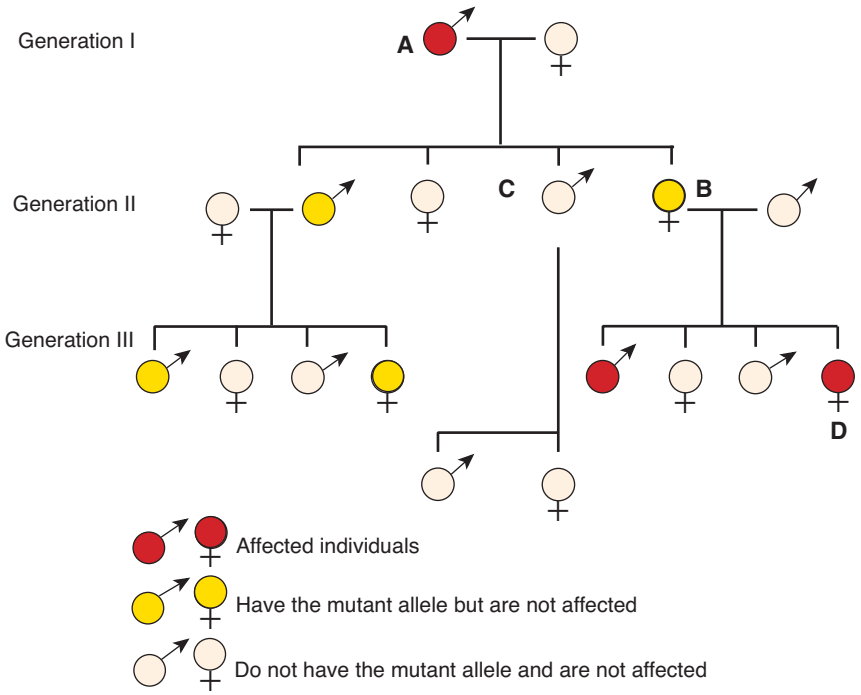


FIGURE 5-11. Pedigree of genetic imprinting. In generation I, male **(A)** has inherited a mutant allele from his affected mother (not shown); the gene is "turned off" during spermatogenesis, and therefore none of his offspring (generation II) will express the mutant allele, regardless of whether they are carriers. However, the gene will be "turned on" again during oogenesis in any of his daughters **(B)** who inherit the allele. All offspring (generation III) who inherit the mutant allele will be affected. All offspring of normal children **(C)** will produce normal offspring. Children of female **(D)** will all express the mutation if they inherit the allele.

conflict occurs in the developing embryo: the male genome attempts to establish larger offspring, whereas the female prefers smaller offspring to conserve her energy for the current and subsequent pregnancies.

It was the pathologic analysis of ovarian teratomas (tumors made up of various cell types derived from an undifferentiated germ cell) and hydatidiform moles (gestational tumors made up of trophoblastic tissue) that yielded the first evidence of genetic imprinting. All ovarian teratomas were found to have a 46,XX karyotype. The results of detailed chromosomal polymorphism analysis confirmed that these tumors developed without the paternally derived genome. Conversely, analysis of hydatidiform moles suggested that they were tumors of paternal origin.

Well-known examples of genomic imprinting are the transmission of the mutations in Prader-Willi and Angelman syndromes. Both syndromes exhibit mental retardation as a common feature. It was also found that both disorders had the same deletion in chromosome 15. When the deletion is inherited from the mother, the infant presents with Angelman ("happy puppet") syndrome; when the same deletion is inherited from the father, Prader-Willi syndrome results. The two conditions exhibit different phenotypes. Prader-Willi syndrome entails mental retardation, severe eating disorder marked by uncontrolled appetite, obesity, and diabetes. Angelman syndrome also exhibits mental retardation, but paroxysms of laughter, ataxia, and seizures accompany the disorder.

A related chromosomal disorder is *uniparental disomy*. This occurs when two chromosomes of the same number are inherited from one parent. Normally, this is not a problem except in cases where a chromosome has been imprinted by a parent. If an allele is inactivated by imprinting, the offspring will have only one working copy of the chromosome, resulting in possible problems.

Mendel Laws

A main feature of inheritance is predictability: given certain conditions, the likelihood of the occurrence or recurrence of a specific trait is remarkably predictable. The units of inheritance are the genes, and the pattern of single-gene expression can often be predicted using the Mendel laws of genetic transmission. Techniques and discoveries since Gregor Mendel's original work was published in 1865 have led to some modification of his original laws.

Mendel discovered the basic pattern of inheritance by conducting carefully planned experiments with simple garden peas. Experimenting with several phenotypic traits in peas, Mendel proposed that inherited traits are transmitted from parents to offspring by means of independently inherited factors—now known as genes—and that these factors are transmitted as recessive and dominant traits. Mendel labeled dominant factors (his round peas) "A" and recessive factors (his wrinkled peas) "a." Geneticists continue to use capital letters to designate dominant traits and lowercase letters to identify recessive traits. The possible combinations that can occur with transmission of single-gene dominant and recessive traits can be described by constructing a figure called a *Punnett square* using capital and lowercase letters (Fig. 5-12).

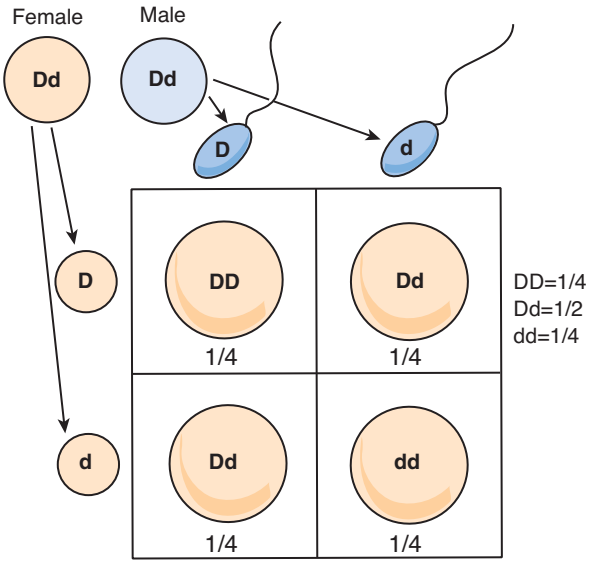


FIGURE 5-12. The Punnett square showing all possible combinations for transmission of a single gene trait (dimpled cheeks). The example shown is when both parents are heterozygous (dD) for the trait. The alleles carried by the mother are on the left and those carried by the father are on the top. The D allele is dominant and the d allele is recessive. The DD and Dd offspring have dimples and the dd offspring does not.

The observable traits of single-gene inheritance are inherited by the offspring from the parents. During maturation, the primordial germ cells (i.e., sperm and ovum) of both parents undergo meiosis, or reduction division, in which the number of chromosomes is divided in half (from 46 to 23). At this time, the two alleles from a gene locus separate so that each germ cell receives only one allele from each pair (i.e., Mendel first law). According to Mendel second law, the alleles from the different gene loci segregate independently and recombine randomly in the zygote. Persons in whom the two alleles of a given pair are the same (AA or aa) are called *homozygotes*. *Heterozygotes* have different alleles (Aa) at a gene locus. A *recessive trait* is one expressed only in a homozygous pairing; a *dominant trait* is one expressed in either a homozygous or a heterozygous pairing. All persons with a dominant allele (depending on the penetrance of the genes) manifest that trait. A *carrier* is a person who is heterozygous for a recessive trait and does not manifest the trait. For example, the genes for blond hair are recessive and those for brown hair are dominant. Therefore, only persons with a genotype having two alleles for blond hair would be blond; persons with either one or two brown alleles would have dark hair.

Pedigree

A *pedigree* is a graphic method for portraying a family history of an inherited trait. It is constructed from a carefully obtained family history and is useful for tracing the pattern of inheritance for a particular trait.

In summary, inheritance represents the likelihood of the occurrence or recurrence of a specific genetic trait. The genotype refers to information stored in the genetic code of a person, whereas the phenotype represents the recognizable traits, physical and biochemical, associated with the genotype. Expressivity refers to the expression of a gene in the phenotype, and penetrance is the ability of a gene to express its function. The point on the DNA molecule that controls the inheritance of a particular trait is called a *gene locus*. Alternate forms of a gene at a gene locus are called *alleles*. The alleles at a gene locus may carry recessive or dominant traits. A recessive trait is one expressed only when two copies (homozygous) of the recessive allele is present. Dominant traits are expressed with either homozygous or heterozygous pairing of the alleles. A pedigree is a graphic method for portraying a family history of an inherited trait.

Gene Technology

The past several decades have seen phenomenal advances in the field of genetics. These advances have included the assembly of physical and genetic maps through the Human Genome Project; the establishment of the International HapMap Project to map the haplotypes of the many closely related single-nucleotide polymorphisms in the human genome; and the development of methods for applying the technology of these projects to the diagnosis and treatment of disease.

Gene Mapping

Genetic mapping is the assignment of genes to specific chromosomes or parts of the chromosome. Another type of mapping strategy, the haplotype map, focuses on identifying the slight variations in the human genome that impact on an individual's susceptibility to disease and responses to environmental factors such as microbes, toxins, and drugs.

There are two types of gene maps: genetic maps and physical maps. Genetic maps are like highway maps. They use linkage studies (e.g., dosage, hybridization) to estimate the distances between chromosomal landmarks (i.e., gene markers). Physical maps are similar to a surveyor's map. They make use of cytogenetic and molecular techniques to determine the actual, physical locations of genes on chromosomes. Genetic maps and physical maps have been refined over the decades. The earliest mapping efforts localized genes on the X chromosome. The initial assignment of a gene to a particular chromosome was made in 1911 for the color blindness gene inherited from the mother (i.e., following the X-linked pattern of inheritance). In 1968, the specific location of the Duffy blood group on the long arm of chromosome 1 was determined.

The Human Genome Project

The Human Genome Project, initiated in 1990, sought to identify all the genes in the human genome. The international project was charged with developing genetic and physical maps that allowed the precise location of genes and with exploration of technologies that would enable the sequencing of large amounts of DNA with high accuracy and low cost. Some of what was revealed was quite unexpected including the revelation that humans have a mere 30,000 genes, rather than the estimated 100,000, and that any two individuals share 99.9% of their DNA sequence, indicating that the remarkable diversity among individuals is vested in about 0.1% of our DNA.

To date, the locations of more than 25,000 genes have been mapped to a specific chromosome, and most of them to a specific region on the chromosome. However, genetic mapping is continuing so rapidly that these numbers are constantly being updated. An excellent source of articles regarding specific chromosome sequencing in humans is the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov/index.html). Another source is the Genome Data Base, a central database for mapped genes and an international repository for most mapping information.

Genetic Mapping Methods

Many methods have been used for developing genetic maps. The most important ones are family linkage studies, gene dosage methods, and hybridization studies. Often, the specific assignment of a gene is made using information from several mapping techniques.

Linkage Studies. Linkage studies assume that genes occur in a linear array along the chromosomes. During meiosis, the paired chromosomes of the diploid germ cell exchange genetic material because of the crossing-over phenomenon (see Fig. 5-8). This exchange usually involves more than one gene; large blocks of genes (representing large portions of the chromosome) are usually exchanged. Although the point at which the block separates from another occurs randomly, the closer together two genes are on the same chromosome, the greater the chance is that they will be passed on together to the offspring. When two inherited traits occur together at a rate greater than would occur by chance alone, they are said to be *linked*.

Several methods take advantage of the crossing over and recombination of genes to map a particular gene. In one method, any gene that has already been assigned to a chromosome can be used as a marker to assign other linked genes. For example, it was found that an extra long chromosome 1 and the Duffy blood group were inherited as a dominant trait, placing the position of the blood group gene close to the extra material on chromosome 1. Color blindness has been linked to classic hemophilia A (i.e., lack of factor VIII) in some pedigrees; hemophilia A has been linked to glucose-6-phosphate dehydrogenase deficiency in others; and color blindness has been linked to glucose-6-phosphate dehydrogenase deficiency in still others. Because the gene for color blindness

is found on the X chromosome, all three genes must be found in a small section of the X chromosome. Linkage analysis can be used clinically to identify affected persons in a family with a known genetic defect. Males, because they have one X and one Y chromosome, are said to be *hemizygous* for sex-linked traits. Females can be homozygous (normal or mutant) or heterozygous for sex-linked traits. Heterozygous females are known as *carriers* for X-linked defects.

One autosomal recessive disorder that has been successfully diagnosed prenatally by linkage studies using amniocentesis is congenital adrenal hyperplasia (due to 21-hydroxylase deficiency), which is linked to an immune response gene (human leukocyte antigen [HLA] type). Postnatal linkage studies have been used in diagnosing hemochromatosis, which is closely linked to another HLA type. Persons with this disorder are unable to metabolize iron, and it accumulates in the liver and other organs. It cannot be diagnosed by conventional means until irreversible damage has been done. Given a family history of the disorder, HLA typing can determine if the gene is present, and if it is present, dietary restriction of iron intake may be used to prevent organ damage.

Gene Dosage Studies. Dosage studies involve measuring enzyme activity. Autosomal genes are normally arranged in pairs, and normally both are expressed. If both alleles are present and both are expressed, the activity of the enzyme should be 100%. If one member of the gene pair is missing, only 50% of the enzyme activity is present, reflecting the activity of the remaining normal allele.

Hybridization Studies. A recent biologic discovery revealed that two somatic cells from different species, when grown together in the same culture, occasionally fuse to form a new hybrid cell. Two types of hybridization methods are used in genomic studies: somatic cell hybridization and in situ hybridization.

Somatic cell hybridization involves the fusion of human somatic cells with those of a different species (typically, the mouse) to yield a cell containing the chromosomes of both species. Because these hybrid cells are unstable, they begin to lose chromosomes of both species during subsequent cell divisions. This makes it possible to obtain cells with different partial combinations of human chromosomes. The enzymes of these cells are then studied with the understanding that for an enzyme to be produced, a certain chromosome must be present and, therefore, the coding for the enzyme must be located on that chromosome.

In situ hybridization involves the use of specific sequences of DNA or RNA to locate genes that do not express themselves in cell culture. DNA and RNA can be chemically tagged with radioactive or fluorescent markers. These chemically tagged DNA or RNA sequences are used as probes to detect gene location. The probe is added to a chromosome spread after the DNA strands have been separated. If the probe matches the complementary DNA of a chromosome segment, it hybridizes and remains at the precise location (therefore the term *in situ*) on a chromosome. Radioactive or fluorescent markers are used to find the location of the probe.

Haplotype Mapping

As work on the Human Genome Project progressed, many researchers reasoned that identifying the common patterns of DNA sequence variations in the human genome would be possible. An international project, known as the *International HapMap Project,* was organized with the intent of developing a haplotype map of these variations. One of the findings of the Human Genome Project was that the genome sequence was 99.9% identical for all people. It is anticipated that the 0.1% variation may greatly affect an individual's response to drugs, toxins, and predisposition to various diseases. Sites in the DNA sequence where individuals differ at a single DNA base are called *single-nucleotide polymorphisms* (SNPs, pronounced "snips"). A haplotype consists of the many closely linked SNPs on a single chromosome that generally are passed as a block from one generation to another in a particular population. One of the motivating factors behind the HapMap project was the realization that the identification of a few SNPs was enough to uniquely identify the haplotypes in a block. The specific SNPs that identify the haplotypes are called *tag SNPs*. A HapMap is a map of these haplotype blocks and their tag SNPs. This approach should prove useful in reducing the number of SNPs required to examine an entire genome and make genome scanning methods much more efficient in finding regions with genes that contribute to disease development.

It is anticipated that the HapMap Project will provide a useful tool for disease diagnosis and management. Much attention has focused on the use of SNPs to decide whether a genetic variant is associated with a higher risk of disease susceptibility in one population versus another. Pharmacogenetics addresses the variability of drug response due to inherited characteristics in individuals. With the availability of SNPs, it may soon be possible to identify persons who can be expected to respond favorably to a drug and those who can be expected to experience adverse reactions. This would result in safer, more effective, and more cost-efficient use of medications.

Recombinant DNA Technology

The term *recombinant DNA* refers to a combination of DNA molecules that are not found together in nature. Recombinant DNA technology makes it possible to identify the DNA sequence in a gene and produce the protein product encoded by a gene. The specific nucleotide sequence of a DNA fragment can often be identified by analyzing the amino acid sequence and mRNA codon of its protein product. Short sequences of base pairs can be synthesized, radioactively labeled, and subsequently used to identify their complementary sequence. In this way, identifying normal and abnormal gene structures is possible.

Tests of DNA sequences are particularly useful in identifying polymorphisms, including the previously discussed SNPs, that are associated with various diseases.

Because genetic variations are so distinctive, DNA fingerprinting (analysis of DNA sequence differences) can be used to determine family relationships or help identify persons involved in criminal acts. The methods of recombinant DNA technology can also be used in the treatment of disease. For example, recombinant DNA technology is employed in the manufacture of human insulin that is used to treat diabetes mellitus.

Gene Isolation and Cloning

The gene isolation and cloning methods used in recombinant DNA technology rely on the fact that the genes of all organisms, from bacteria through mammals, are based on a similar molecular organization. Gene cloning requires cutting a DNA molecule apart, modifying and reassembling its fragments, and producing copies of the modified DNA, its mRNA, and its gene product. The DNA molecule is cut apart by using a bacterial enzyme, called a *restriction enzyme,* that binds to DNA wherever a particular short sequence of base pairs is found and cleaves the molecule at a specific nucleotide site. In this way, a long DNA molecule can be broken down into smaller, discrete fragments, one of which presumably contains the gene of interest. Many restriction enzymes are commercially available that cut DNA at different recognition sites.

The restrictive fragments of DNA can often be replicated through insertion into a unicellular organism, such as a bacterium (Fig. 5-13). To do this, a cloning vector

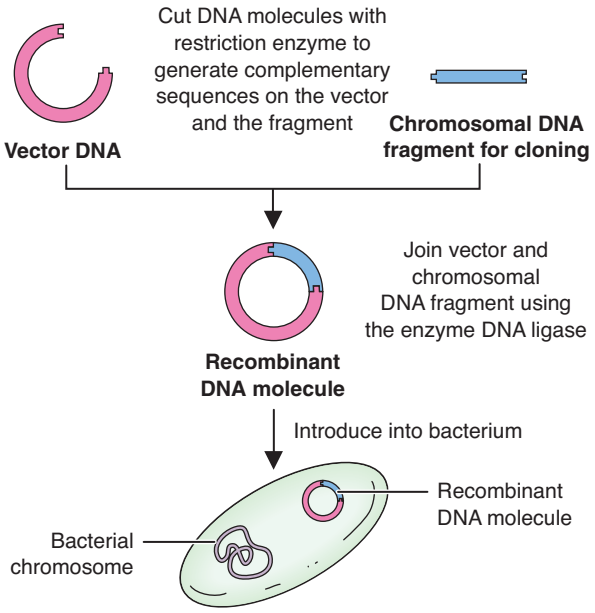


FIGURE 5-13. Recombinant DNA technology. By fragmenting DNA of any origin and inserting it in the DNA of rapidly reproducing foreign cells, billions of copies of a single gene can be produced in a short time. The DNA to be cloned is inserted into a plasmid (a small, self-replicating circular molecule of DNA) that is separate from chromosomal DNA. When the recombinant plasmid is introduced into bacteria, the newly inserted segment will be replicated along with the rest of the plasmid. (U.S. DOE Genomic Image Gallery.)

such as a bacterial virus or a small DNA circle that is found in most bacteria, called a *plasmid,* is used. Viral and plasmid vectors replicate autonomously in the host bacterial cell. During gene cloning, a bacterial vector and the DNA fragment are mixed and joined by a special enzyme called a *DNA ligase*. The recombinant vectors formed are then introduced into a suitable culture of bacteria, and the bacteria are allowed to replicate and express the recombinant vector gene. Sometimes, mRNA taken from a tissue that expresses a high level of the gene is used to produce a complementary DNA molecule that can be used in the cloning process. Because the fragments of the entire DNA molecule are used in the cloning process, additional steps are taken to identify and separate the clone that contains the gene of interest.

Pharmaceutical Applications

Recombinant DNA technology has also made it possible to produce proteins that have therapeutic properties. One of the first products to be produced was human insulin. Recombinant DNA corresponding to the A chain of human insulin was isolated and inserted into plasmids that were in turn used to transform *Escherichia coli*. The bacteria then synthesized the insulin chain. A similar method was used to obtain the B chains. The A and B chains were then mixed and allowed to fold and form disulfide bonds, producing active insulin molecules. Human growth hormone has also been produced in *E. coli*. More complex proteins are produced in mammalian cell culture using recombinant DNA techniques. These include erythropoietin, which is used to stimulate red blood cell production; factor VIII, which is used to treat hemophilia; and tissue plasminogen activator (tPA), which is frequently administered after a heart attack to dissolve the thrombi that are obstructing coronary blood flow.

DNA Fingerprinting

The technique of DNA fingerprinting is based in part on those techniques used in recombinant DNA technology and on those originally used in medical genetics to detect slight variations in the genomes of different individuals. Using restriction enzymes, DNA is cleaved at specific regions (Fig. 5-14). The DNA fragments are separated according to size by electrophoresis and denatured (by heating or treating chemically) so that all the DNA is single stranded. The single-stranded DNA is then transferred to nitrocellulose paper, baked to attach the DNA to the paper, and treated with a series of radioactive probes. After the radioactive probes have been allowed to bond with the denatured DNA, radiography is used to reveal the labeled DNA fragments.

When used in forensic pathology, this procedure is applied to specimens from the suspect and the forensic specimen. Banding patterns are then analyzed to see if they match. With conventional methods of analysis of blood and serum enzymes, a 1 in 100 to 1000 chance exists that the two specimens match because of chance.

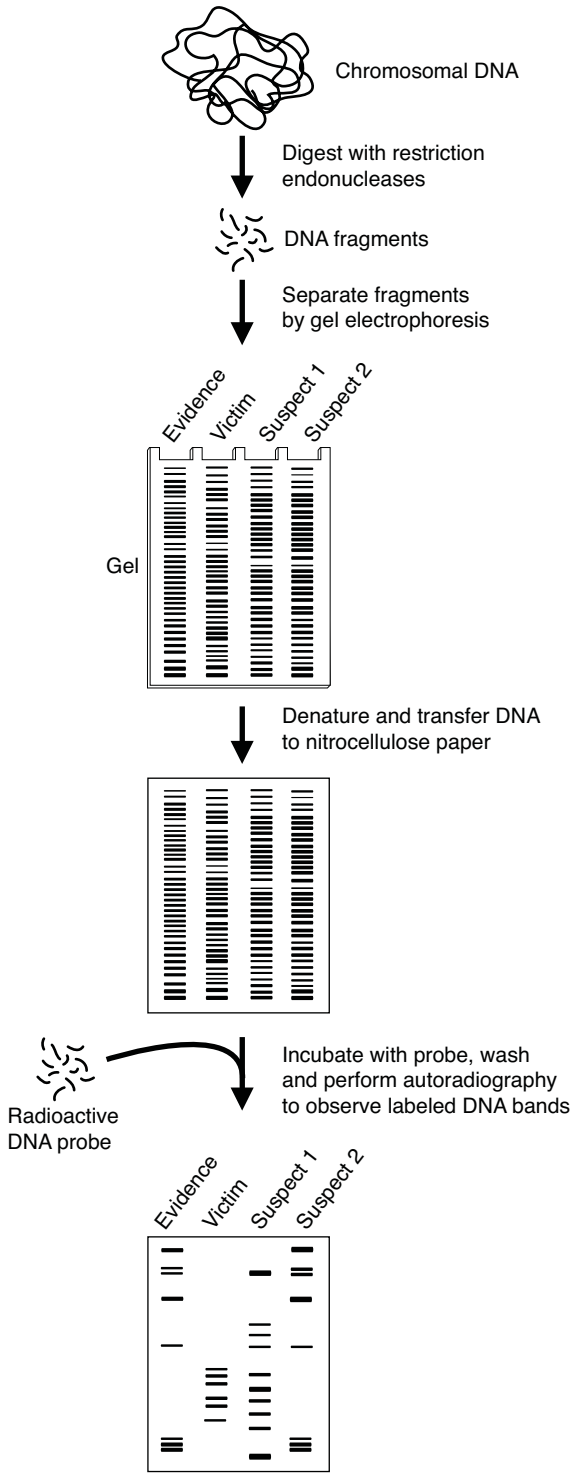


FIGURE 5-14. DNA fingerprinting. Restrictive enzymes are used to break chromosomal DNA into fragments, which are then separated by gel electrophoresis, denatured, and transferred to nitrocellulose paper; DNA bands are labeled with a radioactive probe and observed using autoradiography. (Modified from Smith C., Marks A.D., Lieberman M. [2005]. *Marks' basic medical biochemistry* [2nd ed., p. 309]. Philadelphia: Lippincott Williams & Wilkins.)

With DNA fingerprinting, these odds are 1 in 100,000 to 1 million.

When necessary, the polymerase chain reaction (PCR) can be used to amplify specific segments of DNA (see Chapter 14). It is particularly suited for amplifying regions of DNA for clinical and forensic testing procedures because only a small sample of DNA is required as the starting material. Regions of DNA can be amplified from a single hair or drop of blood or saliva.

Gene Therapy

Although quite different from inserting genetic material into a unicellular organism such as bacteria, techniques are available for inserting genes into the genome of intact multicellular plants and animals. Promising delivery vehicles for these genes are the adenoviruses. These viruses are ideal vehicles because their DNA does not become integrated into the host genome; however, repeated inoculations are often needed because the body's immune system usually targets cells expressing adenovirus proteins. Sterically stable liposomes also show promise as DNA delivery mechanisms. This type of therapy is one of the more promising methods for the treatment of genetic disorders such as cystic fibrosis, certain cancers, and a number of infectious diseases.

Two main approaches are used in gene therapy: transferred genes can replace defective genes or they can selectively inhibit deleterious genes. Cloned DNA sequences are usually the compounds used in gene therapy. However, the introduction of the cloned gene into the multicellular organism can influence only the few cells that get the gene. An answer to this problem would be the insertion of the gene into a sperm or ovum; after fertilization, the gene would be replicated in all of the differentiating cell types. Even so, techniques for cell insertion are limited. Not only are moral and ethical issues involved, but these techniques cannot direct the inserted DNA to attach to a particular chromosome or supplant an existing gene by knocking it out of its place.

To date, gene therapy has been used successfully to treat children with severe combined immunodeficiency disease (see Chapter 16) and in a suicide gene transfer to facilitate treatment of graft-versus-host disease after donor lymphocyte infusion.

RNA Interference Technology

One method of gene therapy focuses on the previously described replacement of missing or defective genes. However, several genetic disorders are not due to missing genes, but to faulty gene activity. With this in mind, some scientists are approaching the problem by using *RNA interference* (RNAi) to stop genes from making unwanted disease proteins. RNAi is a naturally occurring process in which small pieces of double-stranded RNA (small interfering RNA [siRNA]) suppress gene expression. Scientists believe that RNAi may have originated as a defense

against viral infections and potentially harmful genomic invaders. In viral infections, RNAi would serve to control the infection by preventing the synthesis of viral proteins.

With the continued refinement of techniques to silence genes, RNAi has already had a major impact on molecular biology. For example, it has given scientists the ability to practice reverse genomics, in which a gene's function can be inferred through silencing its expression. Increasingly, pharmacologic companies are using RNAi to identify disease-related drug targets. There also is considerable interest in harnessing RNAi for therapeutic purposes, including the treatment of human immunodeficiency virus (HIV) infection and hepatitis C. Before this can occur, however, the therapeutic methods must be shown to be safe and effective, and obstacles to delivering RNAi into targeted cells must be overcome. It is difficult for RNA to cross the cell membrane, and it is quickly broken down by enzymes in the blood.

In summary, the genome is the gene complement of an organism. Genomic mapping is a method used to assign genes to particular chromosomes or parts of a chromosome. The most important ones used are family linkage studies, gene dosage methods, and hybridization studies. Often the specific assignment of a gene is determined by using information from several mapping techniques. Linkage studies assign a chromosome location to genes based on their close association with other genes of known location. Recombinant DNA studies involve the extraction of specific types of mRNA used in the synthesis of complementary DNA strands. The complementary DNA strands, labeled with a radioisotope, bind with the genes for which they are complementary and are used as gene probes. A haplotype consists of the many closely linked SNPs on a single chromosome that generally are passed as a block from one generation to another in a particular population. The International HapMap Project has been developed to map the SNPs on the human genome with the anticipation that it may be useful in the prediction and management of disease.

Genetic engineering has provided the methods for manipulating nucleic acids and recombining genes (recombinant DNA) into hybrid molecules that can be inserted into unicellular organisms and reproduced many times over. As a result, proteins that formerly were available only in small amounts can now be made in large quantities once their respective genes have been isolated. DNA fingerprinting, which relies on recombinant DNA technologies and those of genetic mapping, is often used in forensic investigations. A newer strategy for management of genetic disorders focuses on gene silencing by using RNAi to stop genes from making unwanted disease proteins.

REVIEW EXERCISES

1. The Human Genome Project has revealed that humans have only 30,000 to 35,000 genes. Only about 2% of the genome encodes instructions for protein synthesis, whereas 50% consist of repeat sequences that do not code proteins.

A. Use this information to explain how this small number of protein-encoding genes is able to produce the vast array of proteins needed for organ and structural development in the embryo, as well as those needed for normal function of the body in postnatal life.

2. A child about to undergo surgery is typed for possible blood transfusions. His parents are told that he is type O positive. Both his mother and father are type A positive.

A. How would you go about explaining this variation in blood type to the parents?

3. The posttranslational folding of proteins is essential to their proper functioning and degradation.

A. Hypothesize on how age-related changes in the folding of proteins in the central nervous system could contribute to the development of the neurofibrillary tangles that are characteristics of Alzheimer disease.

4. More than 100,000 people die of adverse drug reactions each year; another 2.2 million experience serious reactions; whereas others fail to respond at all to the therapeutic actions of drugs.

A. Explain how the use of information about *single-nucleotide polymorphisms* might be used to map individual variations in drug responses.

5. Human insulin, prepared by recombinant DNA technology, is now available for the treatment of diabetes mellitus.

A. Explain the techniques used for the production of a human hormone using this technology.

6. Cystic fibrosis is a disorder of the cell membrane chloride channel that causes the exocrine glands of the body to produce abnormally thick mucus resulting in the development of chronic obstructive lung disease, pancreatitis, and infertility in men.

A. Explain how a single mutant gene can produce such devastating effects.

B. The disease is transmitted as a single-gene recessive trait. Describe the inheritance of the disorder using Figure 5-12.

7. Adult polycystic kidney disease is transmitted as an autosomal dominant trait.

A. Explain the parent-to-child transmission of this disorder.

B. Although the disease is transmitted as an autosomal dominant trait, some people who inherit the gene may develop symptoms early in life, others may develop them later in life, and still others may never develop significant symptoms of the disease during their lifetime. Explain.

BIBLIOGRAPHY

Agrawal N., Dasaradhi P.V.N., Mohmmed A., et al. (2003). RNA interference: Biology, mechanism, and applications. *Microbiology and Molecular Biology Reviews* 67, 657–685.

Alberts B., Johnson A., Lewis J., et al. (2008). *Molecular biology of the cell* (5th ed., pp. 195–499). New York: Garland Science.

Cheng J., Kapranov P., Drenkow J., et al. (2005). Transcriptional maps of 10 human chromosomes at 5-nucleotide resolution. *Science* 308, 1149–1154.

Fischer A., Cavazzana-Clavo M. (2006). Wither gene therapy? *The Scientist* 20(2), 36–40.

Gibbs R. (2005). Deeper into the genome. *Nature* 437, 1233–1234.

Gibson G., Muse S.V. (2004). *A primer of genome science*. Sunderland, MA: Sinauer Associates, Inc. Publishers.

Jegalian K., Lahn B.T. (2001). Why the Y is so weird. *Scientific American* February, 56–61.

Jorde L.B., Carey J.C., Bamshad M.J., et al. (2006). *Medical genetics* (3rd ed.). St. Louis: Mosby.

Klug W.S., Cummings M.R. (2005). *Essentials of genetics* (5th ed.). Upper Saddle River, NJ: Pearson Prentice Hall.

McElheny V.K. (2006). The human genome project. *The Scientist* 20(2), 42–48.

Moore K.L., Persaud T.V.N. (2003). *The developing human: Clinically orientated embryology*. (7th ed., pp. 157–185). Philadelphia: Saunders.

Myers S., Bottolo L., Freeman C., et al. (2005). A fine-scale map of recombination rates and hotspots across the human genome. *Science* 310, 321–324.

National Center for Biotechnology Information (NCBI). *NCBI human genome resources site, including site for Human Genome Map*. [Online]. Available: http://www.ncbi.nlm.nih.gov/projects/genome/guide/human//. Accessed December 18, 2008.

National Human Genome Project. *All about the Human Genome Project*. [Online]. Available: http://www.genome.gov/10001772/. Accessed December 18, 2008.

Nussbaum R.L., McInnes R.R., Willard H.F. (2007). *Thompson & Thompson genetics in medicine* (7th ed.). Philadelphia: Saunders Elsevier.

Phimister E.G. (2005). Genomic cartography—Presenting the HapMap. *New England Journal of Medicine* 353(17), 1766–1768.

Sadler R.W. (2003). *Langman's medical embryology* (9th ed., pp. 3–30). Philadelphia: Lippincott Williams & Wilkins.

Shankar P., Manjunath N., Lieberman J. (2005). The prospect of silencing disease using RNA interference. *JAMA* 293(11), 1367–1373.

Smith C., Marks A.D., Lieberman M. (2005). *Marks' basic biochemistry: A clinical approach* (2nd ed., pp. 205–316). Philadelphia: Lippincott Williams & Wilkins.

Stevenson M. (2004). Therapeutic potential of RNA interference. *New England Journal of Medicine* 351(17), 1772–1777.

Villard J. (2004). Transcription regulation and human disease. *Swiss Medicine Weekly* 124, 571–579.

Genetic and Chromosomal Disorders
Single-Gene Disorders
Autosomal Dominant Disorders
Autosomal Recessive Disorders
X-Linked Disorders
Single-Gene Disorders with Atypical Patterns of Inheritance
Multifactorial Inheritance Disorders
Cleft Lip and Cleft Palate
Chromosomal Disorders
Structural Chromosomal Abnormalities
Numeric Disorders Involving Autosomes
Numeric Disorders Involving Sex Chromosomes
Disorders Due to Environmental Influences
Period of Vulnerability
Teratogenic Agents
Radiation
Chemicals and Drugs
Infectious Agents
Prenatal Screening and Diagnosis
Screening and Diagnostic Methods
Ultrasonography
Maternal Serum Markers
Invasive Testing
Cytogenetic and Biochemical Analyses

Chapter 6

Genetic and Congenital Disorders

Congenital defects, sometimes called *birth defects,* are abnormalities of a body structure, function, or metabolism that are present at birth. They affect about a quarter of a million infants in the United States each year and are the leading cause of infant death. Birth defects may be caused by genetic factors (i.e., single-gene or multifactorial inheritance or chromosomal aberrations) or environmental factors that are active during embryonic or fetal development (e.g., maternal disease, infections, or drugs taken during pregnancy). Although congenital defects are present at birth, genetic disorders may make their appearance later in life.

It is important to note that most of the scientific understanding of genetics and developmental disorders has taken place in the past three decades, largely as a result of the Human Genome Project. In fact, the molecular basis for many single-gene disorders is now known or will likely be known within the next few years. Such research has led to new and exciting insights not only in genetics, but also in the basic pathophysiology of disease.

This chapter provides an overview of genetic and congenital disorders and is divided into three parts: (1) genetic and chromosomal disorders, (2) disorders due to environmental agents, and (3) prenatal screening and diagnosis.

Genetic and Chromosomal Disorders

A genetic disorder can be described as a discrete event that affects gene expression in a group of cells related to each other by gene linkage. Most genetic disorders are caused by changes in the deoxyribonucleic acid (DNA) sequence that alters the synthesis of a single-gene product. However, some genetic disorders are caused by chromosomal rearrangements that result in deletion or duplication of a group of closely linked genes, or by an abnormal number of chromosomes resulting from mistakes that occur during meiosis or mitosis.[1,2]

The genes on each person's two chromosomes are arranged in pairs and in strict order, with each gene

occupying a specific location or *locus*. One member of each pair is derived from the person's father and the other from the person's mother. The term *allele* refers to different forms or DNA sequences that a gene may have in a population. If the members of a gene pair are identical (i.e., code the exact same gene product), the person is *homozygous,* and if the two members are different, the person is *heterozygous*. The genetic composition of a person is called a *genotype,* whereas the *phenotype* is the observable expression of a genotype in terms of morphologic, biochemical, or molecular traits. If the trait is expressed in the heterozygote (i.e., only one member of the gene pair codes for the trait), it is said to be *dominant;* if it is expressed only in the homozygote (i.e., both members of the gene pair code for the trait), it is *recessive*. Although gene expression usually follows a dominant or recessive pattern, it is possible for both alleles of a gene pair to be fully expressed in the heterozygote, a condition called *codominance*. Many genes have only one normal version, which geneticists call the *wild-type* allele. Other genes have more than one normal allele (alternate forms) at the same locus. This is called *polymorphism*. Blood group inheritance (e.g., AO, BO, AB) is an example of codominance and polymorphism.

A *gene mutation* is a biochemical event that results in a change in the DNA sequence of a gene. Mutations can involve the substitution of a single-nucleotide base (point mutation) or insertion or deletion of one or two base pairs. Those that affect the germ cells (ovum or spermatozoa) are transmitted to the progeny and may give rise to inherited diseases. Mutations in somatic (body) cells are not transmitted to the progeny but are important in the causation of cancers and some congenital disorders.

Genetic disorders can involve a single-gene trait, multifactorial inheritance, or a chromosomal abnormality. The disorder may be inherited as a family trait or arise as a sporadic case due to a new mutation.

Genetic and Chromosomal Disorders

- Genetic disorders are inherited as autosomal dominant disorders, in which each child has a 50% chance of inheriting the disorder, or as autosomal recessive disorders, in which each child has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected.
- Sex-linked disorders almost always are associated with the X chromosome and are predominantly recessive.
- Chromosomal disorders reflect events that occur at the time of meiosis and result from defective movement of an entire chromosome or from breakage of a chromosome with loss or translocation of genetic material.

Single-Gene Disorders

Single-gene disorders are caused by a single defective or mutant gene. The defective gene may be present on an autosome or the X chromosome and may affect only one member of an autosomal gene pair (matched with a normal gene) or both members of the pair. Single-gene defects follow the mendelian pattern of inheritance (see Chapter 5) and are often called *mendelian disorders*.

A single mutant gene may be expressed in many different parts of the body. Marfan syndrome is a defect in connective tissue that has widespread effects involving skeletal, eye, and cardiovascular structures. In other single-gene disorders, the same defect can be caused by mutations at several different loci. Childhood deafness can result from 16 different types of autosomal recessive mutations.

Virtually all single-gene disorders lead to formation of an abnormal protein or decreased production of a gene product. The disorder can result in a defective enzyme or decreased amounts of an enzyme, defects in receptor proteins and their function, alterations in nonenzyme proteins, or mutations resulting in unusual reactions to drugs. Table 6-1 lists some of the common single-gene disorders and their manifestations.

Autosomal Dominant Disorders

In autosomal dominant disorders, a single mutant allele from an affected parent is transmitted to an offspring regardless of sex. The affected parent has a 50% chance of transmitting the disorder to each offspring[1–4] (Fig. 6-1). The unaffected relatives of the parent or unaffected siblings of the offspring do not transmit the disorder. In many conditions, the age of onset is delayed, and the signs and symptoms of the disorder do not appear until later in life, as in Huntington disease (see Chapter 37).

In some cases, the person with an autosomal dominant disorder does not have an affected parent. Such persons owe their disorder to new mutations involving either the ovum or sperm from which they were derived. Their siblings are neither affected nor at increased risk of developing the disease. Whether the mutation is

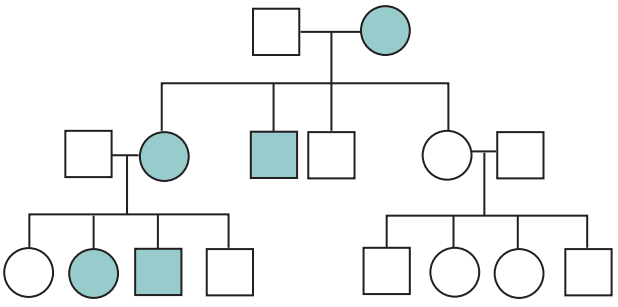


FIGURE 6-1. Simple pedigree for inheritance of an autosomal dominant trait. The *blue-colored square* (male) or *circle* (female) represents an affected parent with a mutant gene. An affected parent with an autosomal dominant trait has a 50% chance of passing the mutant gene on to each child regardless of sex.

TABLE 6-1 Some Disorders of Mendelian or Single-Gene Inheritance and Their Significance

Disorder	Significance
Autosomal Dominant	
Achondroplasia	Short-limb dwarfism
Adult polycystic kidney disease	Chronic kidney disease
Huntington chorea	Neurodegenerative disorder
Familial hypercholesterolemia	Premature atherosclerosis
Marfan syndrome	Connective tissue disorder with abnormalities in the skeletal, ocular, and cardiovascular systems
Neurofibromatosis (NF)	Neurogenic tumors: fibromatous skin tumors, pigmented skin lesions, and ocular nodules in NF-1; bilateral acoustic neuromas in NF-2
Osteogenesis imperfecta	Brittle bone disease due to defects in collagen synthesis
Spherocytosis	Disorder of red blood cells
von Willebrand disease	Bleeding disorder
Autosomal Recessive	
Cystic fibrosis	Disorder of membrane transport of chloride ions in exocrine glands causing lung and pancreatic disease
Glycogen storage diseases	Excess accumulation of glycogen in the liver and hypoglycemia (von Gierke disease); glycogen accumulation in striated muscle in myopathic forms
Oculocutaneous albinism	Hypopigmentation of skin, hair, and eyes as a result of inability to synthesize melanin
Phenylketonuria (PKU)	Lack of phenylalanine hydroxylase with hyperphenylalaninemia and impaired brain development
Sickle cell disease	Red blood cell defect
Tay-Sachs disease	Deficiency of hexosaminidase A; severe mental and physical deterioration beginning in infancy
X-Linked Recessive	
Bruton-type hypogammaglobulinemia	Immunodeficiency
Hemophilia A	Bleeding disorder
Duchenne dystrophy	Muscular dystrophy
Fragile X syndrome	Mental retardation

passed on to the next generation depends on the affected person's reproductive capacity. Many new autosomal dominant mutations are accompanied by reduced reproductive capacity; therefore, the defect is not perpetuated in future generations. If an autosomal defect is accompanied by a total inability to reproduce, essentially all new cases of the disorder will be due to new mutations. If the defect does not affect reproductive capacity, it is more likely to be inherited.

Although there is a 50% chance of inheriting a dominant genetic disorder from an affected parent, there can be wide variation in gene penetration and expression. When a person inherits a dominant mutant gene but fails to express it, the trait is described as having *reduced penetrance*. Penetrance is expressed in mathematical terms: a 50% penetrance indicates that a person who inherits the defective gene has a 50% chance of expressing the disorder. The person who has a mutant gene but does not express it is an important exception to the rule that unaffected persons do not transmit an autosomal dominant trait. These persons can transmit the gene to their descendants and so produce a skipped generation. Autosomal dominant disorders also can display *variable expressivity*, meaning that they can be expressed differently among individuals. Polydactyly or supernumerary digits, for example, may be expressed in either the fingers or the toes.

The gene products of autosomal dominant disorders usually are regulatory proteins involved in rate-limiting components of complex metabolic pathways or key components of structural proteins such as collagen.[2,3] Two disorders of autosomal inheritance, Marfan syndrome and neurofibromatosis (NF), are described in this chapter.

Marfan Syndrome. Marfan syndrome is an autosomal dominant disorder with an estimated prevalence of 1 per 20,000.[3] Approximately 75% of cases are of familial origin, with the rest arising from new mutations in the germ cells of parents. The pathogenesis of Marfan syndrome is related to the dysfunction of the gene that codes for *fibrillin I*, a major component of microfibrils found in the extracellular matrix.[3] Myofibrils serve as scaffolding for deposition of elastin and are considered integral components of elastic fibers. These fibers are essential for maintaining the tissue architecture of various body structures, most notably tendons and other elastin tissue–rich structures, such as heart valves and blood vessels.

Marfan syndrome affects several organ systems, including the ocular system (eyes), the cardiovascular system (heart and blood vessels), and the skeletal system (bones and joints).[3–6] There is a wide range of variation in the expression of the disorder. Persons may have abnormalities of one or all three systems. The skeletal deformities, which are the most obvious features of the

disorder, include a long, thin body with exceptionally long extremities and long, tapering fingers, sometimes called *arachnodactyly* or *spider fingers;* hyperextensible joints; and a variety of spinal deformities, including kyphosis and scoliosis (Fig. 6-2). Chest deformities, pectus excavatum (i.e., deeply depressed sternum), or pigeon chest deformity often is present and may require surgery. The most common eye disorder is bilateral dislocation of the lens due to weakness of the suspensory ligaments. Myopia and predisposition to retinal detachment also are common, the result of increased optic globe length due to altered connective tissue support of ocular structures. However, the most life-threatening aspects of the disorder are the cardiovascular defects, which include mitral valve prolapse, progressive dilation of the aortic valve ring, and weakness of the aorta and other arteries. Dissection and rupture of the aorta may lead to premature death. In women, the risk of aortic dissection is increased in pregnancy.

There is no cure for Marfan syndrome; treatment plans include echocardiograms and electrocardiograms to assess the status of the cardiovascular system, periodic eye examinations, and evaluation of the skeletal system, especially in children and adolescents. Low to moderate activity levels are usually well tolerated. Strenuous activities such as contact sports, weight training, high-impact aerobics, and scuba diving should usually be avoided. Surgical treatment may become necessary in cases of progressive aortic dilation or acute aortic dissection.

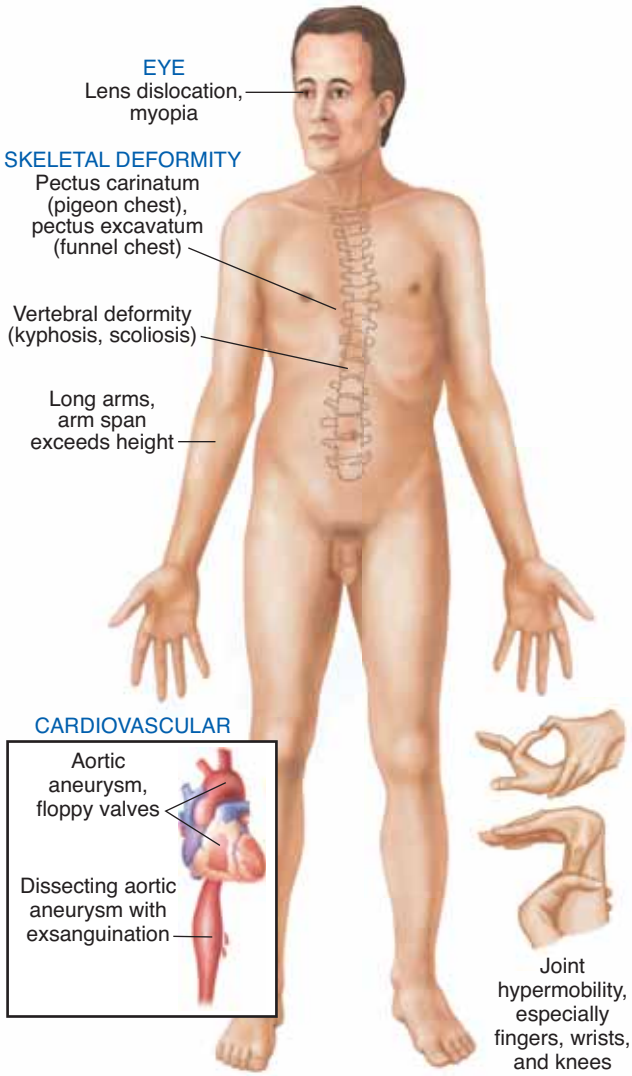


FIGURE 6-2. Clinical features of Marfan syndrome.

Neurofibromatosis. Neurofibromatosis is a condition involving neurogenic tumors that arise from Schwann cells and other elements of the peripheral nervous system.[2,3,7–9] There are at least two genetically and clinically distinct forms of the disorder: type 1 NF (NF-1), also known as *von Recklinghausen disease,* and type 2 bilateral acoustic NF (NF-2). Both of these disorders result from a genetic defect in a tumor-suppressor gene that regulates cell differentiation and growth. The gene for NF-1 has been mapped to chromosome 17 and the gene for NF-2 to chromosome 22.[3]

Type 1 NF is a relatively common disorder, with a frequency of 1 in 3500.[3] Approximately 50% of cases have a family history of autosomal dominant transmission, and the remaining 50% appear to represent a new mutation. The disorder is characterized by multiple neural tumors (neurofibromas) dispersed anywhere on the body; numerous pigmented skin lesions, some of which are café au lait spots; and pigmented nodules (Lisch nodules) of the iris. The cutaneous neurofibromas, which vary in number from a few to many hundreds, manifest as soft, pedunculated lesions that project from the skin. They are the most common type of lesion, often are not apparent until puberty, and are present in greatest density over the trunk (Fig. 6-3). The subcutaneous lesions grow just below the skin; they are firm and round, and may be painful. Plexiform neurofibromas involve the larger peripheral nerves. They tend to form large tumors that cause severe disfigurement of the face, overgrowth of an extremity, or skeletal deformities such as scoliosis. Pigmented nodules of the iris (Lisch nodules), which are specific for NF-1, usually are present after 6 years of age. They do not present any clinical problem but are useful in establishing a diagnosis.

A second major component of NF-1 is the presence of large (usually ≥15 mm in diameter), flat cutaneous pigmentations, known as *café au lait spots*. They are usually a uniform light brown in whites and darker brown in persons of color, with sharply demarcated edges. Although small single lesions may be found in normal children, larger lesions or six or more spots larger than 1.5 cm in diameter suggest NF-1. The skin pigmentations become more evident with age as the melanosomes in the epidermal cells accumulate melanin.

Children with NF-1 are also susceptible to neurologic complications. There is an increased incidence of learning disabilities, attention deficit disorders, and abnormalities of speech. Complex partial and generalized tonic-clonic seizures are a frequent complication. NF-1 is also associated with increased incidence of other neurogenic tumors, including meningiomas, optic gliomas, and pheochromocytomas.[2]

FIGURE 6-3. Neurofibromatosis, type I. Multiple cutaneous neurofibromas are noted on the face and trunk. (From Rubin E., Kileen A.A., Strayer D.S. [2008]. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 201]. Philadelphia: Lippincott Williams & Wilkins.)

Type 2 NF, which is characterized by tumors of the acoustic nerve and multiple meningiomas, is much less common than NF-1. Most often, the disorder is asymptomatic through the first 15 years of life. The most frequent symptoms are headaches, hearing loss, and tinnitus (i.e., ringing in the ears). There may be associated intracranial and spinal meningiomas. The condition is often made worse by pregnancy, and oral contraceptives may increase the growth and symptoms of tumors. Persons with the disorder should be warned that severe disorientation may occur during diving or swimming underwater, and drowning may result. Surgery may be indicated for debulking or removal of the tumors.

Autosomal Recessive Disorders

Autosomal recessive disorders are manifested only when both members of the gene pair are affected. In this case, both parents may be unaffected but are carriers of the defective gene. Autosomal recessive disorders affect both sexes. The occurrence risks in each pregnancy are one in four for a defective child, two in four for a carrier child, and one in four for a normal (noncarrier, unaffected) homozygous child[1–4] (Fig. 6-4). *Consanguineous mating* (mating of two related individuals), or inbreeding, increases the chance that two people who mate will be carriers of an autosomal recessive disorder.

With autosomal recessive disorders, the age of onset is frequently early in life; the symptomatology tends to be more uniform than with autosomal dominant disorders; and the disorders are characteristically caused by loss-of-function mutations, many of which impair or eliminate the function of an enzyme. In the case of a heterozygous carrier, the presence of a mutant gene usually does not produce symptoms because equal amounts of normal and defective enzymes are synthesized. This "margin of safety" ensures that cells with half their usual amount of enzyme function normally. By contrast, the inactivation of both alleles in a homozygote results in complete loss of enzyme activity. Although new mutations for recessive disorders do occur, they are rarely detected clinically because the affected person is an asymptomatic heterozygote. Several generations may pass before the descendents of such a person mate with other heterozygotes and produce affected offspring.[3]

Autosomal recessive disorders include almost all inborn errors of metabolism. Enzyme disorders that impair catabolic pathways result in an accumulation of dietary substances (e.g., phenylketonuria) or cellular constituents (e.g., lysosomal storage diseases). Other disorders result from a defect in the enzyme-mediated synthesis of an essential protein (e.g., the cystic fibrosis transmembrane conductance regulator in cystic fibrosis [see Chapter 23]). Two examples of autosomal recessive disorders that are not covered elsewhere in this book are phenylketonuria and Tay-Sachs disease.

Phenylketonuria. Phenylketonuria (PKU, hyperphenylalaninemia) is a metabolic disorder caused by elevated levels of phenylalanine that are toxic to the brain. The incidence of PKU and hyperphenylalaninemia is 1 per 10,000 in the white and Asian population, but varies widely across geographic areas (e.g., 1 to 4500 in Ireland to less than 1 to 100,000 in Finland).[2] In most cases, the hyperphenylalaninemia results from a deficiency of phenylalanine hydroxylase (PAH), a liver enzyme that converts the amino acid phenylalanine to tyrosine.[1–3,10,11]

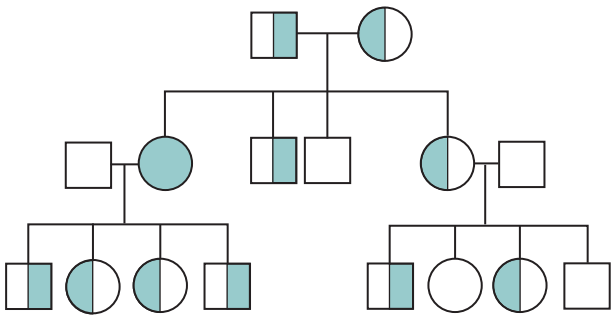


FIGURE 6-4. Simple pedigree for inheritance of an autosomal recessive trait. The half *blue-colored square* (male) and *circle* (female) represent a mutant gene. When both parents are carriers of a mutant gene, there is a 25% chance of having an affected child (*full blue-colored circle or square*), a 50% chance of a carrier child, and a 25% chance of an unaffected or noncarrier child, regardless of sex. All children (100%) of an affected parent are carriers.

Phenylalanine is an essential amino acid derived solely from the diet. In normal children, less than 50% of the dietary intake of phenylalanine is necessary for protein synthesis. The remainder is converted to tyrosine by PAH. When breakdown of phenylalanine is blocked because of a lack of PAH, other minor metabolic pathways are used, yielding several intermediates that are excreted in large amounts in the sweat and urine. These metabolites impart an unpleasant strong musty odor to affected infants. It is believed, however, that phenylalanine rather than its metabolites contribute to the brain damage in PKU. The lack of tyrosine, a precursor of melanin, is responsible for the light color of the hair and skin.

At the molecular level, approximately 400 mutant alleles for the PAH gene have been identified, some of which produce only mild deficiency and others a severe deficiency.[3] The severity of hyperphenylalaninemia depends on the degree of PAH deficiency and can be classified as *classic PKU*, *mild PKU*, and *mild hyperphenylalaninemia* based on blood concentrations of phenylalanine.[11] Infants and children with classic and mild PKU require dietary protein restrictions to prevent mental retardation, microcephaly, and other signs of impaired neurologic development. Affected infants are normal at birth but within a few weeks begin to develop a rising phenylalanine level and signs of impaired brain development. Seizures, other neurologic abnormalities, decreased pigmentation of the hair and skin, and eczema often accompany the mental retardation in untreated infants.

Because the symptoms of untreated PKU develop gradually and would often go undetected until irreversible mental retardation had occurred, newborn infants are routinely screened for abnormal levels of serum phenylalanine.[10–13] Infants with hyperphenylalaninemia are treated with a special diet that restricts phenylalanine intake. The results of dietary therapy of children with PKU have been impressive. The diet can prevent mental retardation as well as other neurodegenerative effects of untreated PKU. However, dietary treatment must be started early in neonatal life to prevent brain damage. Infants with elevated phenylalanine levels should begin treatment by 7 to 10 days of age, indicating the need for early diagnosis. The duration of the dietary restriction remains controversial. Women with PKU who wish to have children require careful attention to their diet, both before conception and during pregnancy, as a means of controlling their phenylalanine levels.[10]

A rare form of hyperphenylalaninemia is caused by a deficiency in tetrahydrobiopterin (BH_4), a cofactor that PAH uses as it converts phenylalanine to tyrosine.[12] In this condition, dietary restriction of phenylalanine does not arrest neurologic deterioration. These children can be treated with sapropterin dihydrochloride, a newly developed oral form of the cofactor BH_4. Although supplementation of BH_4 is indicated for treatment of hyperphenylalaninemia due to a deficiency in BH_4 synthesis, it has also been found to decrease plasma phenylalanine concentrations in mild hyperphenylalaninemia due to PAH deficiency, allowing these children to tolerate a less restricted diet.[12]

Tay-Sachs Disease. Tay-Sachs disease is a variant of a class of lysosomal storage diseases, known as the *gangliosidoses,* in which there is failure of lysosomes to break down the GM_2 ganglioside of cell membranes. Tay-Sachs disease is inherited as an autosomal recessive trait and is predominantly a disorder of Eastern European (Ashkenazi) Jews, in which a carrier rate of 1 in 30 has been reported.[1–3]

The GM_2 ganglioside accumulates in the lysosomes of all organs in Tay-Sachs disease, but is most prominent in the brain neurons and retina. Microscopic examination reveals neurons ballooned with cytoplasmic vacuoles, each of which constitutes a markedly distended lysosome filled with gangliosides. In time, there is progressive destruction of neurons within the brain substance, including the cerebellum, basal ganglia, brain stem, spinal cord, and autonomic nervous system. Involvement of the retina is detected by ophthalmoscopy as a cherry-red spot on the macula.

Infants with Tay-Sachs disease appear normal at birth but begin to manifest progressive weakness, muscle flaccidity, and decreased attentiveness at approximately 6 to 10 months of age. This is followed by rapid deterioration of motor and mental function, often with development of generalized seizures. Retinal involvement leads to visual impairment and eventual blindness. Death usually occurs before 4 to 5 years of age. Although there is no cure for the disease, analysis of the blood serum for the lysosomal enzyme hexosaminidase A, which is deficient in Tay-Sachs disease, allows for accurate identification of genetic carriers for the disease.

X-Linked Disorders

Sex-linked disorders are almost always associated with the X, or female, chromosome, and the inheritance pattern is predominantly recessive.[1–4] Because of the presence of a normal paired X gene, female heterozygotes rarely experience the effects of a defective gene, whereas all males who receive the gene are typically affected. The common pattern of inheritance is one in which an unaffected mother carries one normal and one mutant allele on the X chromosome. This means that she has a 50% chance of transmitting the defective gene to her sons, and her daughters have a 50% chance of being carriers of the mutant gene (Fig. 6-5). When the affected son procreates, he transmits the defective gene to all of his daughters, who become carriers of the mutant gene. Because the genes of the Y chromosome are unaffected, the affected male does not transmit the defect to any of his sons, and they will not be carriers or transmit the disorder to their children. X-linked recessive disorders include glucose-6-phosphate dehydrogenase deficiency (see Chapter 13), hemophilia A (see Chapter 12), and X-linked agammaglobulinemia (see Chapter 16).

Single-Gene Disorders with Atypical Patterns of Inheritance

Several genetic disorders do not follow the mendelian pattern of inheritance. These include diseases caused by

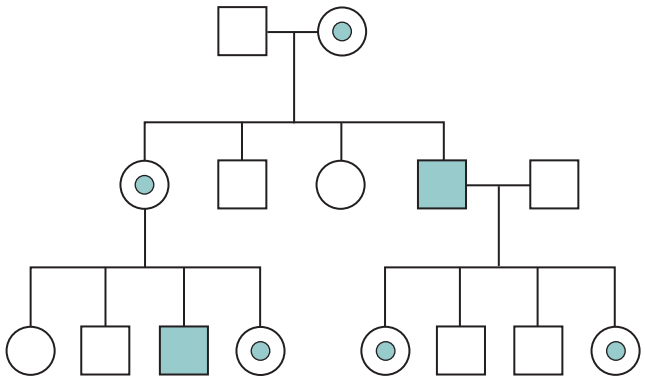


FIGURE 6-5. Simple pedigree for inheritance of an X-linked recessive trait. X-linked recessive traits are expressed phenotypically in the male offspring. A *small blue-colored circle* represents the X chromosome with the defective gene in the female and *the larger blue-colored square* represents the affected male. The affected male passes the mutant gene to all of his daughters, who become carriers of the trait and have a 50% chance of passing the gene to their sons and daughters, who in turn have a 50% chance of being carriers of the gene.

genomic imprinting, triplet repeat mutations, and mutations in mitochondrial genes.[3]

Genomic Imprinting. According to the mendelian pattern of inheritance, a mutant allele of an autosomal gene is equally likely to be transmitted from a parent to an offspring of either sex; similarly, a female is equally likely to transmit a mutated X-linked gene to either sex.[4] Originally, little attention was paid to whether the sex of the parent had any effect on expression of the genes each parent transmits. As discussed in Chapter 5, it is now known that in some genetic disorders such as Prader-Willi and Angelman syndromes, the expression of the disease phenotype depends on whether the mutant allele was inherited from the father or the mother, a phenomenon known as *genomic imprinting*.

Triplet Repeat Mutations: Fragile X Syndrome. Fragile X syndrome is the prototype of disorders in which the mutation is characterized by a long repeating sequence of three nucleotides.[1–3,14,15] The origins of about 40 diseases, including Huntington disease and myotonic dystrophy, have been assigned to pathologic expansions of trinucleotide repeats, and all disorders discovered so far are associated with neurodegenerative changes. In each condition, the expansion of the specific sets of three nucleotides within the gene disrupts its function.

Fragile X syndrome is characterized by mental retardation and an abnormality in the X chromosome. The disorder, which affects approximately 1 in 1250 males and 1 in 2500 females, is the most common form of inherited mental retardation.[2] It is second only to Down syndrome as an identifiable cause of mental retardation. The cytogenetic alteration referred to as the *fragile X* is induced in certain culture conditions and is seen as a discontinuity of staining or constriction in the long arm of the X chromosome.

In addition to mental retardation, the fragile X syndrome is characterized by distinctive features including a large face, a large mandible, and large, everted ears. Hyperextensible joints, a high-arched palate, and mitral valve prolapse, which are observed in some cases, mimic a connective tissue disorder. Some physical abnormalities may be subtle or absent. The most distinctive feature, which is present in 90% of prepubertal boys, is macroorchidism, or large testes. Because girls have two X chromosomes, they are more likely to have relatively normal cognitive development, or they may show a learning disability in a particular area, such as mathematics. Women with the disorder may also experience premature ovarian failure or begin menopause earlier than women who are not affected by fragile X syndrome.[14]

The fragile X syndrome results from a mutation in the *FMR1* (fragile X mental retardation 1) gene that has been mapped to the fragile site on the X chromosome.[2,3] The protein product of the FMR1 gene, the *fragile X mental retardation protein* (FMRP), is a widely expressed ribonucleic acid (RNA)-binding protein. The protein travels from the cytoplasm to the nucleus, where it binds specific messenger RNAs (mRNAs) and then transports them from the nucleus to the synaptic ends of axons and dendrites, where the FMRP–mRNA complexes perform critical roles in regulating the translation of mRNA.[3]

The inheritance of the *FMR1* gene follows the pattern of X-linked traits, with the father passing the gene on to all his daughters but not his sons. However, unlike other X-linked recessive disorders, approximately 20% of males who have been shown to carry the fragile X mutation are clinically and cytogenetically normal. These "carrier males" can transmit the disease to their grandsons through their phenotypically normal daughters. Another peculiarity is the presence of mental retardation in approximately 50% of carrier females. These peculiarities have been related to the dynamic nature of the mutation, which involves repeats of a triplet of cytosine, guanine, guanine (CGG) nucleotides. In the normal population, the number of CGG repeats is small, averaging around 29, whereas affected individuals have 200 to 4000 repeats. The so-called full mutations are thought to arise through an intermediate premutation process that is characterized by expansions in the CGG repeats. A gene with 52 to 200 repeats is generally considered a premutation, and one with more than 200 repeats, a full mutation.[2,3] Carrier males and females have premutations. During oogenesis (but not spermatogenesis), the premutations can be converted to full mutations by further expansion of the CGG repeats, which can then be transmitted to both the sons and daughters of the carrier female. These observations provide an explanation for why some carrier males are unaffected (they have premutations) and some females are affected (they have full mutations).

Mitochondrial Gene Disorders. The mitochondria contain their own DNA, which is distinct from the DNA contained in the cell nucleus. An understanding of the role of mitochondrial DNA (mtDNA) has evolved since 1988, when the first mutation of mtDNA was discovered.[16] Since that time, more than 100 different disease-related

rearrangements and point mutations have been identified.[2] In contrast to the mendelian pattern of inheritance of nuclear DNA, disorders of mtDNA have a maternal form of inheritance. The maternal pattern of inheritance reflects the fact that sperm mitochondria are generally eliminated from the embryo so that disorders of the mtDNA are almost always inherited entirely from the mother.[1]

Mitochondrial DNA, which is packaged in a double-stranded circular chromosome located inside the mitochondria, is often referred to as the "other human genome."[16–19] Mitochondrial DNA contains 37 genes: two ribosomal RNA (rRNA) genes; 22 transfer RNA (tRNA) genes; and 13 structural genes encoding subunits of the mitochondrial respiratory chain enzymes, which participate in oxidative phosphorylation and generation of adenosine triphosphate (ATP; see Chapter 1). Another 74 polypeptides that participate in oxidative phosphorylation are encoded by the nuclear genes. Although a rare disorder in nuclear encoded mitochondrial proteins has been described, most inherited defects in mitochondrial function result from mutations in the mitochondrial genome itself.

Mitochondrial DNA mutations generally affect tissues and organs that are highly dependent on oxidative phosphorylation to meet their high needs for metabolic energy. Thus, mitochondrial diseases frequently affect the brain and neuromuscular system and produce encephalomyopathies, retinal degeneration, loss of extraocular muscle function, lactic acidosis, and deafness.[18,19] The mitochondrial myopathies are often associated with the so-called *ragged red fibers,* a histologic phenotype resulting from degeneration of muscle fibers and massive accumulation of abnormal mitochondria. The range of mitochondrial diseases is broad, however, and may include liver dysfunction, bone marrow failure, pancreatic islet cell dysfunction, and diabetes, as well as other disorders. Table 6-2 describes representative examples of disorders due to mutations in mtDNA.

Multifactorial Inheritance Disorders

Multifactorial inheritance disorders are caused by multiple genes and, in many cases, environmental factors.[1–4] The exact number of genes contributing to multifactorial traits is not known, and these traits do not follow the same clear-cut pattern of inheritance as single-gene disorders. Multifactorial inheritance has been described as a threshold phenomenon in which the factors contributing to the trait can be compared with water filling a glass.[20] Using this analogy, it could be said that expression of the disorder occurs when the glass overflows. Disorders of multifactorial inheritance can be expressed during fetal life and be present at birth, or they may be expressed later in life. Congenital disorders that are thought to arise through multifactorial inheritance include cleft lip or palate, clubfoot, congenital dislocation of the hip, congenital heart disease, and urinary tract malformation. Environmental factors are thought to play a greater role in disorders of multifactorial inheritance that develop in adult life, such as coronary artery disease, diabetes mellitus, hypertension, cancer, and common psychiatric disorders such as bipolar disorder and schizophrenia.

Although multifactorial traits cannot be predicted with the same degree of accuracy as mendelian single-gene mutations, characteristic patterns exist. First, multifactorial congenital malformations tend to involve a single organ or tissue derived from the same embryonic developmental field. Second, the risk of recurrence in future pregnancies is for the same or a similar defect. This means that parents of a child with a cleft palate defect have an increased risk of having another child with a cleft palate, but not with spina bifida. Third, the increased risk

TABLE 6-2 Some Disorders of Organ Systems Associated With Mitochondrial DNA Mutations

Disorder	Manifestations
Chronic progressive external ophthalmoplegia	Progressive weakness of the extraocular muscles
Deafness	Progressive sensorineural deafness, often associated with aminoglycoside antibiotics
Kearns-Sayre syndrome	Progressive weakness of the extraocular muscles of early onset with heart block, retinal pigmentation
Leber hereditary optic neuropathy	Painless, subacute, bilateral visual loss, with central blind spots (scotomas) and abnormal color vision
Leigh disease	Proximal muscle weakness, sensory neuropathy, developmental delay, ataxia, seizures, dementia, and visual impairment due to retinal pigment degeneration
MELAS	*M*itochondrial *E*ncephalomyopathy (cerebral structural changes), *L*actic *A*cidosis, and *S*trokelike syndrome, seizures, and other clinical and laboratory abnormalities; may manifest only as diabetes mellitus
MERRF	*M*yoclonic *E*pilepsy, *R*agged *R*ed *F*ibers in muscle, ataxia, sensorineural deafness
Myoclonic epilepsy with ragged red fibers	Myoclonic seizures, cerebellar ataxia, mitochondrial myopathy (muscle weakness, fatigue)

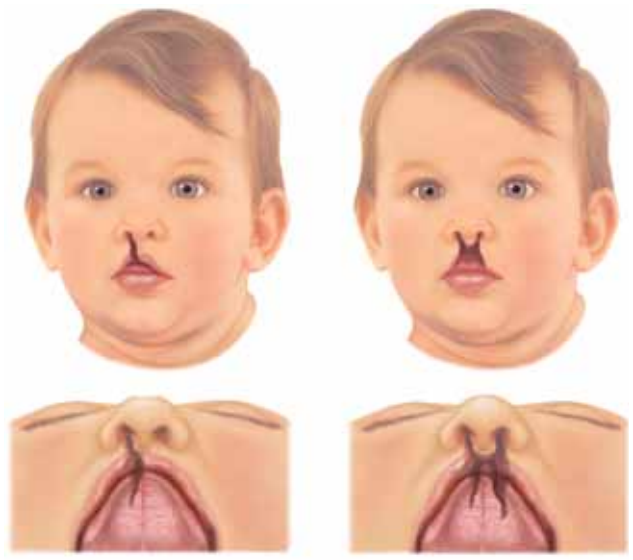
(compared with the general population) among first-degree relatives of the affected person is 2% to 7%, and among second-degree relatives, it is approximately one-half that amount.[4] The risk increases with increasing incidence of the defect among relatives. This means that the risk is greatly increased when a second child with the defect is born to a couple. The risk also increases with severity of the disorder and when the defect occurs in the sex not usually affected by the disorder.

Cleft Lip and Cleft Palate

Cleft lip with or without cleft palate is one of the most common birth defects. It is also one of the more conspicuous birth defects, resulting in an abnormal facial appearance and defective speech. The incidence varies among ethnic groups, ranging from 3.6 per 1000 live births among Native Americans to 2.0 per 1000 among Asians, 1.0 per 1000 among people of European ancestry, to 0.3 per 1000 among Africans.[21] Cleft lip with or without cleft palate is more frequent among boys, whereas isolated cleft palate is twice as common among girls.

Developmentally, the defect has its origin at about the 35th day of gestation when the frontal prominences of the craniofacial structures fuse with the maxillary process to form the upper lip.[2] This process is under the control of many genes, and disturbances in gene expression (hereditary or environmental) at this time may result in cleft lip with or without cleft palate (Fig. 6-6). The defect may also be caused by teratogens (e.g., rubella, anticonvulsant drugs) and is often encountered in children with chromosomal abnormalities.

Cleft lip and palate defects may vary from a small notch in the vermilion border of the upper lip to complete separation involving the palate and extending into the floor of the nose. The clefts may be unilateral or bilateral and may involve the alveolar ridge. The condition may be accompanied by deformed, supernumerary, or absent teeth. Isolated cleft palate occurs in the midline and may involve only the uvula or may extend into or through the soft and hard palates.



Unilateral Bilateral

FIGURE 6-6. Cleft lip and cleft palate.

Children with cleft lip or palate commonly have problems with feeding and speech. The immediate problem in an infant with cleft palate is feeding. Nursing at the breast or nipple depends on suction developed by pressing the nipple against the hard palate with the tongue. Although infants with cleft lip usually have no problems with feeding, those with cleft palate usually require specially constructed, soft artificial nipples with large openings and a squeezable bottle. A specially constructed plastic obturator that fits over the palate defect may be used to facilitate sucking for some infants.[22] Cleft lip and palate can also cause speech defects. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve that separates the nasopharynx from the oropharynx during swallowing and in the production of certain sounds. If the valve does not function properly, it is difficult to build up sufficient pressure in the mouth to make explosive sounds such as *p, b, d, t, h,* and *y*, or the sibilants *s, sh,* and *ch*.[22]

A child with cleft lip or palate may require years of special treatment by health care professionals, including a plastic surgeon, pediatric dentist, orthodontist, speech therapist, and nurse specialist.[23] Surgical closure of the lip is usually performed by 3 months of age, with closure of the palate usually done before 1 year of age. Depending on the extent of the defect, additional surgery may be required as the child grows. Displacement of the maxillary arches and malposition of the teeth usually require orthodontic correction.

Chromosomal Disorders

Chromosomal disorders form a major category of genetic disease, accounting for a large proportion of reproductive wastage (early gestational abortions), congenital malformations, and mental retardation. Specific chromosomal abnormalities can be linked to more than 60 identifiable syndromes that are present in 0.7% of all live births, 2% of all pregnancies in women older than 35 years of age, and 50% of all first-term abortions.[2]

During cell division (i.e., mitosis) in nongerm cells, the chromosomes replicate so that each cell receives a full diploid number. In germ cells, a different form of division (i.e., meiosis) takes place (see Chapter 5). During meiosis, the double sets of 22 autosomes and the two sex chromosomes (normal diploid number) are reduced to single sets (haploid number) in each gamete. At the time of conception, the haploid number in the ovum and that in the sperm join and restore the diploid number of chromosomes.

The aberrations underlying chromosomal disorders may take the form of alterations in the structure of one or more chromosomes or an abnormal number of chromosomes.[1–4] Occasionally, mitotic errors in early development give rise to two or more cell lines characterized by distinctive karyotypes, a condition referred to as *mosaicism*.

Mosaicism can result from mitotic errors during cleavage of the fertilized ovum or in somatic cells. Sometimes, mosaicism consists of an abnormal karyotype and a normal one, in which case the physical deformities caused by the abnormal cell line usually are less severe.

Chromosomal abnormalities are commonly described according to the shorthand description of the karyotype. In this system, the total number of chromosomes is given first, followed by the sex chromosome complement, and then the description of any abnormality. For example, a male with trisomy 21 is designated 47,XY,+21.

Structural Chromosomal Abnormalities

Aberrations in chromosome structure occur when there is a break in one or more of the chromosomes followed by rearrangement or deletion of the chromosome parts.[1–4] Among the factors believed to cause chromosome breakage are exposure to radiation sources, such as x-rays; influence of certain chemicals; extreme changes in the cellular environment; and viral infections. Several patterns of chromosome breakage and rearrangement can occur (Fig. 6-7). There can be a *deletion* of the broken portion of the chromosome. When one chromosome is involved, the broken parts may be *inverted*. *Isochromosome formation* occurs when the centromere, or central portion, of the chromosome separates horizontally instead of vertically. *Ring formation* results from a break involving both telomeric ends of a chromosome, deletion of the acrocentric fragments, and joining of the remaining centric portion of the chromatids to form a ring. *Translocation* occurs when there are simultaneous breaks in two chromosomes from different pairs, with exchange of chromosome parts. With a balanced reciprocal translocation, no genetic information is lost; therefore, persons with translocations usually are normal. However, these persons are translocation carriers and may have normal and abnormal children.

A special form of translocation called a *centric fusion* or *robertsonian translocation* involves two acrocentric chromosomes in which the centromere is near the end, most commonly chromosomes 13 and 14 or 14 and 21. Typically, the break occurs near the centromere, affecting the short arm in one chromosome and the long arm in the other. Transfer of the chromosome fragments leads to one long and one extremely short fragment. The short fragment is usually lost during subsequent divisions. In this case, the person has only 45 chromosomes, but the amount of genetic material that is lost is so small that it often goes unnoticed. The chief clinical importance of this type of translocation is that carriers of a robertsonian translocation involving chromosome 21 are at risk for producing a child with Down syndrome (to be discussed).

The manifestations of aberrations in chromosome structure depend to a great extent on the amount of genetic material that is lost. Many cells sustaining unrestored breaks are eliminated within the next few mitoses because of deficiencies that may in themselves be fatal. This is beneficial because it prevents the damaged cells from becoming a permanent part of the organism or, if it

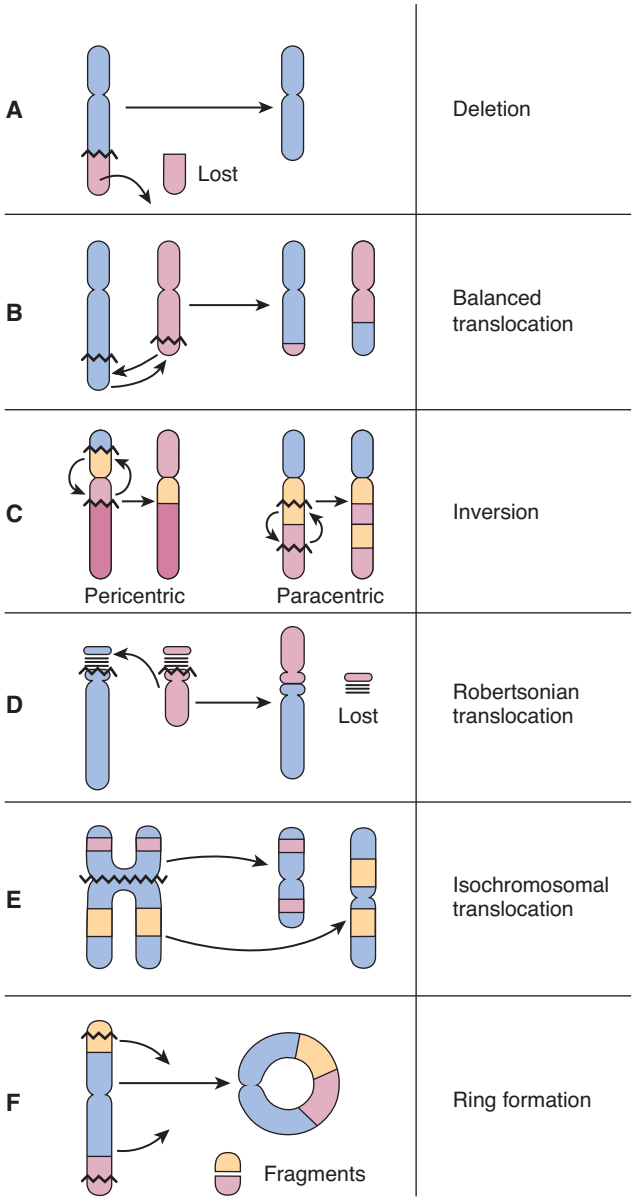


FIGURE 6-7. Structural abnormalities in the human chromosome. **(A)** Deletion of part of a chromosome leads to loss of genetic material and shortening of the chromosome. **(B)** A reciprocal translocation involves two nonhomologous chromosomes, with exchange of the acentric segment. **(C)** Inversion requires two breaks in a single chromosome, with inversion to the opposite side of the centromere (pericentric) or with the fragment inverting but remaining on the same arm (paracentric). **(D)** In robertsonian translocation, two nonhomologous acrocentric chromosomes break near their centromeres, after which the long arms fuse to form one large metacentric chromosome. **(E)** Isochromosomes arise from faulty centromere division, which leads to duplication of the long arm and deletion of the short arm, or the reverse. **(F)** A ring chromosome with breaks in both telomeric portions of a chromosome, deletion of acentric fragments, and fusion of the remaining centric portion. (Adapted from Rubin E., Kileen A.A., Strayer D.S. [2008]. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 187]. Philadelphia: Lippincott Williams & Wilkins.)

occurs in the gametes, from giving rise to grossly defective, nonviable zygotes. Some altered chromosomes, such as those that occur with translocations, are passed on to the next generation.

Numeric Disorders Involving Autosomes

A change in chromosome number is referred to as *aneuploidy*. Among the causes of aneuploidy is a failure of the chromosomes to separate during oogenesis or spermatogenesis. This can occur in either the autosomes or the sex chromosomes and is called *nondisjunction* (Fig. 6-8). Nondisjunction gives rise to germ cells that have an even number of chromosomes (22 or 24). The products of conception formed from this even number of chromosomes have an uneven number of chromosomes, 45 or 47. *Monosomy* refers to the presence of only one member of a chromosome pair. The defects associated with monosomy of the autosomes are severe and usually cause abortion. Monosomy of the X chromosome (45,X), or Turner syndrome, causes less severe defects. *Polysomy,* or the presence of more than two chromosomes to a set, occurs when a germ cell containing more than 23 chromosomes is involved in conception. A variety of trisomies involving autosomal chromosomes 13, 18, 21, and 22 have been described.[2,3] With the exception of trisomy 21, most of these disorders are quite uncommon.

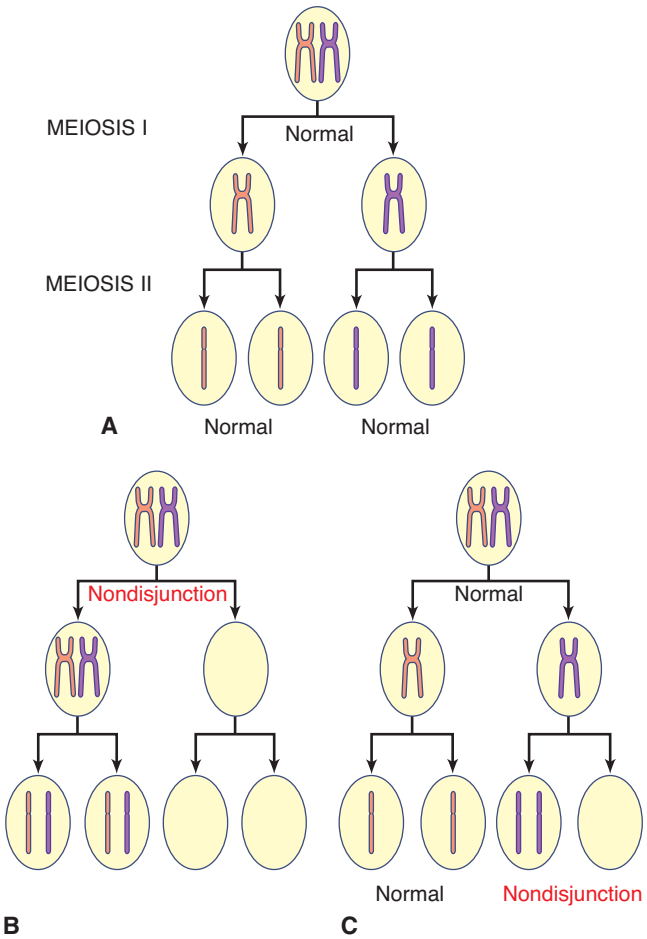


FIGURE 6-8. Nondisjunction as a cause of disorders of chromosomal numbers. **(A)** Normal distribution of chromosomes during meiosis I and II. **(B)** If nondisjunction occurs at meiosis I, the gametes contain either a pair of chromosomes or a lack of chromosomes. **(C)** If nondisjunction occurs at meiosis II, the affected gametes contain two copies of one parental chromosome or a lack of chromosomes.

Down Syndrome. First described in 1866 by John Langon Down, trisomy 21, or Down syndrome, causes a combination of birth defects including some degree of mental retardation, characteristic facial features, and other health problems.[1] According to the National Down Syndrome Association, it is the most common chromosomal disorder, occurring approximately once in every 733 births.[24]

Approximately 95% of cases of Down syndrome are caused by nondisjunction or an error in cell division during meiosis, resulting in a trisomy of chromosome 21. A rare form of Down syndrome can occur in the offspring of persons in whom there has been a robertsonian translocation (see Fig. 6-7) involving the long arm of chromosome 21q and the long arm of one of the acrocentric chromosomes (most often 14 or 22). The translocation adds to the normal long arm of chromosome 21; therefore, the person with this type of Down syndrome has 46 chromosomes, but essentially a trisomy of 21q.[2,3]

The risk of having a child with Down syndrome increases with maternal age. It begins to rise sharply at about age 30, reaching 1 in 25 births at 45 years of age.[2] The reason for the correlation between maternal age and nondisjunction is unknown, but is thought to reflect some aspect of aging of the oocyte. Although men continue to produce sperm throughout their reproductive life, women are born with all the oocytes they ever will have. These oocytes may change as a result of the aging process. With increasing age, there is a greater chance of a woman having been exposed to damaging environmental agents such as drugs, chemicals, and radiation. Unlike trisomy 21, Down syndrome due to a chromosome (21; 14) translocation shows no relation to maternal age but has a relatively high recurrence risk in families when a parent, particularly the mother, is a carrier.

The physical features of a child with Down syndrome are distinctive, and therefore the condition usually is apparent at birth.[1–4,24,25] These features include growth failure and a small and rather square head. There is a flat facial profile, small nose, and somewhat depressed nasal bridge; small folds on the inner corners of the eyes (epicanthal folds) and upward slanting of the eyes; small, low-set, and malformed ears; a fat pad at the back of the neck; an open mouth; and a large, protruding tongue (Fig. 6-9). The child's hands usually are short and stubby, with fingers that curl inward, and there usually is only a single palmar (i.e., simian) crease. There is excessive space between the large and second toe. Hypotonia and joint laxity also are present in infants and young children. There often are accompanying congenital heart defects

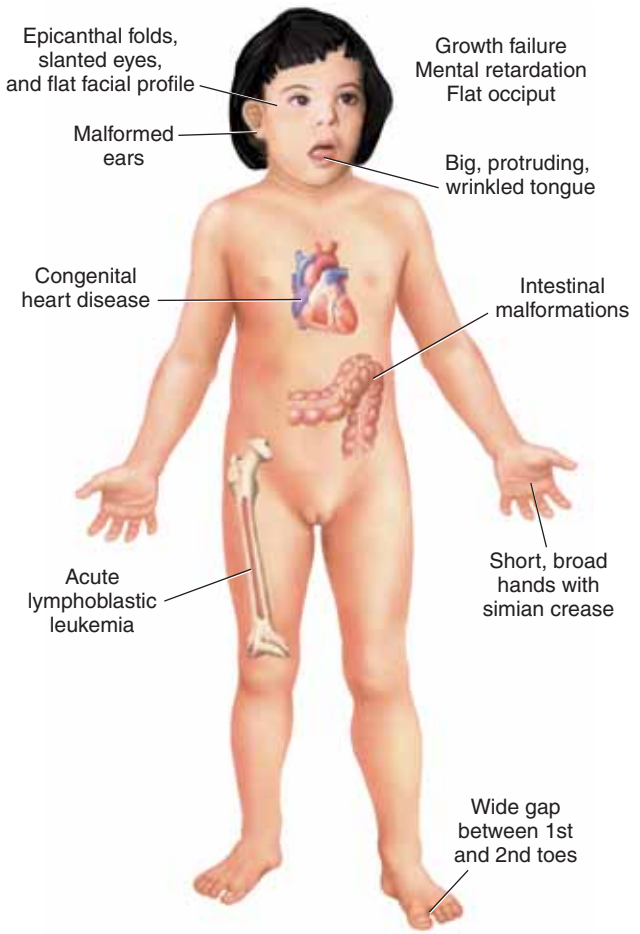


FIGURE 6-9. Clinical features of a child with Down syndrome.

and an increased risk of gastrointestinal malformations. Approximately 1% of persons with trisomy 21 Down syndrome have mosaicism (i.e., cell populations with the normal chromosome number and trisomy 21); these persons may be less severely affected. Of particular concern is the much greater risk of development of acute leukemia among children with Down syndrome—10 to 20 times greater than that of other children.[3] With increased life expectancy due to improved health care, it has also been found that there is an increased risk of Alzheimer disease among older persons with Down syndrome.

There are several prenatal screening tests that can be done to determine the risk of having a child with Down syndrome.[25] The most commonly used are blood tests that measure maternal serum levels of α-fetoprotein, human chorionic gonadotropin (hCG), unconjugated estriol, inhibin A, and pregnancy-associated plasma protein A (PAPP-A, see section on prenatal screening and diagnosis). The results of three or four of these tests, together with the woman's age, often are used to determine the probability of a pregnant woman having a child with Down syndrome. Another test, fetal nuchal translucency (sonolucent space on the back of the fetal neck), uses ultrasonography and can be performed between 10 and 13 weeks' gestation.[26] The fetus with Down syndrome tends to have a greater area of translucency compared with a chromosomally normal infant. The nuchal transparency test is usually used in combination with other screening tests. The only way to accurately determine the presence of Down syndrome in the fetus is through chromosome analysis using chorionic villus sampling, amniocentesis, or percutaneous umbilical blood sampling.

Numeric Disorders Involving Sex Chromosomes

Chromosomal disorders associated with the sex chromosomes are much more common than those related to the autosomes, save for trisomy 21. Furthermore, imbalances (excess or deletions) are much better tolerated than those involving the autosomes. This is related in large part to two factors that are peculiar to the sex chromosomes: (1) the inactivation of all but one X chromosome and (2) the modest amount of genetic material that is carried on the Y chromosome.

Although girls normally receive both a paternal and a maternal X chromosome, the clinical manifestations of X-chromosome abnormalities can be quite variable due to the process of X inactivation (see Chapter 5 and the Lyon principle).[1] In somatic cells of females, only one X chromosome is transcriptionally active. The other chromosome is inactive. The process of X inactivation, which is random, occurs early in embryonic life and is usually complete at about the end of the first week of development. After one X chromosome has become inactivated in a female, all cells descended from that cell have the same inactivated X chromosome. Although much of one X chromosome is inactivated in females, several regions contain genes that escape inactivation and continue to be expressed by both X chromosomes. These genes may explain some of the variations in clinical manifestations seen in cases of numerical abnormalities of the X chromosome, such as Turner syndrome.

Turner Syndrome. Turner syndrome describes an absence of all (45,X/0) or part of the X chromosome.[1–4,27–29] Some women with Turner syndrome may have part of the X chromosome and some may display a mosaicism with one or more additional cell lines. This disorder affects approximately 1 of every 2500 live births, and it has been estimated that almost all fetuses with the 45,X/0 karyotype are spontaneously aborted during the first trimester.[4] Characteristically, the girl with Turner syndrome is short in stature, but her body proportions are normal (Fig. 6-10). Because of the absence of the ovaries, she does not menstruate and shows no signs of secondary sex characteristics. There are variations in the syndrome, with abnormalities ranging from essentially none to webbing of the neck with redundant skin folds, nonpitting lymphedema of the hands and feet, and congenital heart defects, particularly coarctation of the aorta and bicuspid aortic valve. There also may be abnormalities in kidney development (i.e., abnormal location, abnormal vascular supply, or double collecting system). There may be other abnormalities, such as changes in nail growth, high-arched palate, short fourth

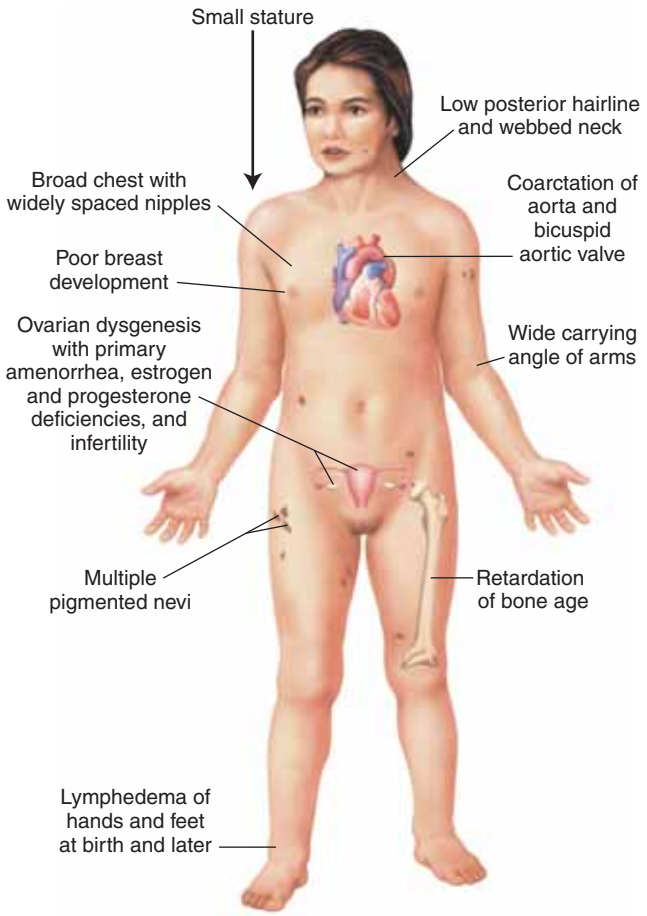


FIGURE 6-10. Clinical features of Turner syndrome.

metacarpal, and strabismus. Although most women with Turner syndrome have normal intelligence, they may have problems with visuospatial organization (e.g., difficulty in driving, nonverbal problem-solving tasks such as mathematics, and psychomotor skills) and attention deficit disorders.

The diagnosis of Turner syndrome often is delayed until late childhood or early adolescence in girls who do not present with the classic features of the syndrome. Early diagnosis is an important aspect of treatment for Turner syndrome. It allows for counseling about the phenotypic characteristics of the disorder; screening for cardiac, renal, thyroid, and other abnormalities; and provision of emotional support for the girl and her family. Because of the potential for delay in diagnosis, it has been recommended that girls with unexplained short stature (height below the fifth percentile), webbed neck, peripheral lymphedema, coarctation of the aorta, or delayed puberty have chromosome studies done.[30]

The management of Turner syndrome begins during childhood and requires ongoing assessment and treatment. Growth hormone therapy is now standard treatment and can result in a gain of 6 to 10 cm in final height. Estrogen therapy, which is instituted around the normal age of puberty, is used to promote development and maintenance of secondary sexual characteristics.[26–30]

There are also health concerns for adult women with Turner syndrome.[27–31] Until recently, females with Turner syndrome received intensive medical care during childhood but were discharged from specialty clinics after induction of puberty and attainment of final height. It is now known that women with Turner disease have increased morbidity due to cardiovascular disease and gastrointestinal, renal, and endocrine disorders. Adults with Turner syndrome continue to have reduced bone mass, and this has been associated with increased risk of fractures.

Klinefelter Syndrome. Klinefelter syndrome is a condition of testicular dysgenesis accompanied by the presence of one or more extra X chromosomes in excess of the normal male XY complement.[2,32–34] Most males with Klinefelter syndrome have one extra X chromosome (47,XXY). In rare cases, there may be more than one extra X chromosome (48,XXXY). The presence of the extra X chromosome in the 47,XXY male results from nondisjunction during meiotic division in one of the parents.

Klinefelter syndrome is characterized by enlarged breasts, sparse facial and body hair, small testes, and the inability to produce sperm (Fig. 6-11).[33,34] Regardless of the number of X chromosomes present, the male phenotype is retained. The condition often goes undetected at birth. The infant usually has normal male genitalia, with a small penis and small, firm testicles. At puberty, the intrinsically abnormal testes do not respond to stimulation from the gonadotropins and undergo degeneration. Low testosterone levels lead to a tall stature with abnormal body proportions in which the lower part of the body is longer than the upper part. Later in life, the body build may become heavy, with a female distribution of subcutaneous fat and variable degrees of breast enlargement. There may be deficient secondary male sex characteristics, such as a voice that remains feminine in pitch and sparse beard and pubic hair. While the intellect usually is normal, most 47,XXY males have some degree of language impairment. They often learn to talk later than do other children and often have trouble with learning to read and write.

Based on studies conducted in the 1970s, including one sponsored by the National Institutes of Health and Human Development, it has been estimated that the 47,XXY syndrome is one of the most common genetic abnormalities known, occurring as frequently as 1 in 500 to 1000 male births.[32] Although the presence of the extra chromosome is fairly common, the signs and symptoms of Klinefelter syndrome are relatively uncommon. Many men live their lives without being aware that they have an additional chromosome. For this reason, it has been suggested that the term *Klinefelter syndrome* be replaced with *47,XXY male*.[32]

Adequate management of Klinefelter syndrome requires a comprehensive neurodevelopmental evaluation. Men with Klinefelter syndrome have congenital hypogonadism, which results in inability to produce normal amounts of testosterone accompanied by an increase in hypothalamic gonadotrophic hormones (see Chapter 39). Androgen therapy is usually initiated when there is

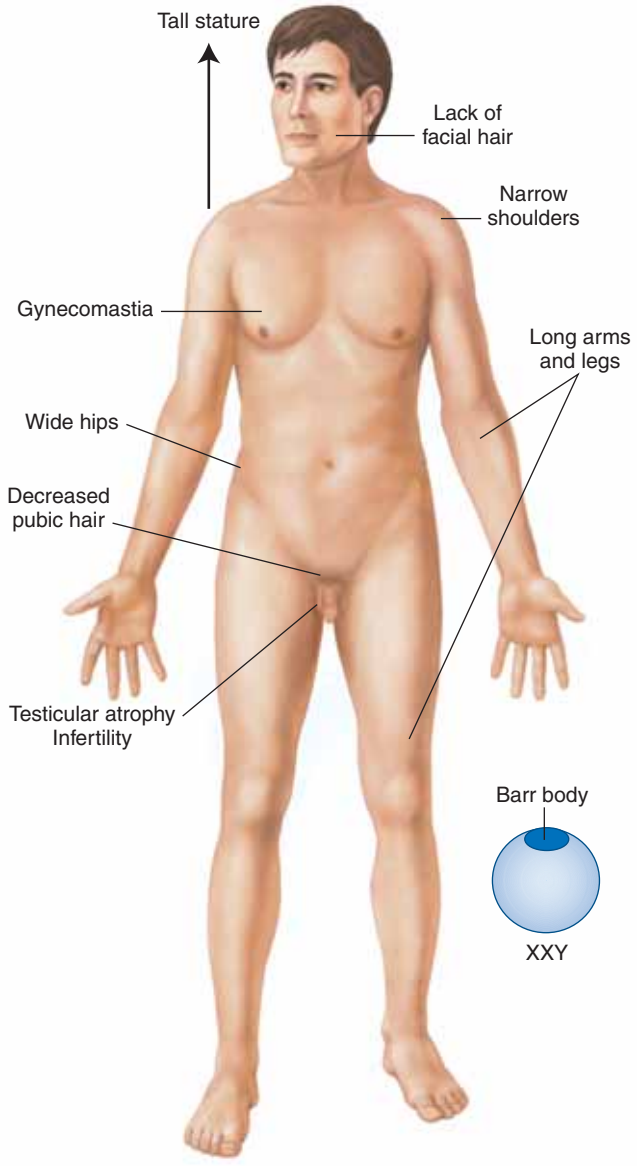


FIGURE 6-11. Clinical features of Klinefelter syndrome.

evidence of a testosterone deficit. This may begin as early as 12 to 14 years of age.[34] Because gynecomastia predisposes to breast cancer, breast self-examination should be encouraged for men with Klinefelter syndrome. Infertility is common in men with Klinefelter syndrome due to a decrease in sperm count. If sperm are present, cryopreservation may be useful for future family planning.

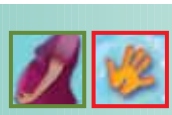
In summary, genetic disorders can affect a single gene (mendelian inheritance) or several genes (polygenic inheritance). Single-gene disorders may be present on an autosome or on the X chromosome and they may be expressed as a dominant or recessive trait. In *autosomal dominant disorders,* a single mutant allele from an affected parent is transmitted to an offspring regardless of sex. The affected parent has a 50% chance of transmitting the disorder to each offspring. *Autosomal recessive disorders* are manifested only when both members of the gene pair are affected. Usually, both parents are unaffected but are carriers of the defective gene. Their chances of having an affected child are one in four; of having a carrier child, two in four; and of having a noncarrier unaffected child, one in four.

Sex-linked disorders, which are associated with the X chromosome, are those in which an unaffected mother carries one normal and one mutant allele on the X chromosome. She has a 50% chance of transmitting the defective gene to her sons who are affected, and her daughters have a 50% chance of being carriers of the mutant gene. Because of a normal paired gene, female heterozygotes rarely experience the effects of a defective gene.

Several genetic disorders do not follow the mendelian pattern of inheritance. These include diseases caused by genomic imprinting, triplet repeat mutations, and mutations in mitochondrial genes. The fragile X syndrome is an inherited form of mental retardation that results from a repeating sequence of three (CGG) nucleotides on a fragile site on the long arm of the X chromosome. This disorder does not follow the mendelian rules of inheritance, but relies on expansion of the CGG nucleotides at the fragile X site. The number of repeats, which averages around 29 in the normal population, expands to 52 to 200 in carriers with permutations, and to 200 to 4000 in affected persons. The mitochondria contain their own DNA, which is distinct from nuclear DNA. Disorders of mtDNA, which are inherited from the mother, interfere with production of cellular energy. Organ systems, such as the nervous system, and heart and skeletal muscles, which have a high need for cellular energy, tend to be the ones most seriously affected by mitochondrial diseases.

Multifactorial inheritance disorders are caused by multiple genes and, in many cases, environmental factors. Although they cannot be predicted with the same accuracy as single-gene disorders, multifactorial traits tend to involve a single organ or tissue derived from the same embryonic developmental field, pose an increased risk for the same or similar defects in later offspring, and carry an increased risk for occurrence of the defect in first-degree relatives.

Chromosomal disorders result from a change in chromosome structure or number. Alterations in chromosome structure involve deletion or addition of genetic material, which may involve a translocation of genetic material from one chromosome pair to another. A change in chromosome number is called *aneuploidy*. *Monosomy* involves the presence of only one member of a chromosome pair; it is seen in Turner syndrome, in which there is monosomy of the X chromosome. *Polysomy* refers to the presence of more than two chromosomes in a set. Klinefelter syndrome involves polysomy of the X chromosome. Trisomy 21 (i.e., Down syndrome) is the most common disorder of the autosomal chromosomes.



Disorders Due to Environmental Influences

The developing embryo is subject to many nongenetic influences. After conception, development is influenced by the environmental factors that the embryo shares with the mother. The physiologic status of the mother—her hormone balance, her general state of health, her nutritional status, and the drugs she takes—undoubtedly influences the development of the unborn child. For example, diabetes mellitus is associated with increased risk of congenital anomalies. Smoking is associated with lower than normal neonatal weight. Alcohol, in the context of chronic alcoholism, is known to cause fetal abnormalities. Some agents cause early abortion. Measles and other infectious agents cause congenital malformations. Other agents, such as radiation, can cause chromosomal and genetic defects and produce developmental disorders.

Period of Vulnerability

The embryo's development is most easily disturbed during the period when differentiation and development of the organs are taking place. This time interval, which is often referred to as the period of *organogenesis*, extends from day 15 to day 60 after conception. Environmental influences during the first 2 weeks after fertilization may interfere with implantation and result in abortion or early resorption of the products of conception. Each organ has a critical period during which it is highly susceptible to environmental derangements[1–4,35] (Fig. 6-12). Often, the effect is expressed at the biochemical level just before the organ begins to develop. The same agent may affect different organ systems that are developing at the same time.

Teratogenic Agents

A teratogenic agent is an environmental agent that produces abnormalities during embryonic or fetal

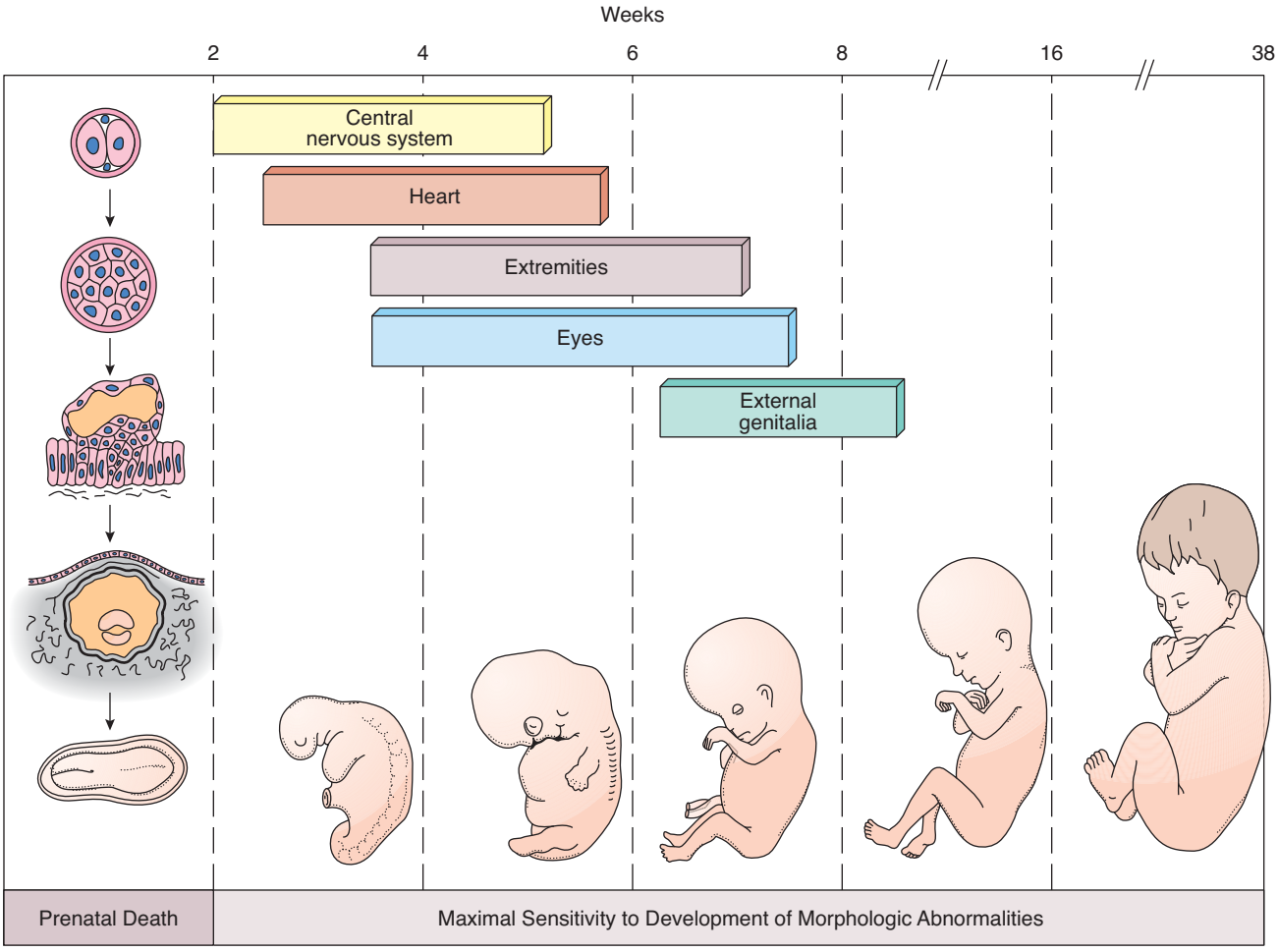


FIGURE 6-12. Sensitivity of specific organs to teratogenic agents at critical periods in embryogenesis. Exposure of adverse influences in the preimplantation and early postimplantation stages of development (*far left*) leads to prenatal death. Periods of maximal sensitivity to teratogens (*horizontal bars*) vary for different organ systems, but overall are limited to the first 8 weeks of pregnancy. (From Rubin E., Kileen A.A., Strayer D.S. [2008]. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 179]. Philadelphia: Lippincott Williams & Wilkins.)

CHART 6-1 Teratogenic Agents*

Radiation

Drugs and Chemical Substances

Alcohol
Anticoagulants
  Warfarin
Anticonvulsants
Cancer drugs
  Aminopterin
  Methotrexate
  6-Mercaptopurine
Isotretinoin (Accutane)
Propylthiouracil
Tetracycline
Thalidomide

Infectious Agents

Viruses
  Cytomegalovirus
  Herpes simplex virus
  Measles (rubella)
  Mumps
  Varicella-zoster virus (chickenpox)
Nonviral factors
  Syphilis
  Toxoplasmosis

*Not inclusive.

development. Maternal disease or altered metabolic state also can affect the environment of the embryo or fetus. Theoretically, environmental agents can cause birth defects in three ways: by direct exposure of the pregnant woman and the embryo or fetus to the agent; through exposure of the soon-to-be-pregnant woman with an agent that has a slow clearance rate such that a teratogenic dose is retained during early pregnancy; or as a result of mutagenic effects of an environmental agent that occur before pregnancy, causing permanent damage to a woman's (or a man's) reproductive cells. For discussion purposes, teratogenic agents have been divided into three groups: radiation, drugs and chemical substances, and infectious agents. Chart 6-1 lists commonly identified agents in each of these groups.

Radiation

Heavy doses of ionizing radiation have been shown to cause microcephaly, skeletal malformations, and mental retardation. There is no evidence that diagnostic levels of radiation cause congenital abnormalities. Because the question of safety remains, however, many agencies require that the day of a woman's last menstrual period be noted on all radiologic requisitions. Other institutions may require a pregnancy test before any extensive diagnostic x-ray studies are performed. Radiation is teratogenic and mutagenic, and there is the possibility of effecting inheritable changes in genetic materials. Administration of therapeutic doses of radioactive iodine (^{131}I) during the 13th week of gestation, the time when the fetal thyroid is beginning to concentrate iodine, has been shown to interfere with thyroid development.

Teratogenic Agents

- Teratogenic agents such as radiation, chemicals and drugs, and infectious organisms are agents that produce abnormalities in the developing embryo.
- The stage of development of the embryo determines the susceptibility to teratogens. The period during which the embryo is most susceptible to teratogenic agents is the time during which rapid differentiation and development of body organs and tissues are taking place, usually from days 15 to 60 postconception.

Chemicals and Drugs

Environmental chemicals and drugs can cross the placenta and cause damage to the developing embryo and fetus. Some of the best-documented environmental teratogens are the organic mercurials, which cause neurologic deficits and blindness. Sources of exposure to mercury include contaminated food (fish) and water.[36] The precise mechanism by which chemicals and drugs exert their teratogenic effects is largely unknown. They may produce cytotoxic (cell-killing), antimetabolic, or growth-inhibiting properties. Often their effects depend on the time of exposure (in terms of embryonic and fetal development) and extent of exposure (dosage).[35]

Drugs top the list of chemical teratogens, probably because they are regularly used at elevated doses. Many drugs can cross the placenta and expose the fetus to both the pharmacologic and teratogenic effects. Factors that affect placental drug transfer and drug effects on the fetus include the rate at which the drug crosses the placenta, the duration of exposure, and the stage of placental and fetal development at the time of exposure.[37] Lipid-soluble drugs tend to cross the placenta more readily and enter the fetal circulation. The molecular weight of a drug also influences the rate of transfer and the amount of drug transferred across the placenta. Drugs with a molecular weight of less than 500 can cross the placenta easily, depending on lipid solubility and degree of ionization; those with a molecular weight of 500 to 1000 cross the placenta with more difficulty; and those with a molecular weight of more than 1000 cross very poorly.[37]

A number of drugs are suspected of being teratogens, but only a few have been identified with certainty. Perhaps the best known of these drugs is thalidomide, which has been shown to give rise to a full range of malformations, including phocomelia (i.e., short, flipperlike appendages) of all four extremities.[2] Other drugs known to cause fetal abnormalities are the antimetabolites that are used in the treatment of cancer, the anticoagulant drug warfarin,

several of the anticonvulsant drugs, ethyl alcohol, and cocaine. More recently, vitamin A and its derivatives (the retinoids) have been targeted for concern because of their teratogenic potential. Concern over the teratogenic effects of vitamin A derivatives became evident with the introduction of the acne drug isotretinoin (Accutane). Fetal abnormalities such as cleft palate, heart defects, retinal and optic nerve abnormalities, and central nervous system malformations were observed in women ingesting therapeutic doses of the drug during the first trimester of pregnancy.[38]

In 1979, the U.S. Food and Drug Administration established a system for classifying drugs according to probable risks to the fetus. This system classifies all drugs approved after 1983 into five pregnancy risk categories: A, B, C, D, and X. Drugs in category A are the least dangerous, and categories B, C, and D are increasingly more dangerous. Those in category X are contraindicated during pregnancy because of proven teratogenicity.[37]

Because many drugs are suspected of causing fetal abnormalities, and even those that were once thought to be safe are now being viewed critically, it is recommended that women in their childbearing years avoid unnecessary use of drugs. This pertains to nonpregnant women as well as pregnant women because many developmental defects occur early in pregnancy. As happened with thalidomide, the damage to the embryo may occur before pregnancy is suspected or confirmed. A drug that is often abused and can have deleterious effects on the fetus is alcohol.

Fetal Alcohol Syndrome. The term *fetal alcohol syndrome* (FAS) refers to a constellation of physical, behavioral, and cognitive abnormalities resulting from maternal alcohol consumption.[39–42] It has been estimated that among the 4 million babies born each year, 1000 to 6000 will be born with FAS.[40] Alcohol, which is lipid soluble and has a molecular weight between 600 and 1000, passes freely across the placental barrier; concentrations of alcohol in the fetus are at least as high as in the mother. Unlike other teratogens, the harmful effects of alcohol are not restricted to the sensitive period of early gestation but extend throughout pregnancy.

Alcohol has widely variable effects on fetal development, ranging from minor abnormalities to FAS. There may be prenatal or postnatal growth retardation; central nervous system (CNS) involvement, including neurologic abnormalities, developmental delays, behavioral dysfunction, intellectual impairment, and skull and brain malformation; and the characteristic set of facial features that include small palpebral fissures (i.e., eye openings), a thin vermillion (upper lip), and an elongated, flattened midface and philtrum (i.e., the groove in the middle of the upper lip) (Fig. 6-13).[39–42] The facial features of FAS may not be as apparent in the newborn but become more prominent as the infant develops. As the children grow into adulthood, the facial features become more subtle, making diagnosis of FAS in older individuals more difficult. Each of these defects can vary in severity, probably reflecting the timing of alcohol consumption in terms of the period of fetal development, amount of alcohol consumed, and hereditary and environmental influences.

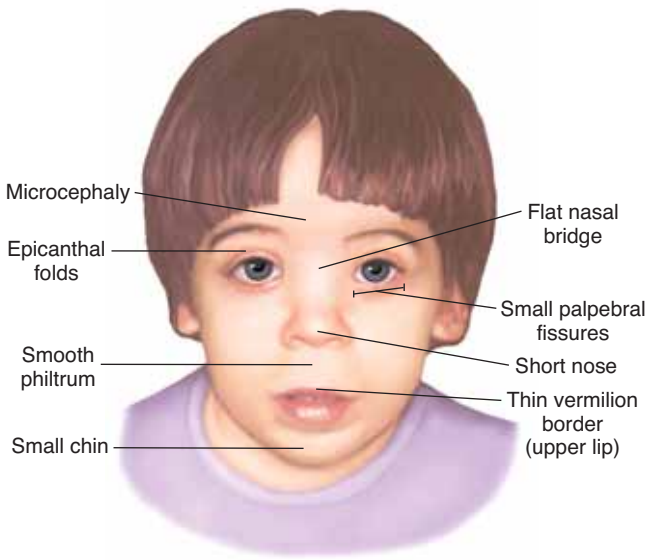


FIGURE 6-13. Clinical features of fetal alcohol syndrome.

In 2004, the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effects published guidelines for the referral and diagnosis of FAS.[39] The criteria for FAS diagnosis require the documented presence of three of the following findings: (1) three facial abnormalities (smooth philtrum, thin vermillion, and small palpebral fissures), (2) growth deficits (prenatal or postnatal height or weight, or both, below the 10th percentile), and (3) CNS abnormalities (e.g., head circumference below 10th percentile, global cognitive or intellectual deficits, motor functioning delays, problems with attention or hyperactivity).

The amount of alcohol that can be safely consumed during pregnancy is unknown. Even small amounts of alcohol consumed during critical periods of fetal development may be teratogenic. For example, if alcohol is consumed during the period of organogenesis, a variety of skeletal and organ defects may result. When alcohol is consumed later in gestation, when the brain is undergoing rapid development, there may be behavioral and cognitive disorders in the absence of physical abnormalities. Chronic alcohol consumption throughout pregnancy may result in a variety of effects, ranging from physical abnormalities to growth retardation and compromised CNS functioning. Evidence suggests that short-lived high concentrations of alcohol such as those that occur with binge drinking may be particularly significant, with abnormalities being unique to the period of exposure. Because of the possible effect on the fetus, it is recommended that women abstain from alcohol during pregnancy.

Folic Acid Deficiency. Although most birth defects are related to exposure to a teratogenic agent, deficiencies of nutrients and vitamins also may be a factor. Folic acid deficiency has been implicated in the development of neural tube defects (e.g., anencephaly, spina bifida, encephalocele). Studies have shown a reduction in

neural tube defects when folic acid was taken before conception and continued during the first trimester of pregnancy.[43,44] The Public Health Service recommends that all women of childbearing age should receive 400 micrograms (μg) of folic acid daily. These recommendations are particularly important for women who have previously had an affected pregnancy, for couples with a close relative with the disorder, and for women with diabetes mellitus and those taking anticonvulsant drugs who are at increased risk for having infants with birth defects.

Since 1998, all enriched cereal grain products in the United States have been fortified with folic acid. To achieve an adequate intake of folic acid, pregnant women should couple a diet that contains folate-rich foods (e.g., orange juice; dark, leafy green vegetables; and legumes) with sources of synthetic folic acid, such as fortified food products.[44]

Infectious Agents

Many microorganisms cross the placenta and enter the fetal circulation, often producing multiple malformations. The acronym *TORCH* stands for *t*oxoplasmosis, *o*ther, *r*ubella (i.e., German measles), *c*ytomegalovirus, and *h*erpes, which are the agents most frequently implicated in fetal anomalies.[2] Other infections include varicella-zoster virus infection, listeriosis, leptospirosis, Epstein-Barr virus infection, and syphilis. Human immunodeficiency virus (HIV) and human parvovirus (B19) have been suggested as additions to the list. The TORCH screening test examines the infant's serum for the presence of antibodies to these agents. These infections tend to cause similar clinical manifestations, including microcephaly, hydrocephalus, defects of the eye, and hearing problems.

Toxoplasmosis is a protozoal infection caused by *Toxoplasma gondii*. The infection can be contracted by eating raw or inadequately cooked meat or food that has come in contact with infected meat.[45] The domestic cat can carry the organism, excreting the protozoa in its feces. It has been suggested that pregnant women should avoid contact with excrement from the family cat. Although the introduction of the rubella vaccine has virtually eliminated the congenital rubella syndrome in most developed countries, it remains endemic in many developing countries, where it is the major preventable cause of hearing impairment, blindness, and adverse neurodevelopmental outcome. The epidemiology of cytomegalovirus infection is largely unknown. Some infants are severely affected at birth, and others, although having evidence of the infection, have no symptoms. In some symptom-free infants, brain damage becomes evident over a span of several years. There also is evidence that some infants contract the infection during the first year of life, and in some of them the infection leads to retardation a year or two later. Herpes simplex virus type 2 infection is considered to be a genital infection and usually is transmitted through sexual contact. The infant acquires this infection in utero or in passage through the birth canal.

In summary, a teratogenic agent is one that produces abnormalities during embryonic or fetal life. It is during the early part of pregnancy (15 to 60 days after conception) that environmental agents are most apt to produce their deleterious effects on the developing embryo. A number of environmental agents can be damaging to the unborn child, including radiation, drugs and chemicals, and infectious agents. The fetal alcohol syndrome is a risk for infants of women who regularly consume alcohol during pregnancy. Because many drugs have the potential for causing fetal abnormalities, often at an early stage of pregnancy, it is recommended that women of childbearing age avoid unnecessary use of drugs. It also has been shown that folic acid deficiency can contribute to neural tube defects. The acronym TORCH stands for *t*oxoplasmosis, *o*ther, *r*ubella, *c*ytomegalovirus, and *h*erpes, which are the infectious agents most frequently implicated in fetal anomalies.

Prenatal Screening and Diagnosis

The purpose of prenatal screening and diagnosis is not just to detect fetal abnormalities. Rather, it has the following objectives: to provide parents with information needed to make an informed choice about having a child with an abnormality; to provide reassurance and reduce anxiety among high-risk groups; and to allow parents at risk for having a child with a specific defect, who might otherwise forgo having a child, to begin a pregnancy with the assurance that knowledge about the presence or absence of the disorder in the fetus can be confirmed by testing.[1] Prenatal screening cannot be used to rule out all possible fetal abnormalities. It is limited to determining whether the fetus has (or probably has) designated conditions indicated by late maternal age, family history, or well-defined risk factors.

Screening and Diagnostic Methods

Among the methods used for prenatal screening and diagnosis are ultrasonography, maternal serum (blood) screening tests, amniocentesis, chorionic villus sampling, and percutaneous umbilical fetal blood sampling[1,22,46] (Fig. 6-14). Amniocentesis, chorionic villus sampling, percutaneous umbilical cord blood sampling, and fetal biopsy are invasive procedures that carry a small risk for the fetus.

Ultrasonography

Ultrasonography is a noninvasive diagnostic method that uses reflections of high-frequency sound waves to visualize soft tissue structures. Since its introduction in 1958, it has been used during pregnancy to determine number of fetuses, fetal size and position, amount of amniotic fluid,

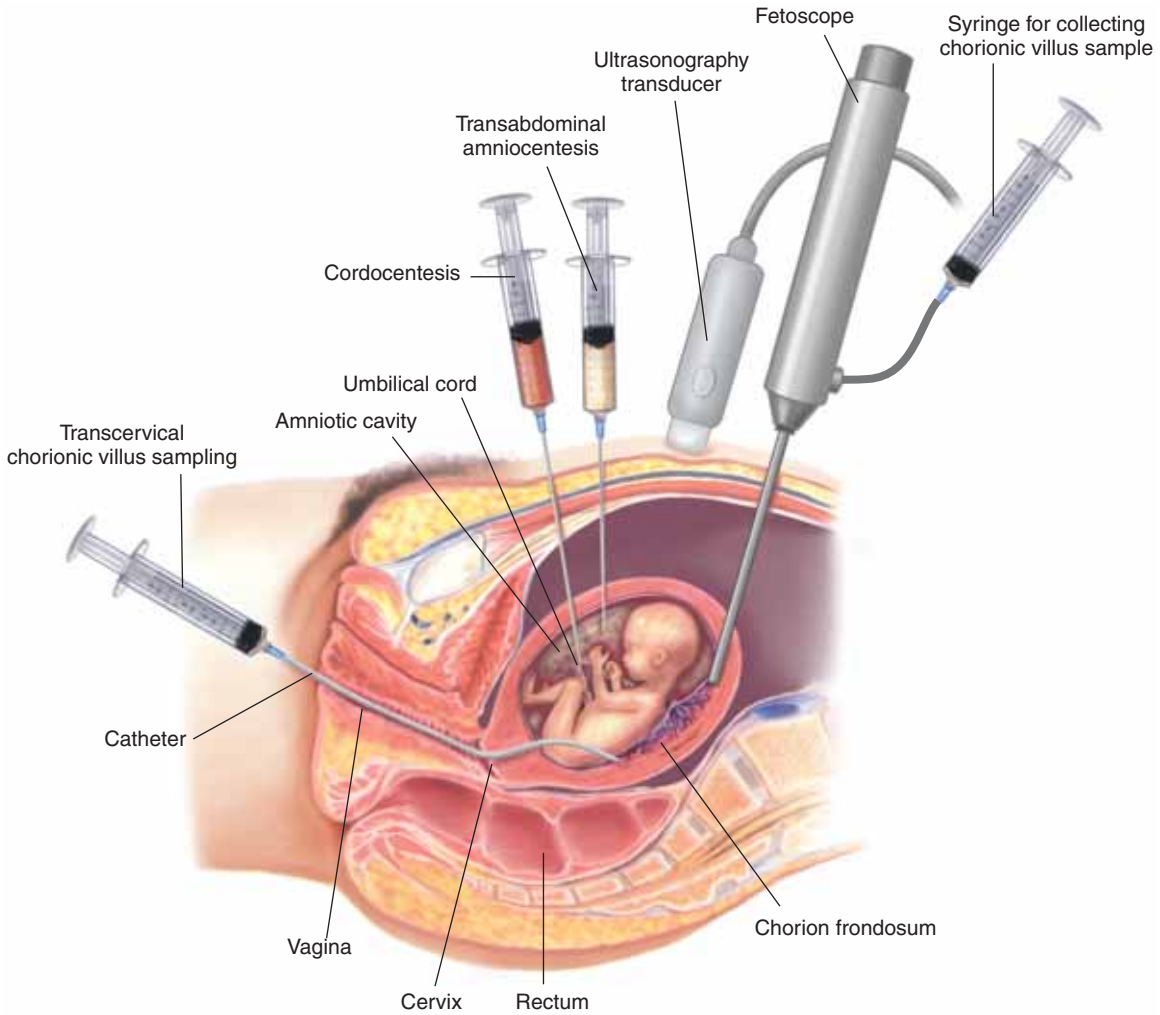


FIGURE 6-14. Methods of prenatal screening.

and placental location. It also is possible to assess fetal movement, breathing movements, and heart pattern. There is also good evidence that early ultrasonography (i.e., before 14 weeks) accurately determines gestational age.

Improved resolution and real-time units have enhanced the ability of ultrasound scanners to detect congenital anomalies. With this more sophisticated equipment, it is possible to obtain information such as measurements of hourly urine output in a high-risk fetus. Ultrasonography makes possible the in utero diagnosis of hydrocephalus, spina bifida, facial defects, congenital heart defects, congenital diaphragmatic hernias, disorders of the gastrointestinal tract, and skeletal anomalies. Cardiovascular abnormalities are the most commonly missed malformation. A four-chamber view of the fetal heart improves the detection of cardiac malformations. Intrauterine diagnosis of congenital abnormalities permits planning of surgical correction shortly after birth, preterm delivery for early correction, selection of cesarean section to reduce fetal injury, and, in some cases, intrauterine therapy. When a congenital abnormality is suspected, a diagnosis made using ultrasonography usually can be obtained by weeks 16 to 18 of gestation.

Maternal Serum Markers

Maternal blood testing began in the early 1980s with the test for α-fetoprotein (AFP). Since that time, many serum factors have been studied as screening tests for fetal anomalies. Current maternal testing uses three distinct tests (AFP, human chorionic gonadotropin [hCG], and unconjugated estriol) to screen for trisomy syndromes in low-risk women while incorporating the detection of neural tube defects. The combined use of the three maternal serum markers between 15 and 22 weeks of pregnancy has been shown to detect as many as 60% of Down syndrome pregnancies.[1] The use of ultrasound to verify fetal age can reduce the number of false-positive tests with this screening method.

AFP is a major fetal plasma protein and has a structure similar to the albumin that is found in postnatal life. AFP is made initially by the yolk sac, gastrointestinal tract, and liver. Fetal plasma levels peak at approximately 10 to 13 weeks' gestation and then decline progressively until

term, while maternal levels peak in the third trimester.[47] Maternal and amniotic fluid levels of AFP are elevated in pregnancies where the fetus has a neural tube defect (i.e., anencephaly and open spina bifida) or certain other malformations such as an anterior abdominal wall defect in which the fetal integument is not intact. Screening of maternal blood samples usually is done between weeks 16 and 18 of gestation.[1,47] Although neural tube defects have been associated with elevated levels of AFP, decreased levels have been associated with Down syndrome.

A complex glycoprotein, hCG is produced exclusively by the outer layer of the trophoblast shortly after implantation in the uterine wall. It increases rapidly in the first 8 weeks of gestation, declines steadily until 20 weeks, and then plateaus. The single maternal serum marker that yields the highest detection rate for Down syndrome is an elevated level of hCG. Unconjugated estriol is produced by the placenta from precursors provided by the fetal adrenal glands and liver. It increases steadily throughout pregnancy to a higher level than that normally produced by the liver. Unconjugated estriol levels are decreased in Down syndrome and trisomy 18.

Other maternal serum markers include pregnancy-associated plasma protein A (PAPP-A) and inhibin A. PAPP-A, which is secreted by the placenta, has been shown to play an important role in promoting cell differentiation and proliferation in various body systems. In complicated pregnancies, the PAPP-A concentration increases with gestational age until term. Decreased PAPP-A levels in the first trimester (between 10 to 13 weeks) have been shown to be associated with Down syndrome. When used along with maternal age, free β-hCG, and ultrasound measurement of nuchal translucency, serum PAPP-A levels can reportedly detect 85% to 95% of affected pregnancies with a false-positive rate of approximately 5%.[48] Inhibin A, which is secreted by the corpus luteum and fetoplacental unit, is also a maternal serum marker for fetal Down syndrome.[49]

Invasive Testing

Amniocentesis. Amniocentesis involves the withdrawal of a sample of amniotic fluid from the pregnant uterus using either a transabdominal or transcervical approach (Fig. 6-14). The procedure is useful in women older than 35 years of age, who have an increased risk of giving birth to an infant with Down syndrome; in parents who have another child with chromosomal abnormalities; and in situations in which a parent is known to be a carrier of an inherited disease. Ultrasound is used to gain additional information and to guide the placement of the amniocentesis needle. The amniotic fluid and cells that have been shed by the fetus are studied. Amniocentesis is performed on an outpatient basis typically at the 15th to 16th week after the first day of the last menstrual period.[1] For chromosomal analysis, the fetal cells are grown in culture and the result is available in 10 to 14 days. The amniotic fluid also can be tested using various biochemical tests.

Chorionic Villus Sampling. Sampling of the chorionic villi usually is done after 10 weeks of gestation.[50] Doing the test before that time is not recommended because of the danger of limb reduction defects in the fetus. The chorionic villi are the site of exchange of nutrients between the maternal blood and the embryo—the chorionic sac encloses the early amniotic sac and fetus, and the villi are the primitive blood vessels that develop into the placenta. The sampling procedure can be performed using either a transabdominal or transcervical approach (Fig. 6-14). The tissue that is obtained can be used for fetal chromosome studies, DNA analysis, and biochemical studies. The fetal tissue does not have to be cultured, and fetal chromosome analysis can be made available in 24 hours. DNA analysis and biochemical tests can be completed within 1 to 2 weeks.[50]

Percutaneous Umbilical Cord Blood Sampling. Percutaneous umbilical cord blood sampling involves the transcutaneous insertion of a needle through the uterine wall and into the umbilical artery. It is performed under ultrasound guidance and can be done any time after 16 weeks of gestation. It is used for prenatal diagnosis of hemoglobinopathies, coagulation disorders, metabolic and cytogenetic disorders, and immunodeficiencies. Fetal infections such as rubella and toxoplasmosis can be detected through measurement of immunoglobulin M antibodies or direct blood cultures. Results from cytogenetic studies usually are available within 48 to 72 hours. Because the procedure carries a greater risk of pregnancy loss than amniocentesis, it usually is reserved for situations in which rapid cytogenetic analysis is needed or in which diagnostic information cannot be obtained by other methods.

Fetal Biopsy. Fetal biopsy is done with a fetoscope under ultrasound guidance. It is used to detect certain genetic skin defects that cannot be diagnosed with DNA analysis. It also may be done to obtain muscle tissue for use in diagnosis of Duchenne muscular dystrophy.

Cytogenetic and Biochemical Analyses

Amniocentesis and chorionic villus sampling yield cells that can be used for cytogenetic and DNA analyses. Biochemical analyses can be used to detect abnormal levels of AFP and abnormal biochemical products in the maternal blood and in specimens of amniotic fluid and fetal blood. Cytogenetic studies are used for fetal karyotyping to determine the chromosomal makeup of the fetus. They are done to detect abnormalities of chromosome number and structure. Karyotyping also reveals the sex of the fetus. This may be useful when an inherited defect is known to affect only one sex.

Analysis of DNA is done on cells extracted from the amniotic fluid, chorionic villus sampling, or fetal blood from percutaneous umbilical sampling to detect genetic defects such as inborn errors of metabolism. The defect may be established through direct demonstration of the molecular defect or through methods that break the DNA into fragments so that the fragments may be studied to determine the presence of an abnormal gene. Direct demonstration of the molecular defect is done by growing the amniotic fluid cells in culture and measuring

the enzymes that the cultured cells produce. Many of the enzymes are expressed in the chorionic villi; this permits earlier prenatal diagnosis because the cells do not need to be subjected to prior culture. DNA studies are used to detect genetic defects that cause inborn errors of metabolism, such as Tay-Sachs disease, glycogen storage diseases, and familial hypercholesterolemia.

In summary, prenatal diagnosis includes the use of ultrasonography, maternal blood screening, amniocentesis, chorionic villus sampling, and percutaneous umbilical fetal blood sampling. Ultrasonography is used for determination of fetal size and position and for the presence of structural anomalies. Maternal blood screening, which measures α-fetoprotein (AFP), unconjugated estriol, and chorionic gandotropin (hCG), is used to assess for neural tube defects (AFP) and Down syndrome (AFP, unconjugated estriol, and hCG). Amniocentesis, chorionic villus sampling, and percutaneous umbilical blood sampling are used to obtain specimens for cytogenetic and biochemical studies.

REVIEW EXERCISES

1. A 23-year-old woman with sickle cell disease and her husband want to have a child, but worry that the child will be born with the disease.

A. What is the mother's genotype in terms of the sickle cell gene? Is she heterozygous or homozygous?
B. If the husband is found not to have the sickle cell gene, what is the probability of their child having the disease or being a carrier of the sickle cell trait?

2. A couple has a child who was born with a congenital heart disease.

A. Would you consider the defect to be the result of a single-gene or a polygenic trait?
B. Would these parents be at greater risk of having another child with a heart defect or would they be at equal risk of having a child with a defect in another organ system, such as cleft palate?

3. A couple has been informed that their newborn child has the features of Down syndrome and it was suggested that genetic studies be performed.

A. The child is found to have trisomy 21. Use Figure 6-7 to describe the events that occur during meiosis to explain the origin of the third chromosome.
B. If the child had been found to have the robertsonian chromosome, how would you explain the origin of the abnormal chromosome?

4. A 26-year-old woman is planning to become pregnant.

A. What information would you give her regarding the effects of medications and drugs on the fetus? What stage of fetal development is associated with the greatest risk?
B. What is the rationale for ensuring that she has an adequate intake of folic acid before conception?
C. She and her husband have an indoor cat. What precautions should she use in caring for the cat?

REFERENCES

1. Nassbaum R.L., McInnes R.R., Willard H.F., et al. (2007). *Thompson & Thompson genetics in medicine* (7th ed., pp. 33–94,157–179, 359–389). Philadelphia: Saunders Elsevier.
2. Killeen A.A., Rubin E., Strayer D.S. (2008). In Rubin R., Strayer D.S. (Eds). *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 177–228). Philadelphia: Lippincott Williams & Wilkins.
3. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran pathologic basis of medicine* (8th ed, pp. 135–182). Philadelphia: Saunders Elsevier.
4. Jorde L.B., Carey J.C., Barmshad M.J., et al. (2006). *Medical genetics* (3rd ed., pp. 57–101, 107–135, 248–278). St. Louis: Mosby.
5. Dean J.C.S. (2002). Management of Marfan syndrome. *Heart* 88, 97–103.
6. Ryan-Krause P. (2002). Identify and manage Marfan syndrome in children. *Nurse Practitioner* 27(10), 26–36.
7. Theos A., Korf B.R. (2006). Pathophysiology of neurofibromatosis type I. *Annals of Internal Medicine* 144(11), 842–849.
8. Yohay K. (2006). Neurofibromatosis type 1 and 2. *Neurologist* 12(2), 86–93.
9. Ferner R.E. (2007). Neurofibromatosis 1 and neurofibromatosis 2: A twenty first century perspective. *Neurology: Lancet* 6, 340–350.
10. National Institutes of Health Consensus Development Panel. (2001). National Institute of Health Consensus Development Conference Statement. Phenylketonuria: Screening and management, October 16-18, 2000. *Pediatrics* 108, 972–982.
11. Rezvani I. (2004). Phenylalanine. In Behrman R.E., Kliegman R.M., Jensen H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 398–402). Philadelphia: Saunders.
12. Burnett J.R. (2007). Sapropterin dihydrochloride (Kuvan/Phenoptin), an orally synthetic form of BH_4 for treatment of phenylalanine. *IDrugs* 10(11), 805–813.
13. Agency for Health Care Research and Quality. (2008). *Screening for phenylketonuria: Reaffirmation recommendation statement.* [Online] Available: http://www.ahrq.gov/clinic/uspstf08/pku/pkurs.htm. Accessed December 10, 2008.
14. National Institutes of Health. (2003). *Families and fragile X syndrome.* U.S. Department of Health and Human Services, Public Health Services, NIH Publication No 96-3402. [Online]. Available: http://www.nichd.nih.gov/publications/pubs/upload/fragileX.pdf. Accessed December 11, 2008.
15. Oostra B.A., Chiurazzi P. (2001). The fragile X gene and its function. *Clinical Genetics* 60, 399–408.
16. Johns D.R. (1995). Mitochondrial DNA and disease. *New England Journal of Medicine* 333, 638–644.

17. Johnston M.V. (2004). Mitochondrial encephalomyopathies. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 2025–2027). Philadelphia: Saunders.
18. Dimauro S., Schon E.A. (2003). Mitochondrial respiratory chain disease. *New England Journal of Medicine* 348, 2656–2668.
19. Dimauro S., Davidzon G. (2005). Mitochondrial DNA and disease. *Annals of Medicine* 37, 222–232.
20. Riccardi V.M. (1977). *The genetic approach to human disease* (p. 92). New York: Oxford University Press.
21. Schutte B.C., Murray J.C. (1999). The many faces and factors of orofacial clefts. *Human Molecular Genetics* 10, 1853–1859.
22. Tinanoff N. (2004). Cleft lip and palate. In Behrman R.E., Kliegman R.M., Jensen H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 1207–1208). Philadelphia: Saunders.
23. Mulliken J.B. (2004). The changing faces of children with cleft lip and palate. *New England Journal of Medicine* 351(8), 745–747.
24. National Down Syndrome Society. (2008). *Down syndrome fact sheet.* [Online]. Available: http://www.ndss.org/index.php?option=com_content&view=article&id=54&Itemid=74. Accessed May 10, 2010.
25. Roizen N.J., Patterson D. (2003). Down syndrome. *Lancet* 361, 1281–1289.
26. Cunniff C., American Academy Committee of Pediatrics Committee on Genetics. (2004). Prenatal screening and diagnosis for pediatricians. *Pediatrics* 114(3), 889–894.
27. Sybert V.P., McCauley E. (2004). Turner's syndrome. *New England Journal of Medicine* 351, 1227–1238.
28. Morgan T. (2007). Turner syndrome: Diagnosis and management. *American Family Physician* 76, 405–410.
29. Gravholt C.H. (2004). Epidemiological, endocrine and metabolic features in Turner syndrome. *European Journal of Endocrinology* 151, 657–687.
30. Elsheikh M., Dunger D.B., Conway G.S., et al. (2002). Turner syndrome in adulthood. *Endocrine Reviews* 21, 120–140.
31. Frías J.L., Davenport M.L., American Academy of Pediatrics Committee on Genetics, Section on Endocrinology. (2005). Health supervision of children with Turner syndrome. *Pediatrics* 111, 692–702.
32. Robert Bock (Office of Research Reporting, National Institute Child Health and Human Development). (2006). *Understanding Klinefelter syndrome: A guide for XXY males and their family.* (Online). Available: http://www.nichd.nih.gov/publications/pubs/klinefelter.cfm. Accessed May 10, 2010.
33. Lanfranco F., Kamischke A., Zitzmann M., et al. (2004). Klinefelter syndrome. *Lancet* 364, 273–283.
34. Wattendorf D.J., Muenke M. (2005). Klinefelter syndrome. *American Family Physician* 72(11), 2259–2262.
35. Brent R.L. (2004). Environmental causes of congenital malformations: The pediatricians role in with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics* 113, 957–968.
36. Steurerwald U., Weibe P., Jorgensen P.J., et al. (2000). Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *Journal of Pediatrics* 136, 599–605.
37. Koda-Kimble M.A., Young L., Kradian W.A. (Eds.). (2005). *Applied therapeutics: The clinical use of drugs* (8th ed., pp. 47-1–47-15). Philadelphia: Lippincott Williams & Wilkins.
38. Ross S.A., McCaffery P.J., Drager U.C., et al. (2000). Retinoids in embryonal development. *Physiological Reviews* 80, 1021–1055.
39. Bertrand J., Floyd R.L., Weber M.K., et al., National Task Force on Fetal Alcohol and Fetal Alcohol Effects (2004). *Fetal alcohol syndromes: Guidelines for referral and diagnosis.* Atlanta: Centers for Disease Control and Prevention.
40. Sokol R.J., Delaney-Black V., Nordstrom B. (2003). Fetal alcohol syndrome. *JAMA* 290(22), 2996–2999.
41. Wattendorf D.J., Muenke M. (2005). Fetal alcohol spectrum disorders. *American Family Physician* 72(2), 279–285.
42. Riley E.P., McGee C.L. (2005). Fetal alcohol spectrum disorders: An overview with emphasis on changes in brain and behavior. *Experimental Biology and Medicine* 230(6), 357–365.
43. Centers for Disease Control and Prevention. (1992). Recommendations for use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *Morbidity and Mortality Weekly Report* 41, 1–8.
44. Bailey L.B. (2000). New standard for dietary folate intake in pregnant women. *American Journal of Clinical Nutrition* 71(Suppl), 1304S–1307S.
45. Jones J., Lopez A., Wilson M. (2003). Congenital toxoplasmosis. *American Family Physician* 67, 2131–2138.
46. Kirkham C., Harris S., Grzybowski S. (2005). Evidence-based prenatal care: Part I. General prenatal care and counseling issues. *American Family Physician* 71(7), 1307–1316.
47. Graves J.C., Miller K.E. (2002). Maternal serum triple analyte screening in pregnancy. *American Family Physician* 65(5), 915–920.
48. Qin Q-P., Christiansen M., Pettersson K. (2002). Point of care time-resolved immunofluorometric assay of human pregnancy-associated plasma protein A: Use in first-trimester screening for Down syndrome. *Clinical Chemistry* 48(3), 473–483.
49. Lambert-Messerlian G.M., Canick J.A. (2004). Clinical application of inhibin a measurement: Prenatal serum screening for Down syndrome. *Seminars in Reproductive Medicine* 22(3), 235–242.
50. Wilson R.D. (2000). Amniocentesis and chorionic villus sampling. *Current Opinion in Obstetrics and Gynecology* 12, 81–86.

Characteristics of Benign and Malignant Neoplasms
Terminology
Biology of Benign and Malignant Tumors
Benign Neoplasms
Malignant Neoplasms
Tumor Cell Characteristics
Tumor Growth
Invasion
Metastatic Spread
Etiology of Cancer
Genetic and Molecular Basis of Cancer
Cancer-Associated Genes
Epigenetic Mechanisms
Molecular and Cellular Pathways
Tumor Cell Transformation
Host and Environmental Factors
Heredity
Hormones
Obesity
Immunologic Mechanisms
Chemical Carcinogens
Radiation
Viral and Microbial Agents
Clinical Manifestations
Systemic Manifestations
Anorexia and Cachexia
Fatigue and Sleep Disorders
Paraneoplastic Syndromes
Screening, Diagnosis, and Treatment
Screening
Diagnostic Methods
Tumor Markers
Cytologic, Histologic, and Gene Profiling Methods
Staging and Grading of Tumors
Cancer Treatment
Surgery
Radiation Therapy
Chemotherapy
Hormone and Antihormone Therapy
Biotherapy
Targeted Therapy
Childhood Cancers
Incidence and Types of Childhood Cancers
Biology of Childhood Cancers
Diagnosis and Treatment
Survivors of Childhood and Adolescent Cancers

Chapter 7

Neoplasia

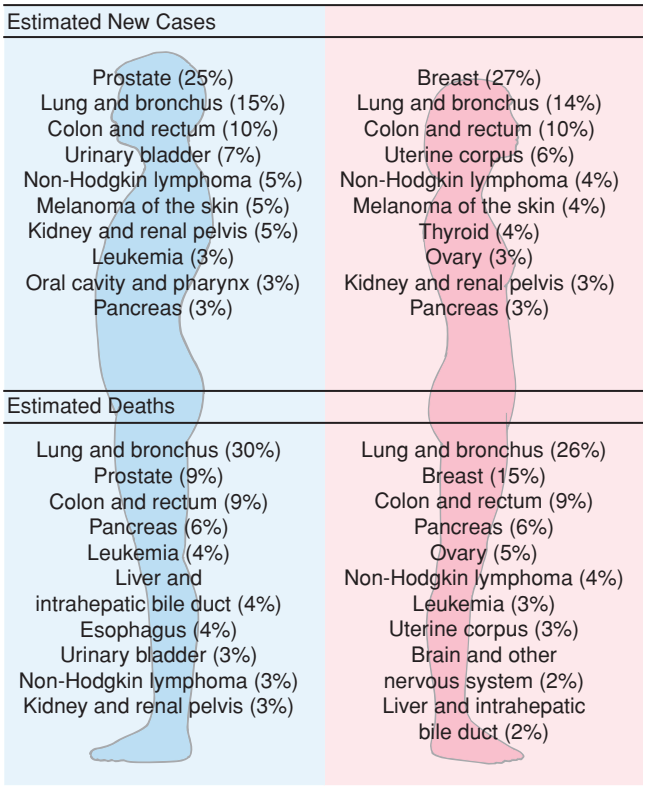
Cancer is the second leading cause of death (after heart disease) in developed countries of the world.[1] The disease affects all age groups, causing more death in children 3 to 15 years of age than any other disease. It was estimated that 1.48 million people in the United States would be newly diagnosed with cancer in 2009 and 562,340 people would die of the disease.[2] During the same time period, it was estimated that 171,000 new cases of cancer would be diagnosed and 75,300 deaths from cancer would occur in Canada.[3] As age-adjusted cancer mortality rates increase and heart disease mortality decreases, it is predicted that cancer will become the leading cause of death in a few decades. The good news, however, is that the survival rates have improved to the extent that almost 64% of people who develop cancer each year will be alive 5 years later.[1]

Cancer is not a single disease. It can originate in almost any organ, with skin cancers being the most common site in persons in the United States. Excluding skin cancers, the prostate is the most common site in men and the breast is the most common site in women (Fig. 7-1).[2] The ability of cancer to be cured varies considerably and depends on the type of cancer and the extent of the disease at the time of diagnosis. Cancers such as acute lymphoblastic leukemia, Hodgkin disease, testicular cancer, and osteosarcoma, which only a few decades ago had poor prognoses, are cured in many cases today. However, lung cancer, which is the leading cause of death in men and women in the United States[2] and Canada,[3] is resistant to therapy. Although some progress has been made in its treatment, mortality rates remain high.

This chapter is divided into five sections: characteristics of benign and malignant neoplasms, etiology of cancer, clinical manifestations, diagnosis and treatment, and childhood cancers. Hematologic malignancies (lymphomas and leukemias) are presented in Chapter 11.

Characteristics of Benign and Malignant Neoplasms

Cancer is a disorder of altered cell differentiation and growth. The resulting process is called *neoplasia,* meaning "new growth," and the new growth is called a *neoplasm*. Unlike the processes of hypertrophy and hyperplasia that are discussed in Chapter 2, the cell changes that occur with neoplasia tend to be relatively



*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Note: Estimates are rounded to the nearest 10.

FIGURE 7-1. Cancer incidence and mortality by site and sex. (Adapted from Jemel A., Seigel R., Ward E., et al. [2009]. Cancer statistics, 2009. *CA: A Cancer Journal for Clinicians* 59, 228.)

uncoordinated and autonomous in that they lack normal regulatory controls over cell growth and division.

Normal renewal and repair involves two components: cell proliferation and differentiation (see Chapter 4). *Proliferation*, or the process of cell division, is an inherent adaptive mechanism for cell replacement when old cells die or additional cells are needed. Fundamental to the origin of all neoplasms are the genetic changes that allow excessive and uncontrolled proliferation that is unregulated by normal growth-regulating stimuli.

Differentiation is the process of specialization whereby new cells acquire the structural, microscopic, and functional characteristics of the cells they replace. Neoplasms are commonly classified as benign or malignant. *Benign neoplasms* are composed of well-differentiated cells that resemble the normal counterpart both in terms of structure and function but have lost the ability to control cell proliferation. *Malignant neoplasms* are less differentiated and have lost the ability to control both cell proliferation and differentiation. In general, the better the differentiation of a neoplasm, the slower its rate of growth and the more completely it retains the functional capabilities found in its normal counterparts. For example, benign neoplasms and even well-differentiated cancers of endocrine glands frequently elaborate the hormones characteristic of their origin.

Benign and Malignant Neoplasms

- A neoplasm, benign or malignant, represents a new growth.
- Benign neoplasms are well-differentiated tumors that resemble the tissues of origin but have lost the ability to control cell proliferation. They grow by expansion, are enclosed in a fibrous capsule, and do not cause death unless their location is such that it interrupts vital body functions.
- Malignant neoplasms are less–well-differentiated tumors that have lost the ability to control both cell proliferation and differentiation. They grow in a disorganized and uncontrolled manner to invade surrounding tissues, have cells that break loose and travel to distant sites to form metastases, and inevitably cause suffering and death unless their growth can be controlled through treatment.

Apoptosis, which is discussed in Chapter 2, is a form of programmed cell death that eliminates senescent cells, deoxyribonucleic acid (DNA), and damaged or unwanted cells. In adult tissues, the size of a population of cells is determined by the rates of cell proliferation and death by apoptosis. In malignant neoplasms, the accumulation of neoplastic cells may result not only from excessive and uncontrolled proliferation, but also from evasion of apoptosis.

All tumors benign and malignant are composed of two types of tissue: parenchymal and supporting.[4] The *parenchymal* tissue, which is made up of the transformed or neoplastic cells of a tumor, determines its behavior and is the component for which the tumor is named. The supporting nonneoplastic stromal tissue component is made up of connective tissue, extracellular matrix (ECM), and blood vessels. It is essential to the growth of the tumor since it carries the blood supply and provides support for the parenchymal tumor cells.

Terminology

Cancers are commonly referred to as *tumors* or *neoplasms*. Although defined in the medical literature as a swelling that can be caused by a number of conditions, including inflammation and trauma, the term *tumor* is increasingly being used to describe a neoplasm. *Oncology*, from the Greek term for a "swelling," *onkos*, refers to the study or science of neoplasms. *Clinical oncology* deals with neoplastic disorders in the clinical setting, primarily in terms of diagnosis and treatment.

Benign tumors usually are named by adding the suffix *-oma* to the parenchymal tissue type from which the growth originated.[4,5] Thus, a benign epithelial neoplasm of glandular tissue is called an *adenoma*, and a benign tumor arising in fibrous tissue is called a *fibroma*. The

TABLE 7-1 Names of Selected Benign and Malignant Tumors According to Tissue Types

Tissue Type	Benign Tumors	Malignant Tumors
Epithelial		
Surface	Papilloma	Squamous cell carcinoma
Glandular	Adenoma	Adenocarcinoma
Connective		
Fibrous	Fibroma	Fibrosarcoma
Adipose	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Blood vessels	Hemangioma	Hemangiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Lymph tissue		Lymphosarcoma
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Neural Tissue		
Nerve cell	Neuroma	Neuroblastoma
Glial tissue	Glioma	Glioblastoma, astrocytoma, medulloblastoma, oligodendroglioma
Nerve sheaths	Neurilemmoma	Neurilemmal sarcoma
Meninges	Meningioma	Meningeal sarcoma
Hematologic		
Granulocytic		Myelocytic leukemia
Erythrocytic		Erythrocytic leukemia
Plasma cells		Multiple myeloma
Lymphocytic		Lymphocytic leukemia or lymphoma
Monocytic		Monocytic leukemia
Endothelial Tissue		
Blood vessels	Hemangioma	Hemangiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma

term *carcinoma* is used to designate a malignant tumor of epithelial tissue origin. In the case of malignancies that originate from glandlike structures, the term *adenocarcinoma* is used, and for those that originate from squamous cells, the term *squamous cell carcinoma* is used. Malignant tumors of mesenchymal origin are called *sarcomas*. A cancer of fibrous tissue is a *fibrosarcoma* and a malignant tumor composed of chondrocytes is a *chondrosarcoma*.

Papillomas are benign microscopic or macroscopic fingerlike projections that grow on any surface. A *polyp* is a growth that projects from a mucosal surface, such as the intestine. Although the term usually implies a benign neoplasm, some malignant tumors also appear as polyps. Adenomatous polyps are considered precursors to adenocarcinomas of the colon. Table 7-1 lists the names and tissue types of selected benign and malignant tumors.

Biology of Benign and Malignant Tumors

The differences between benign and malignant tumors are determined by (1) the characteristics of the tumor cells, (2) the rate of growth, (3) local invasion, and (4) the ability to metastasize. The characteristics of benign and malignant neoplasms are summarized in Table 7-2.

Benign Neoplasms

Benign tumors are composed of well-differentiated cells that resemble the cells of the tissues of origin and are generally characterized by a slow, progressive rate of growth that may come to a standstill or regress.[4,5] For unknown reasons, benign tumors have lost the ability to suppress the genetic program for cell proliferation but have retained the program for normal cell differentiation. They grow by expansion and remain localized to their site of origin and do not have the capacity to infiltrate, invade, or metastasize to distant sites. Because they expand slowly, they develop a surrounding rim of compressed connective tissue called a *fibrous capsule*.[4] The capsule is responsible for a sharp line of demarcation between the benign tumor and the adjacent tissues, a factor that facilitates surgical removal.

Malignant Neoplasms

In contrast to benign tumors, malignant neoplasms tend to grow rapidly, invade and infiltrate nearby tissue, and spread to other parts of the body. They lack a well-defined

TABLE 7-2 Characteristics of Benign and Malignant Neoplasms

Characteristics	Benign	Malignant
Cell characteristics	Well-differentiated cells that resemble cells in the tissue of origin	Cells are undifferentiated, with anaplasia and atypical structure that often bears little resemblance to cells in the tissue of origin
Rate of growth	Usually progressive and slow; may come to a standstill or regress	Variable and depends on level of differentiation; the more undifferentiated the cells, the more rapid the rate of growth
Mode of growth	Grows by expansion without invading the surrounding tissues; usually encapsulated	Grows by invasion, sending out processes that infiltrate the surrounding tissues
Metastasis	Does not spread by metastasis	Gains access to blood and lymph channels to metastasize to other areas of the body

capsule and their margins are not clearly separated from the normal surrounding tissue.[4,5] Because of their rapid rate of growth, malignant tumors may compress blood vessels and outgrow their blood supply, causing ischemia and tissue injury. Some malignancies secrete hormones and/or cytokines, liberate enzymes and toxins, and/or induce an inflammatory response that injures normal tissue as well as the tumor itself.

There are two categories of malignant neoplasms—solid tumors and hematologic cancers. Solid tumors initially are confined to a specific tissue or organ. As the growth of the primary solid tumor progresses, cells detach from the original tumor mass, invade the surrounding tissue, and enter the blood and lymph system to spread to distant sites, a process termed *metastasis*. Hematologic cancers involve cells normally found within the blood and lymph, thereby making them disseminated diseases from the beginning.

Cancer in situ is a localized preinvasive lesion. As an example, in breast ductal carcinoma in situ the cells have not crossed the basement membrane. Depending on its location, in situ lesions usually can be removed surgically or treated so that the chances of recurrence are small. For example, cancer in situ of the cervix is essentially 100% curable.

Tumor Cell Characteristics

Whether a tumor is benign or malignant is determined by an examination of its cells. Typically, such an examination includes macroscopic (naked eye) inspection to determine the presence or absence of a tumor capsule and invasion of the surrounding tissue, supplemented by microscopic examination of histologic sections of the tumor. Additional information may be obtained from electron microscopy, immunochemistry techniques, chromosomal studies, and DNA analysis. The growth and behavior of tumor cells may be studied using culture techniques.

Differentiation and Anaplasia. Differentiation refers to the extent to which the parenchymal cells of a tumor resemble their normal forbearers morphologically and functionally. Malignant neoplasms that are composed of poorly differentiated or undifferentiated cells are described as being *anaplastic;* the term *anaplasia* literally means to "form backward" to an earlier dedifferentiated state.[4,5] On histologic examination, benign tumors are composed of cells that resemble the tissue from which they have arisen. By contrast, the cells of malignant tumors are characterized by wide changes of parenchymal cell differentiation from well differentiated to completely undifferentiated.

Undifferentiated cancer cells are marked by a number of morphologic changes. Both the cells and nuclei display variations in size and shape, a condition referred to as *pleomorphism*. Their nuclei are variable in size and bizarre in shape, their chromatin is coarse and clumped, and their nucleoli are often considerably larger than normal (Fig. 7-2A). Characteristically, the nuclei contain an abundance of DNA and are extremely dark staining. The cells of undifferentiated tumors usually display a large number of mitoses, reflecting a higher rate of proliferation. They also display atypical, bizarre mitotic figures, sometimes producing tripolar, tetrapolar, or multipolar spindles (Fig. 7-2B). Highly anaplastic cancer cells, whatever their tissue of origin, begin to resemble undifferentiated or embryonic cells more than they do their tissue of origin.

Some cancers display only slight anaplasia and others marked anaplasia. The cytologic/histologic grading of tumors is based on the degree of differentiation and the number of proliferating cells. The closer the tumor cells resemble comparable normal tissue cells, both morphologically and functionally, the lower the grade. Accordingly, on a scale ranging from grade I to IV, grade I neoplasms are well differentiated and grade IV are poorly differentiated and display marked anaplasia.[3]

Genetic Instability and Chromosomal Abnormalities. Most cancer cells exhibit a characteristic called *genetic instability* that is often considered to be a hallmark of cancer. The concept came about after the realization that uncorrected mutations in normal cells are rare due to many cellular mechanisms to prevent them. To account for the high frequency of mutations in cancer cells, it is thought that cancer cells have a "mutation phenotype" with genetic instability that contributes to the development and progression of cancer.[6]

Characteristics of genetic instability include chromosomal abnormalities. Benign tumors usually have a normal number of chromosomes. By contrast, malignant

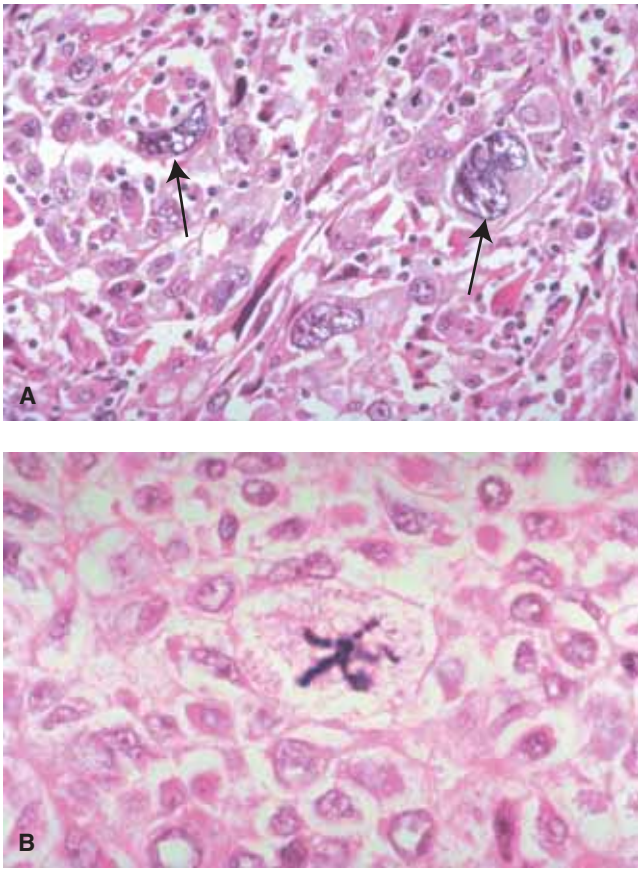


FIGURE 7-2. Anaplastic features of malignant tumors. **(A)** The cells of this anaplastic carcinoma are highly pleomorphic (i.e., they vary in size and shape). The nuclei are hyperchromatic and are large relative to the cytoplasm. Multinucleated tumor giant cells are present (*arrows*). **(B)** A malignant cell in metaphase exhibits an abnormal mitotic figure. (From Giordan A., DeFalco G., Rubin E. [2008]. Neoplasia. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 141]. Philadelphia: Lippincott Williams & Wilkins.)

cells often display a feature called *aneuploidy*, meaning that they have an abnormal number of chromosomes.[4,5] The chromosomes may be structurally abnormal due to insertions, deletions, amplifications, or translocations of parts of their arms (see Chapter 6). They may also display microsatellite instability, which involves short repetitive sequences of DNA, and point mutations.

Growth Properties. The characteristics of altered proliferation and differentiation are associated with a number of growth and behavioral changes that distinguish cancer cells from their normal counterparts. Many changes, which have been observed using in vitro methods, include growth factor independence, lack of cell density–dependent inhibition, impaired cohesiveness and adhesion, loss of anchorage dependence, faulty cell-to-cell communication, and an indefinite cell life span (immortality).

Cell growth in test tubes or culture dishes is referred to as *in vitro cell culture* because the first containers used for these cultures were made of glass (*vitrium*, meaning "glass" in Latin).[7] It is assumed that the in vivo (in the body) growth of tumor cells mimics that of in vitro studies. Most normal cells require a complex growth media and survive for only a limited time in vitro. In the case of cancer cells, the addition of serum, which is rich in growth factors, is unnecessary for the cancers to proliferate. Some cancer cells produce their own growth factors and secrete them into the culture medium, while others have abnormal receptors or signaling proteins that may inappropriately activate growth signaling pathways within the cells. Breast cancer cells that do not express estrogen receptors are an example. These cancer cells grow even in the absence of estrogen, which is the normal growth stimulus for breast duct epithelial cells.

Normal cells that are grown in culture tend to display a feature called *cell density–dependent inhibition,* in which they stop dividing after the cells reach a particular density.[7,8] This is sometimes referred to as *contact inhibition* since cells often stop growing when they come into contact with each other. In wound healing, for example, contact inhibition causes fibrous tissue growth to cease at the point where the edges of the wound come together. Malignant cells show no such contact inhibition and grow rampantly without regard for adjacent tissue. There is also a reduced tendency of cancer cells to stick together (i.e., loss of *cohesiveness* and *adhesiveness*) owing, in part, to a loss of cell surface adhesion molecules. This permits shedding of the tumor's surface cells; these cells appear in the surrounding body fluids or secretions and often can be detected using cytologic examination.

Cancer cells also display a feature called *anchorage independence*.[7–9] Studies in culture show that normal cells, with the exception of hematopoietic cells, will not grow and proliferate unless they are attached to a solid surface such as the ECM. For some cell types, including epithelial tissue cells, even survival depends on such attachments. If normal epithelial cells become detached, they often undergo a type of apoptosis known as *anoikis* due to not having a "home." In contrast to normal cells, cancer cells often survive in microenvironments different from those of the normal cells. They frequently remain viable and multiply without normal attachments to other cells and the ECM.

Another characteristic of cancer cells is faulty *cell-to-cell communication*, a feature that may contribute to the growth and survival of cancer cells. Impaired cell-to-cell communication may interfere with formation of intercellular connections and responsiveness to membrane-derived signals. For example, changes in gap junction proteins, which enable cytoplasmic continuity and communication between cells, has been described in some types of cancer.[10]

Cancer cells also differ from normal cells by being *immortal* with an unlimited life span. If normal noncancerous cells are harvested from the body and grown under culture conditions, most cells divide a limited number of times, usually about 50 population doublings, then achieve senescence and fail to divide further. In contrast to the limited life span of normal cells, cancer cells may divide an infinite number of times, and hence achieve immortality. Telomeres are short repetitive nucleotide

sequences at the outermost extremities of chromosome arms (see Chapter 2). Most cancer cells maintain high levels of telomerase, an enzyme that prevents telomere shortening, which keeps telomeres from aging and attaining a critically short length that is associated with cellular replicative senescence.

Functional Features. Because of their lack of differentiation, cancer cells tend to function on a more primitive level than normal cells, retaining only those functions that are essential for their survival and proliferation. Cancer cells may also acquire some new features and become quite different from normal cells. For example, many transformed cancer cells revert to earlier stages of gene expression and produce antigens that are immunologically distinct from the antigens that are expressed by cells of the well-differentiated tissue from which the cancer originated. Some cancers may elaborate fetal antigens that are not produced by comparable cells in the adult. Tumor antigens may be clinically useful as markers to indicate the presence, recurrence, or progressive growth of a cancer. Response to treatment can also be evaluated based on an increase or decrease in tumor antigens.

Cancers may also engage in the abnormal production of substances that affect body function. For example, cancer cells may produce procoagulant materials that affect the clotting mechanisms, or tumors of nonendocrine origin may assume the ability to engage in hormone synthesis. These conditions are often referred to as *paraneoplastic syndromes* (to be discussed).

Tumor Growth

In cells that have an adequate blood supply, the rate of tissue growth in normal and cancerous tissue depends on three factors: (1) the number of cells that are actively dividing or moving through the cell cycle, (2) the duration of the cell cycle, and (3) the number of cells that are being lost relative to the number of new cells being produced. One of the reasons cancerous tumors often seem to grow so rapidly relates to the size of the cell pool that is actively engaged in cycling. It has been shown that the cell cycle time of cancerous tissue cells is not necessarily shorter than that of normal cells. Rather, cancer cells do not die on schedule and growth factors prevent cells from exiting the cycle cell and entering the G_0 phase (see Chapter 4). Thus, a greater percentage of cells are actively engaged in cycling than occurs in normal tissue.

The ratio of dividing cells to resting cells in a tissue mass is called the *growth fraction*. The *doubling time* is the length of time it takes for the total mass of cells in a tumor to double. As the growth fraction increases, the doubling time decreases. When normal tissues reach their adult size, equilibrium between cell birth and cell death is reached. Cancer cells, however, continue to divide until limitations in blood supply and nutrients inhibit their growth. When this occurs, the doubling time for cancer cells decreases. If tumor growth is plotted against time on a semilogarithmic scale, the initial growth rate is exponential and then tends to decrease or flatten out over time. This characterization of tumor growth is called the *Gompertzian model*.[11]

By conventional radiographic methods, a tumor usually is undetectable until it has doubled 30 times and contains more than 1 billion (10^9) cells. At this point, it is approximately 1 cm in size (Fig. 7-3). Methods to identify tumors at smaller sizes are under investigation; in some cases the application of ultrasound and magnetic resonance imaging (MRI) enable detection of tumors less than 1 cm. After

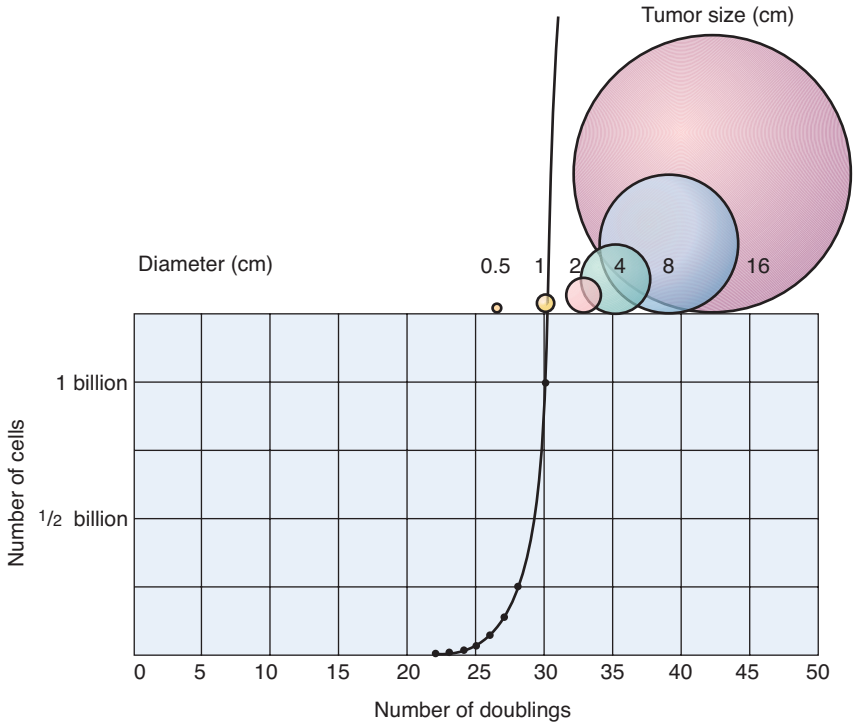


FIGURE 7-3. Growth curve of a hypothetical tumor on arithmetic coordinates. Notice the number of doubling times before the tumor reaches an appreciable size. (Adapted from Collins V.P., Loeffler R.K., Tivey H. [1956]. Observations of growth rates of human tumors. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine* 76, 988.)

35 doublings, the mass contains more than 1 trillion (10^{12}) cells, which is a sufficient number to kill the host.

Invasion

The word *cancer* is derived from the Latin word meaning *crablike* because cancers grow and spread by sending crablike projections into the surrounding tissues. Unlike benign tumors, which grow by expansion and usually are surrounded by a capsule, cancer spreads by direct invasion and extension, seeding of cancer cells in body cavities, and metastatic spread.

Most cancers synthesize and secrete enzymes that break down proteins and contribute to the infiltration, invasion, and penetration of the surrounding tissues. The lack of a sharp line of demarcation separating them from the surrounding tissue makes the complete surgical removal of malignant tumors more difficult than removal of benign tumors. Often it is necessary for the surgeon to excise portions of seemingly normal tissue bordering the tumor for the pathologist to establish that cancer-free margins are present around the excised tumor and to ensure that the remaining tissue is cancer free.

The *seeding* of cancer cells into body cavities occurs when a tumor erodes and sheds cells into these spaces.[4,5] Most often, the peritoneal cavity is involved, but other spaces such as the pleural cavity, pericardial cavity, and joint spaces may be involved. Seeding into the peritoneal cavity is particularly common with ovarian cancers. Similar to tissue culture, tumors in these sites grow in masses and often produce fluid (e.g., ascites, pleural effusion).[5] The seeding of cancers is often a concern during the surgical removal of cancers, where it is possible to inadvertently introduce free cancer cells into a body cavity such as the peritoneal cavity.[12]

Metastatic Spread

The term *metastasis* is used to describe the development of a secondary tumor in a location distant from the primary tumor.[4,5] Metastatic tumors frequently retain many of the microscopic characteristics of the primary tumor from which they were derived. Because of this, it usually is possible to determine the site of the primary tumor from the cellular characteristics of the metastatic tumor. Some tumors tend to metastasize early in their developmental course, while others do not metastasize until later. Occasionally, a metastatic tumor will be found far advanced before the primary tumor becomes clinically detectable. Malignant tumors disseminate by one of two pathways: lymph channels (lymphatic spread) or blood vessels (hematogenous spread).[4] Lymphatic spread is more typical of carcinomas, whereas hematogenous spread is favored by sarcomas.

Lymphatic Spread. In many types of cancer, the first evidence of disseminated disease is the presence of tumor cells in the lymph nodes that drain the tumor area. When metastasis occurs by way of the lymphatic channels, the tumor cells lodge first in the initial lymph node that receives drainage from the tumor site. Once in this lymph node, the cells may die because of the lack of a proper environment, remain dormant for unknown reasons, or grow into a discernible mass (Fig. 7-4). If they survive and grow, the cancer cells may spread from more distant lymph nodes to the thoracic duct, and then gain access to the blood vasculature. Furthermore, cancer cells may gain access to the blood vasculature from the initial node and more distant lymph nodes by way of tumor-associated blood vessels that may infiltrate the tumor mass.[13]

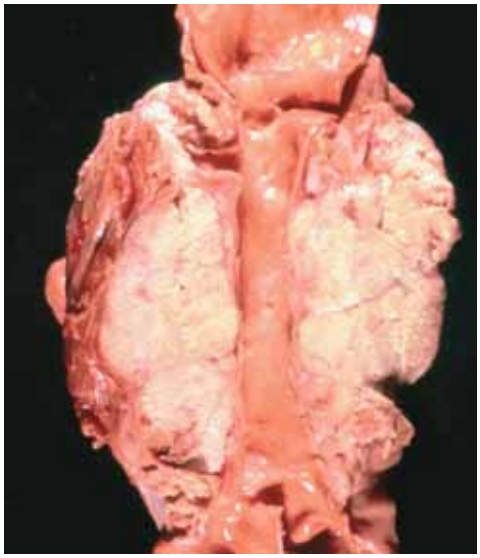


FIGURE 7-4. Metastatic carcinoma in periaortic lymph nodes. Aorta has been opened and nodes bisected. (From Giordano A., De Falco G., Rubin E., et al. [2008]. Neoplasia. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 146]. Philadelphia: Lippincott Williams & Wilkins.)

The term *sentinel node* is used to describe the initial lymph node to which the primary tumor drains.[14] Because the initial metastasis in breast cancer is almost always lymphatic, lymphatic spread and, therefore, extent of disease may be determined through lymphatic mapping and sentinel lymph node biopsy. This is done by injecting a radioactive tracer and blue dye into the tumor to determine the first lymph node in the route of lymph drainage from the cancer. Once the sentinel lymph node is identified, it is examined to determine the presence or absence of cancer cells. The procedure is also used to map the spread of melanoma and other cancers that have their initial metastatic spread through the lymphatic system.

Hematogenous Spread. With hematogenous spread, cancer cells commonly invade capillaries and venules, whereas thicker-walled arterioles and arteries are relatively resistant. With venous invasion, blood-borne cells follow the venous flow draining the site of the neoplasm with tumor cells, often stopping in the first capillary bed they encounter. Since venous blood from the gastrointestinal tract, pancreas, and spleen is routed through the portal vein to the liver, and all vena caval blood flows to the lungs, the liver and lungs are the most frequent

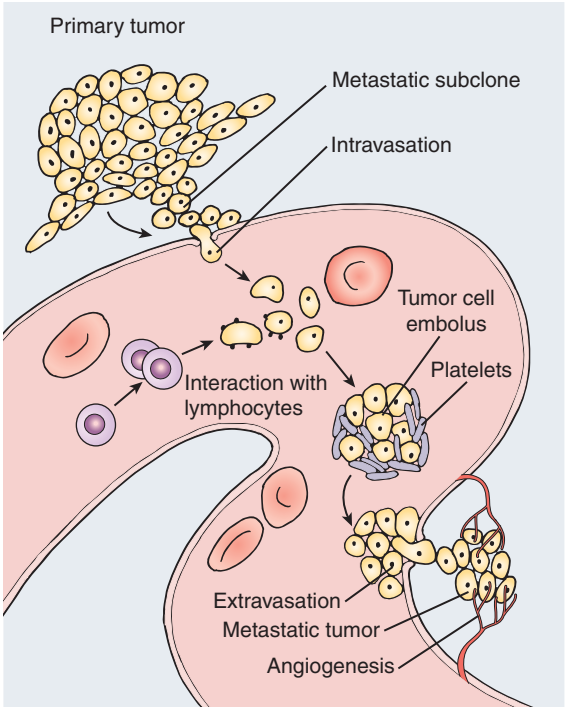


FIGURE 7-5. The pathogenesis of metastasis. (Adapted from Kumar V., Abbas A.K., Fausto N. [Eds.]. [2005]. *Robbins and Cotran pathologic basis of disease* [7th ed., p. 311]. Philadelphia: Elsevier Saunders.)

metastatic sites for hematogenous spread.[4,5] Although the site of hematologic spread usually is related to vascular drainage of the primary tumor, some tumors metastasize to distant and unrelated sites. For example, prostatic cancer preferably spreads to bone, bronchogenic cancer to the adrenals and brain, and neuroblastomas to the liver and bones.

The selective nature of hematologic spread indicates that metastasis is a finely orchestrated, multistep process, and only a small, select clone of cancer cells has the right combination of gene products to perform all of the steps needed for establishment of a secondary tumor (Fig. 7-5). To metastasize, a cancer cell must be able to break loose from the primary tumor, invade the surrounding extracellular matrix, gain access to a blood vessel, survive its passage in the bloodstream, emerge from the bloodstream at a favorable location, invade the surrounding tissue, begin to grow, and establish a blood supply.

Considerable evidence suggests that cancer cells capable of metastasis secrete enzymes that break down the surrounding ECM, allowing them to move through the degraded matrix and gain access to a blood vessel. Once in the circulation, the tumor cells are vulnerable to destruction by host immune cells. Some tumor cells gain protection from the antitumor host cells by aggregating and adhering to circulating blood components, particularly platelets, to form tumor emboli. Exit of the tumor cells from the circulation involves adhesion to the vascular endothelium followed by movement through the capillary wall into the site of secondary tumor formation by mechanisms similar to those involved in invasion.

Once in the distant site, the process of metastatic tumor development depends on the establishment of blood vessels and specific growth factors that promote proliferation of the tumor cells. Tumor cells as well as other cells in the microenvironment secrete angiogenesis factors that enable the development of new blood vessels within the tumor, a process termed *angiogenesis* (to be discussed).[15] The presence of stimulatory or inhibitor growth factors correlates with the site-specific pattern of metastasis. For example, a potent growth-stimulating factor has been isolated from lung tissue, and stromal cells in bone have been shown to produce a factor that stimulates growth of prostatic cancer cells.[15]

Recent evidence indicates that chemoattractant cytokines called *chemokines* that regulate the trafficking of leukocytes and other cell types under a variety of inflammatory and noninflammatory conditions may play a critical role in cancer invasion and metastasis.[16,17] Tumor cells have been shown to express functional chemokine receptors, which can sustain cancer cell proliferation, angiogenesis, and survival and promote organ-specific localization of metastasis. Insights into the presence and role of chemokines in cancer spread and metastasis provide directions for development of future diagnostic and treatment methods. The implications include methods to diminish metastasis by blocking the action of selected chemokines and/or their receptors.

In summary, the term *neoplasm* refers to an abnormal mass of tissue in which the uncontrolled proliferation of cells exceeds and is uncoordinated with that of the normal tissues. Differentiation refers to the extent to which neoplastic cells resemble their normal counterpart. *Benign* tumors are enclosed in a fibrous capsule, grow by expansion, and have fully differentiated cells that resemble their normal counterpart. By contrast, *malignant neoplasms* are disorders of cell proliferation and differentiation that grow in a poorly controlled fashion, invade surrounding tissues, and have the ability to break loose and form distant metastases.

The term *anaplasia* is used to describe the loss of cell differentiation in cancerous tissue. Undifferentiated cancer cells are marked by a number of morphologic changes, including variations in size and shape, a condition referred to as *pleomorphism*. The characteristics of altered proliferation and differentiation are associated with a number of other changes in cell characteristics and cell function including genetic instability; growth factor independence; loss of cell density–dependent inhibition, cohesiveness and adhesion, and anchorage dependence; faulty cell-to-cell communication; an indefinite cell life span (immortality); and expression of fetal antigens not produced by their normal counterparts and abnormal production of hormones and substances that affect body function.

The rate of growth of cancerous tissue depends on the ratio of dividing to resting cells (growth fraction) and the time it takes for the total cells in the tumor to double

(doubling time). A tumor is usually undetectable until it has doubled 30 times and contains more than a billion cells. The spread of cancer occurs through three pathways: direct invasion and extension, seeding of cancer cells in body cavities, and metastatic spread through lymphatic or vascular pathways. Only a proportionately small clone of cancer cells is capable of metastasis. To metastasize, a cancer cell must be able to break loose from the primary tumor, invade the surrounding ECM, gain access to a blood vessel, survive its passage in the bloodstream, emerge from the bloodstream at a favorable location, and invade the surrounding tissue. Once in the distant tissue site, the metastatic process depends on the establishment of blood vessels and specific growth factors that promote proliferation of the tumor cells.

Etiology of Cancer

The cause or causes of cancer can be viewed from two perspectives: (1) the genetic and molecular mechanisms that characterize the transformation of normal cells into cancer cells and (2) the external and more contextual factors such as age, heredity, and environmental agents that contribute to its development and progression. Together, both mechanisms contribute to a multidimensional web of causation by which cancers develop and progress over time.

Genetic and Molecular Basis of Cancer

The molecular pathogenesis of most cancers is thought to originate from genetic damage or mutation with resultant changes in cell physiology that transform a normally functioning cell into a cancer cell. *Epigenetic factors* that involve silencing of a gene or genes may also be involved in the pathogenesis of cancer. In recent years, an important role of cancer stem cells in the pathogenesis of cancer has been identified and continues to be elucidated. Finally, the cellular microenvironment that involves the ECM and a complex milieu of cytokines, growth factors, and other cell types is also recognized as an important contributor to cancer development, its growth, and progression.

Cancer-Associated Genes

Most cancer-associated genes can be classified into two broad categories based on whether gene overactivity or underactivity increases the risk for cancer. The category associated with gene overactivity involves *proto-oncogenes,* which are normal genes that become cancer-causing *oncogenes* if mutated.[4,5,18] Proto-oncogenes encode for normal cell proteins such as growth factors, growth factor receptors, growth factor signaling molecules, and transcription factors that promote cell growth or increase growth factor–dependent signaling. The category of cancer-associated underactivity genes includes the *tumor-suppressor genes,* which, by being less active, create an environment in which cancer is promoted.

Genetic Events Leading to Oncogene Formation or Activation. There are a number of genetic events that can cause or activate oncogenes. A common event is a point mutation in which there is a single nucleotide base change due to an insertion, deletion, or substitution. An example of an oncogene caused by point mutations is the *RAS* oncogene, which has been found in many cancers.[4] Members of the ras proto-oncogene family are important signal-relaying proteins that transmit growth signals to the cell nucleus. Hence, activation of the ras oncogene can increase cell proliferation.

Chromosomal translocations have traditionally been associated with cancers such as Burkitt lymphoma and chronic myeloid leukemia (CML). In Burkitt lymphoma the C-myc gene, which encodes a growth signal protein, is translocated from its normal position on chromosome 8 to chromosome 14, placing it at the site of an immunoglobulin gene.[4] The outcome of the translocation in CML is the appearance of the so-called *Philadelphia chromosome* involving chromosomes 9 and 22 and the formation of an abnormal fusion protein that promotes cell proliferation[5] (see Chapter 11, Fig. 11-6). Recent advances in biotechnology and genomics are enabling the identification and increased understanding of how gene translocations, even within the same chromosome, contribute to tumorigenesis by the creation of abnormal fusion proteins that promote cell proliferation.

Another genetic event that is common in cancer is gene amplification. Multiple copies of certain genes may cause overexpression with higher than normal levels of proteins that increase cell proliferation. For example, the human epidermal growth factor receptor-2 (HER-2/neu) gene is amplified in up to 30% of breast cancers and indicates a tumor that is aggressive with a poor prognosis.[19] One of the agents used in treatment of HER-2/neu overexpressing breast cancers is trastuzumab (Herceptin), a monoclonal antibody that selectively binds to HER-2, thereby inhibiting the proliferation of tumor cells that overexpress HER-2.

Genetic Events Leading to Loss of Tumor-Suppressor Gene Function. Normal cells have regulatory genetic mechanisms that protect them against activated or newly acquired oncogenes. These genes are called tumor-suppressor genes. When this type of gene is inactivated, a genetic signal that normally inhibits cell proliferation is removed, thereby causing unregulated growth to begin.[4,5] Mutations in tumor-suppressor genes are generally recessive, in that cells tend to behave normally until both genes are deleted, inactivated, or silenced.

The two best-known tumor-suppressor genes are the p53 and retinoblastoma (RB) genes. The p53 gene, named after the molecular weight of the protein it encodes, is the most common target for genetic alteration in human cancers. Mutations in the p53 gene can occur in virtually every type of cancer including lung, breast, and colon cancer—the three leading causes of cancer death.[4] Sometimes called the "guardian of the genome," the p53 gene acts as a molecular policeman that prevents the propagation of genetically damaged cells.[4] Located on the short arm of chromosome 17, the

p53 gene normally senses DNA damage and assists in DNA repair by causing arrest of the cell cycle in G_1 and inducing DNA repair or initiating apoptosis in a cell that cannot be repaired.[4,5] With homologous loss of p53 gene activity, DNA damage goes unrepaired and mutations occur in dividing cells leading to malignant transformations. The p53 gene also appears to initiate apoptosis in radiation- and chemotherapy-damaged tumor cells. Thus, tumors that retain normal p53 function are more likely to respond to such therapy than tumors that carry a defective p53 gene.[4]

The RB gene was isolated in studies involving a malignant tumor of the eye known as *retinoblastoma*. The tumor occurs in a hereditary and sporadic form and becomes evident in early life. Approximately 60% of cases are sporadic, and the remaining 40% are hereditary, inherited as an autosomal dominant trait.[4] Known as the "two hit" hypothesis of carcinogenesis, both normal alleles of the RB gene must be inactivated for the development of retinoblastoma (Fig. 7-6).[4,5] In hereditary cases, one genetic change ("first hit") is inherited from an affected parent and is therefore present in all somatic cells of the body, whereas the second mutation ("second hit") occurs in one of the retinal cells (which already carries the first mutation). In sporadic (noninherited) cases, both mutations ("hits") occur within a single somatic cell, whose progeny then form the cancer.

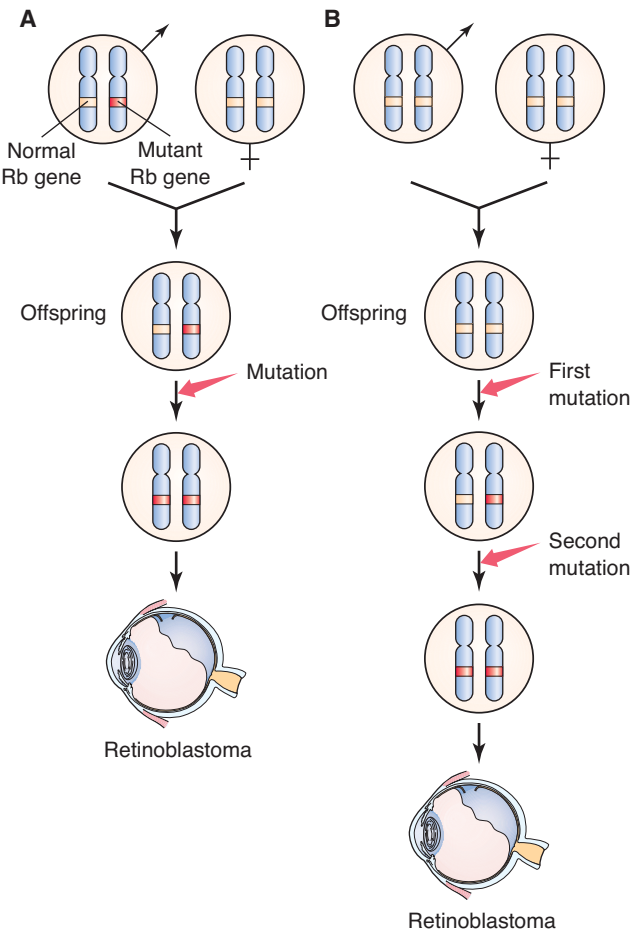


FIGURE 7-6. Pathogenesis of retinoblastoma. Two mutations of the mutant retinoblastoma (Rb) gene lead to development of neoplastic proliferation of retinal cells. **(A)** In the familial form all offspring become carriers of the mutant Rb gene. A second mutation affects the other Rb gene locus after birth. **(B)** In the sporadic form, both mutations occur after birth.

The RB gene represents a model for other genes that act similarly. In persons carrying an inherited mutation, such as a mutated RB allele, all somatic cells are perfectly normal, except for the risk of developing cancer. That person is said to be *heterozygous* at the gene locus. Cancer develops when a person becomes homozygous for the mutant allele, a condition referred to as *loss of heterozygosity*.[4] For example, loss of heterozygosity is known to occur in hereditary cancers, in which a mutated gene is inherited from a parent and other conditions (e.g., radiation exposure) are present that make individuals more susceptible to cancer.

MicroRNA Genes. A third category of genes, microribonucleic acid (microRNA) genes, do not encode proteins. Instead, the products of these genes consist of a single RNA strand that serves to regulate gene expression.[18,20] Mapping of numerous microRNA genes has shown that many occur in chromosomal regions that undergo rearrangements, deletions, and amplifications. A microRNA can pair with a messenger RNA (mRNA) containing a nucleotide sequence that complements the sequence of microRNA, thereby blocking protein translation or degradation of the mRNA. A microRNA gene can be a tumor suppressor if in a given cell its critical target is an oncogene or it can be an oncogene if its target is a tumor-suppressor gene. MicroRNA genes can be upregulated or down-regulated in cancer cells. For example, the miR155 gene is overexpressed in B-cell lymphoma, the aggressive form of chronic lymphocytic leukemia, and in breast, lung, and colon cancers.

Epigenetic Mechanisms

In addition to mechanisms that involve DNA and chromosomal structural changes, there are molecular and cellular mechanisms termed "epigenetic" mechanisms that involve changes in the patterns of gene expression without a change in the DNA.[21] Epigenetic mechanisms may "silence" genes, such as tumor-suppressor genes, so that even though the gene is present, it is not expressed and a cancer-suppressing protein is not made. One such mechanism of epigenetic silencing is by methylation of the promoter region of the gene, a change that prevents transcription and causes gene inactivity. Genes silenced by hypermethylation can be inherited, and epigenetic silencing of genes can be considered a "first hit" in the "two hit" hypothesis described earlier.[22]

Molecular and Cellular Pathways

There are numerous molecular and cellular mechanisms with myriad associated pathways and genes that are known or suspected to facilitate the development of cancer. These mechanisms include defects in DNA repair mechanisms, disorders in growth factor signaling pathways,

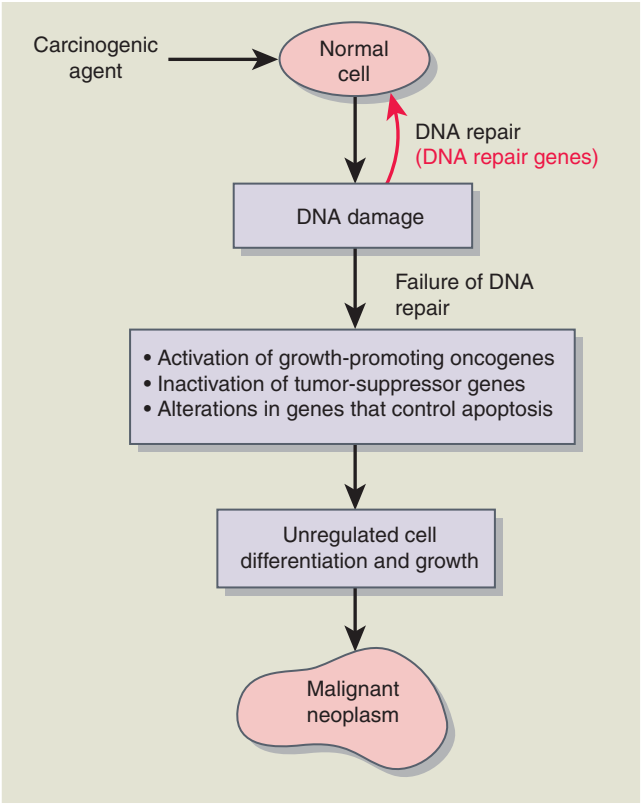


FIGURE 7-7. Flow chart depicting the stages in the development of a malignant neoplasm resulting from exposure to an oncogenic agent that produces DNA damage. When DNA repair genes are present (*red arrow*), the DNA is repaired and gene mutation does not occur.

evasion of apoptosis, development of sustained angiogenesis, and evasion of metastasis.

Mechanisms and genes that regulate repair of damaged DNA have been implicated in the process of oncogenesis (Fig. 7-7). The DNA repair genes affect cell proliferation and survival indirectly through their ability to repair nonlethal damage in other genes including proto-oncogenes, tumor-suppressor genes, and the genes that control apoptosis.[4,5] These genes have been implicated as the principal targets of genetic damage occurring during the development of a cancer cell. Such genetic damage may be caused by the action of chemicals, radiation, or viruses, or it may be inherited in the germ line. Significantly, it appears that the acquisition of a single-gene mutation is not sufficient to transform normal cells into cancer cells. Instead, cancerous transformation appears to require the activation of many independently mutated genes.

A relatively common pathway by which cancer cells gain autonomous growth is by mutations in genes that control signaling pathways. These signaling pathways couple growth factor receptors to their nuclear targets.[4] Under normal conditions, cell proliferation involves the binding of a growth factor to its receptor on the cell membrane, activation of the growth factor receptor on the inner surface of the cell membrane, transfer of the signal across the cytosol to the nucleus via signal-transducing proteins that function as second messengers, induction and activation of regulatory factors that initiate DNA transcription, and entry of the cell into the cell cycle (Fig. 7-8). Many of the proteins involved in the signaling pathways that control the action of growth factors exert their effects through enzymes called *kinases* that phosphorylate proteins. In some types of cancer such as chronic myeloid leukemia, mutation in a proto-oncogene controlling tyrosine kinase activity occurs, causing unregulated cell growth and proliferation.

The accumulation of cancer cells may result not only from the activation of growth-promoting oncogenes or inactivation of tumor-suppressor genes, but also from genes that regulate cell death through apoptosis.[4,5,23,24] Faulty apoptotic mechanisms have an important role in cancer. The failure of cancer cells to undergo apoptosis in a normal manner may be due to a number of problems. There may be altered cell survival signaling, down-regulation of death receptors, stabilization of the mitochondria, or inactivation of proapoptotic proteins. Alterations in apoptotic and antiapoptotic pathways have been found in many

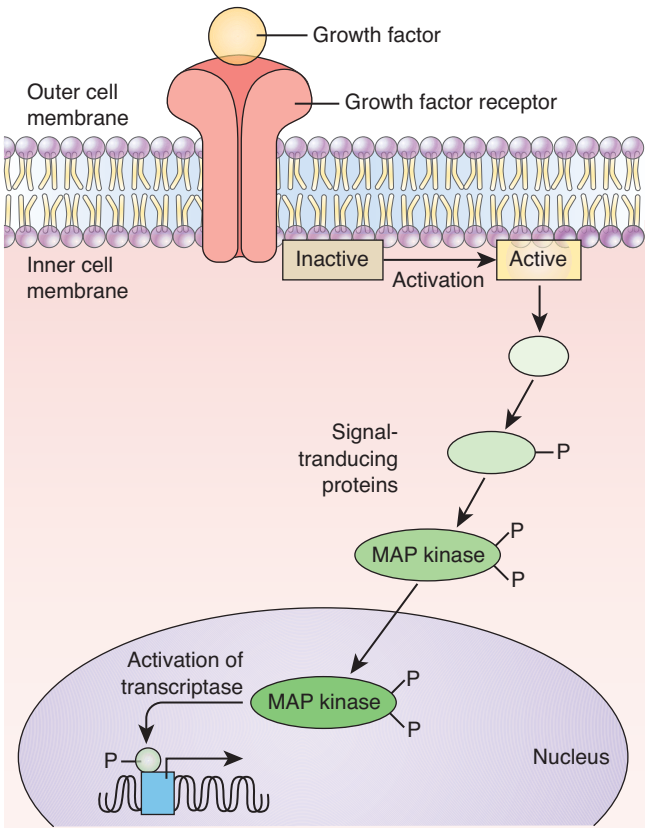


FIGURE 7-8. Pathway for genes regulating cell growth and replication. Stimulation of a normal cell by a growth factor results in activation of the growth factor receptor and signaling proteins that transmit the growth-promoting signal to the nucleus, where it modulates gene transcription and progression through the cell cycle. Many of these signaling proteins exert their effects through enzymes called *kinases* that phosphorylate (P) proteins. MAP, mitogen-activating protein.

cancers. One example is the high levels of the antiapoptotic protein Bcl-2 that occur secondary to a chromosomal translocation in certain B-cell lymphomas. The mitochondrial membrane is a key regulator of the balance between cell death and survival. Proteins in the Bcl-2 family reside in the inner mitochondrial membrane and are either proapoptotic or antiapoptotic. Since apoptosis is considered a normal cellular response to DNA damage, loss of normal apoptotic pathways may contribute to cancer by enabling DNA-damaged cells to survive.

Even with all the genetic abnormalities described earlier, tumors cannot enlarge unless angiogenesis occurs and supplies them with the blood vessels necessary for survival. Angiogenesis is required not only for continued tumor growth, but also for metastasis.[4,5,25] The molecular basis for the angiogenic switch is unknown, but it appears to involve increased production of angiogenic factors or loss of angiogenic inhibitors. These factors may be produced directly by the tumor cells themselves or by inflammatory cells (e.g., macrophages) or other stromal cells associated with the tumors. In normal cells, the p53 gene can stimulate expression of antiangiogenic molecules, such as thrombospondin-1, and repress expression of proangiogenic molecules, such as vascular endothelial growth factor (VEGF).[4] Thus, loss of p53 activity in cancer cells both promotes angiogenesis and removes an antiangiogenic switch. Because of the crucial role of angiogenic factors in tumor growth, much interest is focused on the development of antiangiogenesis therapy.

Finally, multiple genes and molecular and cellular pathways are known to be involved in invasion and metastasis. Evidence suggests that genetic programs that are normally operative in stem cells during embryonic development may become operative in cancer stem cells, enabling them to detach, cross tissue boundaries, escape death by anoikis or apoptosis, and colonize new tissues.[26] The *MET* proto-oncogene, which is expressed in both stem and cancer cells, is a key regulator of invasive growth. Recent findings suggest that adverse conditions such as tissue hypoxia, which are commonly present in cancerous tumors, trigger this invasive behavior by activating the MET tyrosine kinase receptor.

Tumor Cell Transformation

The process by which carcinogenic agents cause normal cells to become cancer cells is hypothesized to be a multistep mechanism that can be divided into three stages: initiation, promotion, and progression (Fig. 7-9). *Initiation* involves the exposure of cells to appropriate doses of a carcinogenic agent that makes them susceptible to malignant transformation.[4] The carcinogenic agents can be chemical, physical, or biologic, and they produce irreversible changes in the genome of a previously normal cell. Because the effects of initiating agents are irreversible, multiple divided doses may achieve the same effects as single exposures of the same comparable dose or small amounts of highly carcinogenic substances. The most susceptible cells for mutagenic alterations in the genome are the cells that are actively synthesizing DNA.

Promotion involves the induction of unregulated accelerated growth in already initiated cells by various chemicals and growth factors.[4] Promotion is reversible if the promoter substance is removed. Cells that have been irreversibly initiated may be promoted even after long latency periods. The latency period varies with the type of agent, the dosage, and the characteristics of the target cells. Many chemical carcinogens are called *complete carcinogens* because they can initiate and promote neoplastic transformation. *Progression* is the process whereby tumor cells acquire malignant phenotypic changes that promote invasiveness, metastatic competence, autonomous growth tendencies, and increased karyotypic instability.

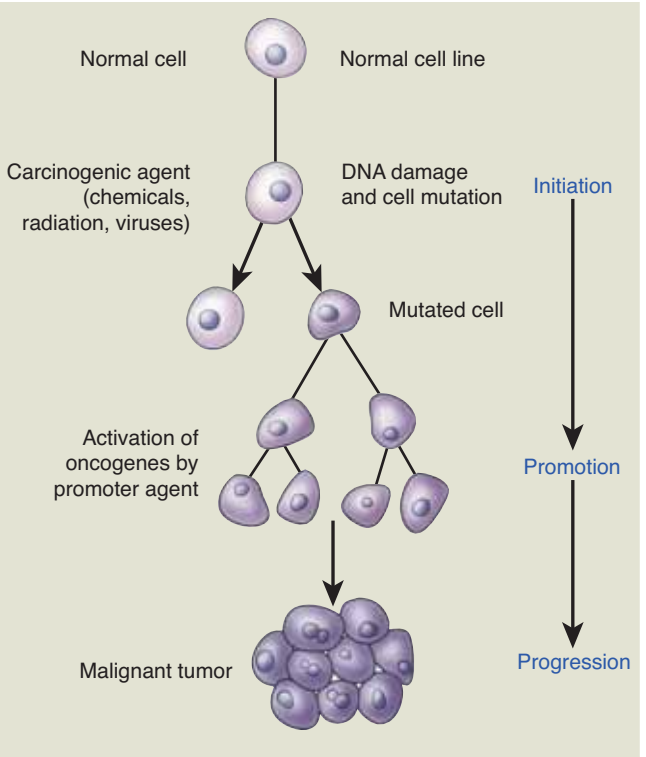


FIGURE 7-9. The processes of initiation, promotion, and progression in the clonal evolution of malignant tumors. Initiation involves the exposure of cells to appropriate doses of a carcinogenic agent; promotion, the unregulated and accelerated growth of the mutated cells; and progression, the acquisition of malignant characteristics by the tumor cells.

Host and Environmental Factors

Because cancer is not a single disease, it is reasonable to assume that it does not have a single cause. More likely, cancers develop because of interactions among host factors and repeated exposure to chemical carcinogens, radiation, and microorganisms in the environment. Among the host factors that have been linked to cancer are heredity, hormonal factors, obesity, and immunologic mechanisms.

Heredity

For many types of cancer there exists not only an environmental risk, but also a hereditary predisposition. Breast cancer, for example, occurs more frequently in women

whose grandmothers, mothers, aunts, and sisters also have experienced a breast malignancy. The genetic predisposition for development of cancer has been documented for a number of cancerous and precancerous lesions that follow mendelian inheritance patterns. Two tumor suppressor genes, called *BRCA-1* (breast carcinoma 1) and *BRCA-2* (breast carcinoma 2), have been implicated in a genetic susceptibility to breast cancer.[4,5] These genes have also been associated with an increased risk of ovarian, prostate, pancreatic, colon, and other cancers.

Several cancers exhibit an autosomal dominant inheritance pattern that greatly increases the risk of developing a tumor. The inherited mutation is usually a point mutation occurring in a single allele of a tumor-suppressor gene. Persons who inherit the mutant gene are born with one normal and one mutant copy of the gene. In order for cancer to develop, the normal gene must be inactivated, usually through a somatic mutation. As previously discussed, retinoblastoma is an example of a cancer that follows an autosomal dominant inheritance pattern. Approximately 40% of retinoblastomas are inherited, and carriers of the mutant RB suppressor gene have a 10,000-fold increased risk of developing retinoblastoma, usually with bilateral involvement.[4] Familial adenomatous polyposis of the colon also follows an autosomal dominant inheritance pattern. In people who inherit this gene, hundreds of adenomatous polyps may develop, some of which inevitably become malignant.[4]

Hormones

Hormones have received considerable research attention with respect to cancer of the breast, ovary, and endometrium in women and of the prostate and testis in men. Although the link between hormones and the development of cancer is unclear, it has been suggested that it may reside with the ability of hormones to drive the cell division of a malignant phenotype.[4] Because of the evidence that endogenous hormones affect the risk of these cancers, concern exists regarding the effects on cancer risk if the same or closely related hormones are administered for therapeutic purposes.

Obesity

There has been recent interest in obesity as a risk factor for certain types of cancer, including breast, endometrial, and prostate cancer.[27] The process relating obesity to cancer development is multifactorial and involves a network of metabolic and immunologic mechanisms. Obesity has been associated with insulin resistance and increased production of pancreatic insulin, both of which can have a carcinogenic effect. Insulin enhances insulin-like growth factor-1 (IGF-1) synthesis and its bioavailability. Both insulin and IGF-1 are anabolic molecules that can promote tumor development by stimulating cell proliferation and inhibiting apoptosis. Obesity has also been associated with increased levels of sex hormones (androgens and estrogens), which can act as mitogens that stimulate cell proliferation, inhibit apoptosis, and therefore increase the chance of malignant cell transformation, particularly of endometrial and breast tissue, and possibly of other organs (e.g., prostate and colon cancer). And lastly, obesity has been related to a condition of chronic inflammation characterized by abnormal production of inflammatory cytokines that can contribute to the development of malignant disease.

Immunologic Mechanisms

There is substantial evidence for the participation of the immune system in resistance against the progression and spread of cancer.[4,5,28] The central concept, known as the *immune surveillance hypothesis,* which was first proposed by Paul Ehrlich in 1909, postulates that the immune system plays a central role in resistance against the development of tumors.[29] In addition to cancer–host interactions as a mechanism of cancer development, immunologic mechanisms provide a means for the detection, classification, and prognostic evaluation of cancers and a potential method of treatment. *Immunotherapy* (discussed later in this chapter) is a cancer treatment modality designed to heighten the patient's general immune responses so as to increase tumor destruction.

It has been suggested that the development of cancer might be associated with impairment or decline in the surveillance capacity of the immune system. For example, increases in cancer incidence have been observed in people with immunodeficiency diseases and in those with organ transplants who are receiving immunosuppressant drugs. The incidence of cancer also is increased in the elderly, in whom there is a known decrease in immune activity. The association of Kaposi sarcoma with acquired immunodeficiency syndrome (AIDS) further emphasizes the role of the immune system in preventing malignant cell proliferation (discussed in Chapter 16).

It has been shown that most tumor cells have molecular configurations that can be specifically recognized by immune T cells or by antibodies and hence are termed *tumor antigens*. The most relevant tumor antigens fall into two categories: unique tumor-specific antigens found only on tumor cells, and tumor-associated antigens found on tumor cells and on normal cells. Quantitative and qualitative differences permit the use of these tumor-associated antigens to distinguish cancer cells from normal cells.[4]

Virtually all of the components of the immune system have the potential for eradicating cancer cells, including T and B lymphocytes, natural killer (NK) cells, and macrophages (see Chapter 15). The T-cell response is undoubtedly one of the most important host responses for controlling the growth of antigenic tumor cells; it is responsible for direct killing of tumor cells and for activation of other components of the immune system. The T-cell immunity to cancer cells reflects the function of two subsets of T cells: $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells. The finding of tumor-reactive antibodies in the serum of people with cancer supports the role of the B lymphocyte as a member of the immune surveillance team. Antibodies can destroy cancer cells through complement-mediated mechanisms or through antibody-dependent cellular cytotoxicity, in which the antibody binds the cancer cell to another effector cell, such as the NK cell, that does the actual killing of the cancer cell. NK cells do not require antigen recognition and can lyse a wide variety of target cells.

Chemical Carcinogens

A carcinogen is an agent capable of causing cancer. The role of environmental agents in causation of cancer was first noted in 1775 by Sir Percivall Pott, who related the high incidence of scrotal cancer in chimneysweeps to their exposure to coal soot.[4,5] Coal tar has since been found to contain potent polycyclic aromatic hydrocarbons. Since then, many chemicals have been suspected of being carcinogens. Some have been found to cause cancers in animals, and others are known to cause cancers in humans (Chart 7-1).

Chemical carcinogens can be divided into two groups: (1) direct-reacting agents, which do not require activation in the body to become carcinogenic, and (2) indirect-reacting agents, called *procarcinogens* or *initiators,* which become active only after metabolic conversion.[4,5] Direct- and indirect-acting initiators form highly reactive species (i.e., electrophiles and free radicals) that bind with the nucleophilic residues on DNA, RNA, or cellular proteins. The action of these reactive species tends to cause cell mutation or alteration in synthesis of cell enzymes and structural proteins in a manner that alters cell replication and interferes with cell regulatory controls. The carcinogenicity of some chemicals is augmented by agents called *promoters* that, by themselves, have little or no cancer-causing ability. It is believed that promoters exert their effect by changing the expression of genetic material in a cell, increasing DNA synthesis, enhancing gene amplification (i.e., number of gene copies that are made), and altering intercellular communication.

Exposure to many chemical carcinogens is associated with lifestyle risk factors such as smoking or industrial exposure. Cigarette smoke contains both procarcinogens and promoters. It is directly associated with lung and laryngeal cancer and has been linked with cancers of the mouth, nasal cavities, pharynx, esophagus, pancreas, liver, kidney, uterus, cervix, and bladder and myeloid leukemias. Not only is the smoker at risk, but others passively exposed to cigarette smoke are at risk. Chewing tobacco or tobacco products increases the risk of cancers of the oral cavity and esophagus. Some polycyclic hydrocarbons are metabolized in the liver to electrophilic epoxides, which in turn react with proteins and nucleic acids.[5] For example, vinyl chloride, the simple two-carbon molecule that is widely used in the plastic polyvinyl chloride, is metabolized to an epoxide. Some workers exposed to the vinyl chloride monomer in the ambient atmosphere have later developed hepatic angiosarcoma.[5]

There is also strong evidence that certain elements in the diet contain chemicals that contribute to cancer risk. Most known dietary carcinogens occur either naturally in plants (e.g., aflatoxins) or are produced during food preparation.[4,5] For example, benzo[*a*]pyrene and other polycyclic hydrocarbons are converted to carcinogens when foods are fried in fat that has been reused multiple times. Among the most potent of the procarcinogens are the polycyclic aromatic hydrocarbons. The polycyclic aromatic hydrocarbons are of particular interest because they are produced from animal fat in the process of charcoal-broiling meats and are present in smoked meats and fish. They also are produced in the combustion of tobacco and are present in cigarette smoke. Nitrosamines, which are powerful carcinogens, are formed in foods that are smoked, salted, cured, or pickled using nitrites or nitrates as preservatives. Formation of these nitrosamines may be inhibited by the presence of antioxidants such as vitamin C found in fruits and vegetables. Cancer of the colon has been associated with high dietary intake of fat and red meat and a low intake of dietary fiber.[30] A high-fat diet is thought to be carcinogenic because it increases the flow of primary bile acids that are converted to secondary bile acids in the presence of anaerobic bacteria in the colon, producing carcinogens or promoters.

Alcohol is associated with a variety of cancers and the mechanisms are very complex. The first and most toxic metabolite of ethanol is acetaldehyde, a known carcinogen that interferes with DNA synthesis and repair and that causes point mutations in some cells.[31] The carcinogenic effect of cigarette smoke can be enhanced by concomitant consumption of alcohol; persons who smoke and drink considerable amounts of alcohol are at increased risk for development of cancer of the oral cavity, larynx and esophagus.

The effects of carcinogenic agents usually are dose dependent—the larger the dose or the longer the duration of exposure, the greater the risk that cancer will develop. Some chemical carcinogens may act in concert

CHART 7-1 Major Chemical Carcinogens[4,5]

Direct-Acting Alkylating Agents
- Anticancer drugs (e.g., cyclophosphamide, cisplatin, busulfan)

Polycyclic and Heterocyclic Aromatic Hydrocarbons
- Tobacco combustion (cigarette smoke)
- Animal fat in broiled and smoked meats
- Benzo(a)pyrene
- Vinyl chloride

Aromatic Amines and Azo Dyes
- β-Naphthylamine
- Aniline dyes

Naturally Occurring Carcinogens
- Aflatoxin B1
- Griseofulvin
- Betel nuts

Nitrosamines and Amides
- Formed in gastrointestinal tract from nitro-stable amines and nitrates used in preserving processed meats and other foods

Miscellaneous Agents
- Asbestos
- Chromium, nickel, and other metals when volatilized and inhaled in industrial settings
- Insecticides, fungicides
- Polychlorinated biphenyls

with other carcinogenic influences, such as viruses or radiation, to induce neoplasia. There usually is a time delay ranging from 5 to 30 years from the time of chemical carcinogen exposure to the development of overt cancer. This is unfortunate because many people may have been exposed to the agent and its carcinogenic effects before the association was recognized.

Radiation

The effects of *ionizing radiation* in carcinogenesis have been well documented in atomic bomb survivors, in patients diagnostically exposed, and in industrial workers, scientists, and physicians who were exposed during employment. Malignant epitheliomas of the skin and leukemia were significantly elevated in these populations. Between 1950 and 1970, the death rate from leukemia alone in the most heavily exposed population groups of the atomic bomb survivors in Hiroshima and Nagasaki was 147 per 100,000 persons, 30 times the expected rate.[32]

The type of cancer that developed depended on the dose of radiation, the sex of the person, and the age at which exposure occurred. The length of time between exposure and the onset of cancer is related to the age of the individual. For example, children exposed to ionizing radiation in utero have an increased risk for developing leukemias and childhood tumors, particularly 2 to 3 years after birth. Therapeutic irradiation to the head and neck can give rise to thyroid cancer years later. The carcinogenic effect of ionizing radiation is related to its mutagenic effects in terms of causing chromosomal breakage, translocations, and, less frequently, point mutations.[4]

The association between sunlight and the development of skin cancer (see Chapter 46) has been reported for more than 100 years. *Ultraviolet radiation* emits relatively low-energy rays that do not deeply penetrate the skin. The evidence supporting the role of ultraviolet radiation in the cause of skin cancer includes skin cancer that develops primarily on the areas of skin more frequently exposed to sunlight (e.g., the head and neck, arms, hands, and legs), a higher incidence in light-complexioned individuals who lack the ultraviolet-filtering skin pigment melanin, and the fact that the intensity of ultraviolet exposure is directly related to the incidence of skin cancer, as evidenced by higher rates occurring in Australia and the American Southwest. There also are studies that suggest that intense, episodic exposure to sunlight, particularly during childhood, is more important in the development of melanoma than prolonged low-intensity exposure. As with other carcinogens, the effects of ultraviolet radiation usually are additive, and there usually is a long delay between the time of exposure and the time that cancer can be detected.

Viral and Microbial Agents

An oncogenic virus is one that can induce cancer. Many DNA and RNA viruses have proved to be oncogenic in animals, ranging from amphibian to primates. However, only four DNA viruses have been implicated in human cancers: the human papilloma virus (HPV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), and human herpesvirus 8 (HHV-8).[4,6,33] HHV-8, which causes Kaposi sarcoma in persons with AIDS, is discussed in Chapter 16. There is also an association between infection with the bacterium *Helicobacter pylori* and gastric adenocarcinoma and gastric lymphomas[4,5] (discussed in Chapter 29).

There are over 70 genetically different types of HPV.[4] Some types (i.e., types 1, 2, 4, 7) have been shown to cause benign squamous papillomas (i.e., warts). By contrast, high-risk HPVs (e.g., types 16 and 18) are implicated in the pathogenesis squamous cell carcinoma of the cervix and anogenital region.[4,5] Thus, cervical cancer can be viewed as a sexually transmitted disease, caused by transmission of HPV. In addition, at least 20% of oropharyngeal cancers are associated with high-risk HPVs.[4] A vaccine to protect against HPV types 6, 11, 16 and 18 is now available, and vaccination of 11- to 26-year-old girls/women is being encouraged as a means of preventing cervical cancer[34] (see Chapter 40).

EBV is a member of the herpes virus family. It has been implicated in the pathogenesis of several human cancers, including Burkitt lymphoma, nasopharyngeal cancer, B-cell lymphomas in immunosuppressed individuals such as those with AIDS, and some cases of Hodgkin lymphoma. Burkitt lymphoma, a tumor of B lymphocytes, is endemic in parts of East Africa and occurs sporadically in other areas worldwide. In persons with normal immune function, the EBV-driven B-cell proliferation is readily controlled and the person becomes asymptomatic or experiences a self-limited episode of infectious mononucleosis (see Chapter 11). In regions of the world where Burkitt lymphoma is endemic, concurrent malaria or other infections cause impaired immune function, allowing sustained B-lymphocyte proliferation. The incidence of nasopharyngeal cancer is high in some areas of China, particularly southern China, and in the Cantonese population in Singapore. An increased risk of B-cell lymphomas is seen in individuals with drug-suppressed immune systems (e.g., individuals with transplanted organs).

There is strong epidemiologic evidence linking chronic HBV and hepatitis C virus (HCV) infection with hepatocellular carcinoma (discussed in Chapter 30). It has been estimated that 70% to 85% of hepatocellular cancers worldwide are due to infection with HBV and HCV.[4] The precise mechanism by which HBV and HCV induce hepatocellular cancer has not been fully determined. It seems probable that the oncogenic effects of HBV and HCV are multifactorial, with immunologically mediated chronic inflammation leading to persistent liver damage, regeneration, and genomic damage. The regeneration process is mediated by a vast array of growth factors, cytokines, chemokines, and bioactive substances produced by immune cells that promote cell survival, tissue remodeling, and angiogenesis.

Although there are a number of retroviruses (RNA viruses) that cause cancer in animals, human T-cell leukemia virus-1 (HTLV-1) is the only known retrovirus to cause cancer in humans. HTLV-1 is associated with a form of T-cell leukemia that is endemic in certain parts of Japan and some areas of the Caribbean and Africa, and is found sporadically elsewhere, including the United States and Europe.[4] Similar to the AIDS virus, HTLV-1 is

attracted to the $CD4^+$ T cells, and this subset of T cells is therefore the major target for cancerous transformation. The virus requires transmission of infected T cells by way of sexual intercourse, infected blood, or breast milk.

In summary, the causes of cancer are highly complex and can be viewed from two perspectives: the molecular and cellular origins and mechanisms, and the external and contextual causative factors including heredity and environmental agents that influence its inception and growth. In most cases, the molecular pathogenesis of cancer is thought to have its origin in genetic damage or mutation that changes cell physiology and transforms a normally functioning cell into a cancer cell. However, the complexity of causation and pathogenesis is increasing as more is learned about the roles of epigenetic mechanisms, cancer stem cells, and the microenvironment in tumorigenesis.

The types of genes involved in cancer are numerous, with two main categories being the proto-oncogenes, which control cell growth and replication, and tumor-suppressor genes, which are growth-inhibiting regulatory genes. Genetic and molecular mechanisms that increase susceptibility to cancer and/or facilitate cancer include defects in DNA repair mechanisms, defects in growth factor signaling pathways, evasion of apoptosis, development of sustained angiogenesis, invasion, and metastasis. Because cancer is not a single disease, it is likely that multiple factors interact at the molecular and cellular level to transform normal cells into cancer cells. Genetic and epigenetic damage may be the result of interactions between multiple risk factors or repeated exposure to a single carcinogenic (cancer-producing) agent. Among the risk factors that have been linked to cancer are heredity, hormonal factors, obesity, immunologic mechanisms, and environmental agents such as chemicals, radiation, and cancer-causing viruses and microbes.

Clinical Manifestations

There probably is not a single body function left unaffected by the presence of cancer. Because tumor cells replace normally functioning parenchymal cells, the initial manifestations of cancer usually reflect the function of the primary site of involvement. For example, cancer of the lung initially produces impairment of respiratory function; as the tumor grows and metastasizes, other body structures become affected. As cancers grow, they may also compress and erode blood vessels, causing ulceration and necrosis along with frank bleeding and sometimes hemorrhage. Cancer has no regard for normal anatomic boundaries; as it grows, it invades and compresses adjacent structures. Abdominal cancer, for example, may compress the viscera and cause bowel obstruction.

The development of effusions (i.e., fluid) in the pleural, pericardial, or peritoneal spaces may be the presenting sign of some tumors.[35] Direct involvement of the serous surface seems to be the most significant inciting factor, although many other mechanisms such as obstruction of lymphatic flow may play a role. Most persons with pleural effusions are symptomatic at presentation with chest pain, shortness of breath, and cough. More than any other malignant neoplasms, ovarian cancers are associated with the accumulation of fluid in the peritoneal cavity. Complaints of abdominal discomfort, swelling and a feeling of heaviness, and increase in abdominal girth, which reflect the presence of peritoneal effusions or ascites, are the most common presenting symptoms in ovarian cancer, occurring in up to 65% of women with the disease.[35]

Anemia is common in persons with various types of cancers. It may be related to blood loss, hemolysis, impaired red cell production, or treatment effects.[36,37] For example, drugs used in treatment of cancer are cytotoxic and can decrease red blood cell production. Also, there are many mechanisms through which erythrocyte production can be impaired in persons with malignancies including nutritional deficiencies, bone marrow failure, and a blunted erythropoietin response to hypoxia. Inflammatory cytokines generated in response to tumors decrease erythropoietin synthesis, resulting in a decrease in erythrocyte production. Cancer-related anemia is associated with reduced treatment effectiveness, increased mortality, increased transfusion requirements, and reduced performance and quality of life. Hypoxia, a characteristic feature of advanced solid tumors, has been recognized as a critical factor in promoting tumor resistance to radiotherapy and some chemotherapeutic agents. Cancer-related anemia is often treated with recombinant human erythropoietin (rHuEPO, epoetin alfa).

Systemic Manifestations

Cancer also produces generalized manifestations such as anorexia and cachexia, fatigue and sleep disorders, and symptoms unrelated to the tumor site (paraneoplastic syndromes). Many of these manifestations are compounded by the side effects of methods used to treat the disease. In its late stages, cancer often causes pain (see Chapter 35). Pain is probably one of the most dreaded aspects of cancer, and pain management is one of the major treatment concerns for persons with incurable cancers. Although research has produced amazing insights into the causes and cures for cancer, only recently have efforts focused on the associated side effects of the disease.

Anorexia and Cachexia

Many cancers are associated with weight loss and wasting of body fat and muscle tissue, accompanied by profound weakness, anorexia, and anemia. This wasting syndrome is often referred to as the *cancer anorexia–cachexia syndrome*.[38–40] It is a common manifestation of most solid tumors with the exception of breast cancer. The condition is more common in children and elderly persons and becomes more pronounced as the disease progresses. Persons with cancer cachexia also respond less well to chemotherapy and are more prone to toxic side effects.

The cause of the cancer anorexia–cachexia syndrome is probably multifactorial, resulting from a persistent inflammatory response in conjunction with production of specific cytokines and catabolic factors by the tumor. Although anorexia, reduced food intake, and abnormalities of taste are common in people with cancer and often are accentuated by treatment methods, the extent of weight loss and protein wasting cannot be explained in terms of diminished food intake alone. There also is a disparity between the size of the tumor and the severity of cachexia, which supports the existence of other mediators in the development of cachexia. It has been demonstrated that tumor necrosis factor (TNF)-α and other cytokines including interleukin-1 (IL-1) and IL-6 can produce the wasting syndrome in experimental animals.[5] High serum levels of these cytokines have been observed in persons with cancer, and their levels appear to correlate with progress of the tumor. TNF-α, secreted primarily by macrophages in response to tumor cell growth or gram-negative bacterial infections, was the first identified cytokine associated with cachexia and wasting. It causes anorexia by suppressing satiety centers in the hypothalamus and increasing the synthesis of lipoprotein lipase, an enzyme that facilitates the release of fatty acids from lipoproteins so that they can be used by tissues. IL-1 and IL-6 share many of the features of TNF-α in terms of the ability to initiate cachexia.

Fatigue and Sleep Disorders

Fatigue and sleep disturbances are two of the most frequent side effects experienced by persons with cancer.[41–43] Cancer-related fatigue is characterized by feelings of tiredness, weakness, and lack of energy and is distinct from the normal tiredness experienced by healthy individuals in that it is not relieved by rest or sleep. It occurs both as a consequence of the cancer itself and as a side effect of cancer treatment. Cancer-related fatigue may be an early symptom of malignant disease and has been reported by as many as 40% of patients at the time of diagnosis.[43] Furthermore, the symptom often remains for months or even years after treatment.

The cause of cancer-related fatigue is largely unknown but is probably multifactorial and involves the dysregulation of several interrelated physiologic, biochemical, and psychological systems. The basic mechanisms of fatigue have been broadly categorized into two components: peripheral and central.[42] Peripheral fatigue, which has its origin in the neuromuscular junction and muscles, results from the inability of the peripheral neuromuscular apparatus to perform a task in response to central stimulation. Mechanisms implicated in peripheral fatigue include a lack of adenosine triphosphate (ATP) and the buildup of metabolic by-products such as lactic acid. Central fatigue arises in the central nervous system (CNS) and is often described as the difficulty in initiating or maintaining voluntary activities. One hypothesis proposed to explain cancer-related fatigue is that cancer and cancer treatments result in dysregulation of brain serotonin (5-HT) levels or function. There is also evidence that proinflammatory cytokines, such as TNF-α, can influence 5-HT metabolism.[42]

Paraneoplastic Syndromes

In addition to signs and symptoms at the sites of primary and metastatic disease, cancer can produce manifestations in sites that are not directly affected by the disease. Such manifestations are collectively referred to as *paraneoplastic syndromes*.[44,45] Some of these manifestations are caused by the elaboration of hormones by cancer cells, and others result from the production of circulating factors that produce hematopoietic, neurologic, and dermatologic syndromes (Table 7-3). These syndromes are most commonly associated with lung, breast, and hematologic malignancies.[4]

TABLE 7-3 Common Paraneoplastic Syndromes

Type of Syndrome	Associated Tumor Type	Proposed Mechanism
Endocrinologic		
Syndrome of inappropriate ADH	Small cell lung cancer, others	Production and release of ADH by tumor
Cushing syndrome	Small cell lung cancer, bronchial carcinoid cancers	Production and release of ACTH by tumor
Hypercalcemia	Squamous cell cancers of the lung, head, neck, ovary	Production and release of polypeptide factor with close relationship to PTH
Hematologic		
Venous thrombosis	Pancreatic, lung, other cancers	Production of procoagulation factors
Nonbacterial thrombolytic endocarditis	Advanced cancers	
Neurologic		
Eaton-Lambert syndrome	Small cell lung cancer	Autoimmune production of antibodies to motor end-plate structures
Myasthenia gravis	Thymoma	
Dermatologic		
Acanthosis nigricans	Gastric carcinoma	Possibly caused by production of growth factors (epidermal) by tumor cells

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; PTH, parathyroid hormone.

A variety of peptide hormones are produced by both benign and malignant tumors. Although not normally expressed, the biochemical pathways for the synthesis and release of peptide hormones (e.g., antidiuretic [ADH], adrenocorticotropic [ACTH], and parathyroid [PTH] hormones) are present in most cells.[45] Thus, the three most common endocrine syndromes associated with cancer are the syndrome of inappropriate ADH secretion (see Chapter 8), Cushing syndrome due to ectopic ACTH production (see Chapter 32), and hypercalcemia (see Chapter 8).[44,45] Hypercalcemia of malignancy does not appear to be related to PTH but to a PTH-related protein, which shares several biologic actions with PTH. Hypercalcemia also can be caused by osteolytic processes induced by cancer such as multiple myeloma or bony metastases from other cancers.

Some paraneoplastic syndromes are associated with the production of circulating mediators that produce hematologic complications.[44] For example, a variety of cancers may produce procoagulation factors that contribute to an increased risk for venous thrombosis and nonbacterial thrombotic endocarditis. Sometimes, unexplained thrombotic events are the first indication of an undiagnosed malignancy. The precise relationship between coagulation disorders and cancer is still unknown. Several malignancies, such as mucin-producing adenocarcinomas, release thromboplastin and other substances that activate the clotting system.

The symptomatic paraneoplastic neurologic disorders are relatively rare with the exception of the Lambert-Eaton myasthenic syndrome, which affects about 3% of persons with small cell lung cancer, and myasthenia gravis, which affects about 15% of people with thymoma.[46] The *Lambert-Eaton syndrome*, or reverse myasthenia gravis, is seen almost exclusively in small cell lung cancer. It produces muscle weakness in the limbs rather than the initial bulbar and ocular muscle weakness seen in myasthenia gravis. The origin of paraneoplastic neurologic disorders is thought to be immune mediated.[46,47] The altered immune response is initiated by the production of onconeural antigens (e.g., antigens normally expressed in the nervous system) by the cancer cells. The immune system, in turn, recognizes the onconeural antigens as foreign and mounts an immune response. In many cases, the immune attack controls the growth of the cancer. The antibodies and cytotoxic T cells are not sufficient to cause neurologic disease unless they cross the blood-brain barrier and react with neurons expressing the onconeural antigen.[46]

The paraneoplastic syndromes may be the earliest indication that a person has cancer, and should be regarded as such. They may also represent significant clinical problems, may be potentially lethal in persons with cancer, and may mimic metastatic disease and confound treatment. Diagnostic methods focus on both identifying the cause of the disorder and locating the malignancy responsible for the disorder. Techniques for precise identification of minute amounts of polypeptides may allow for early diagnosis of curable malignancies in asymptomatic individuals.[45] The treatment of paraneoplastic syndromes involves concurrent treatment of the underlying cancer and suppression of the mediator causing the syndrome.

In summary, there probably is no single body function left unaffected by the presence of cancer. Because tumor cells replace normally functioning parenchymal tissue, the initial manifestations of cancer usually reflect the primary site of involvement. Cancer compresses blood vessels, obstructs lymph flow, disrupts tissue integrity, invades serous cavities, and compresses visceral organs. It may result in development of effusions (i.e., fluid) in the pleural, pericardial, or peritoneal spaces; generalized manifestations such as anorexia and cachexia; fatigue and sleep disorders; and anemia. It may also produce paraneoplastic syndromes that arise from the ability of neoplasms to elaborate hormones and other chemical mediators to produce endocrine, hematopoietic, neurologic, and dermatologic syndromes. Many of these manifestations are compounded by the side effects of methods used to treat the disease.

Screening, Diagnosis, and Treatment

Screening

Screening represents a secondary prevention measure for the early recognition of cancer in an otherwise asymptomatic population.[48,49] Screening can be achieved through observation (e.g., skin, mouth, external genitalia), palpation (e.g., breast, thyroid, rectum and anus, prostate, lymph nodes), and laboratory tests and procedures (e.g., Papanicolaou [Pap] smear, colonoscopy, mammography). It requires a test that will specifically detect early cancers or premalignancies, is cost effective, and results in improved therapeutic outcomes. For most cancers, stage at presentation is related to curability, with the highest rates reported when the tumor is small and there is no evidence of metastasis. For some tumors, however, metastasis tends to occur early, even from a small primary tumor. For other cancers, such as cancer of the pancreas, no screening methods are currently available. More sensitive screening methods such as tumor markers are being developed for these forms of cancer.

Cancers for which current screening or early detection has led to improvement in outcomes include cancers of the breast (breast self-examination and mammography, discussed in Chapter 40), cervix (Pap smear, Chapter 40), colon and rectum (rectal examination, fecal occult blood test, and flexible sigmoidoscopy and colonoscopy, Chapter 29), prostate (prostate-specific antigen testing and transrectal ultrasonography, Chapter 39), and malignant melanoma (self-examination, Chapter 46). While not as clearly defined, it is recommended that screening for other types of cancers such as cancers of the thyroid, testicles, ovaries, lymph nodes, and oral cavity be done at the time of periodic health examinations.

Diagnostic Methods

The methods used in the diagnosis and staging of cancer are determined largely by the location and type of cancer suspected. A number of procedures are used in the diagnosis of cancer including blood tests for tumor markers, cytologic studies and tissue biopsy, endoscopic examinations, ultrasound, x-ray studies, magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans.

Tumor Markers

Tumor markers are antigens expressed on the surface of tumor cells or substances released from normal cells in response to the presence of tumor.[4,50] Some substances, such as hormones and enzymes, that are produced normally by the involved tissue become overexpressed as a result of cancer. Tumor markers are used for screening, establishing prognosis, monitoring treatment, and detecting recurrent disease. Table 7-4 identifies some of the more commonly used tumor markers and summarizes their source and the cancers associated with them.

The serum markers that have proven most useful in clinical practice are the human chorionic gonadotropin (hCG), prostate-specific antigen (PSA), CA-125, α-fetoprotein (AFP), CD blood cell antigens, and carcinoembryonic antigen (CEA). The hCG is a hormone normally produced by the placenta. It is used as a marker for diagnosing, prescribing treatment, and following the disease course in persons with high-risk gestational trophoblastic tumors. PSA is used as a marker in prostate cancer, and CA-125 is used as a marker in ovarian cancer. Markers for leukemia and lymphomas are grouped by so-called *clusters of differentiation* (CD) antigens. The CD antigens help to distinguish among T and B lymphocytes, monocytes, granulocytes, and natural killer cells and immature variants of these cells.[4,5]

Some cancers express fetal antigens that are normally present only during embryonal development and induced to reappear as a result of neoplasia.[4] The two that have proved most useful as tumor markers are AFP and CEA. AFP is synthesized by the fetal liver, yolk sac, and gastrointestinal tract and is the major serum protein in the fetus. Elevated levels are encountered in people with primary liver cancers and have also been observed in some testicular, ovarian, pancreatic, and stomach cancers. CEA normally is produced by embryonic tissue in the gut, pancreas, and liver and is elaborated by a number of different cancers, including colorectal carcinomas, pancreatic cancers, and gastric and breast tumors. As with most other tumor markers, elevated levels of CEA and AFP are found in other, noncancerous conditions, and elevated levels of both depend on tumor size so that neither is useful as an early test for cancer.

As diagnostic tools, tumor markers have limitations. Nearly all markers can be elevated in benign conditions,

TABLE 7-4 Tumor Markers

Marker	Source	Associated Cancers
Oncofetal Antigens		
α-Fetoprotein (AFP)	Fetal yolk sac and gastrointestinal structures early in fetal life	Primary liver cancers; germ cell cancer of the testis
Carcinoembryonic antigen (CEA)	Embryonic tissues in gut, pancreas, and liver	Colorectal cancer and cancers of the pancreas, lung, and stomach
Hormones		
Human chorionic gonadotropin (hCG)	Hormone normally produced by placenta	Gestational trophoblastic tumors; germ cell cancer of testis
Calcitonin	Hormone produced by thyroid parafollicular cells	Thyroid cancer
Catecholamines (epinephrine, norepinephrine) and metabolites	Hormones produced by chromaffin cells of the adrenal gland	Pheochromocytoma and related tumors
Specific Proteins		
Monoclonal immunoglobulin	Abnormal immunoglobulin produced by neoplastic cells	Multiple myeloma
Prostate-specific antigen (PSA)	Produced by the epithelial cells lining the acini and ducts of the prostate	Prostate cancer
Mucins and Other Glycoproteins		
CA-125	Produced by müllerian cells of ovary	Ovarian cancer
CA-19-9	Produced by alimentary tract epithelium	Cancer of the pancreas, and colon
Cluster of Differentiation		
CD antigens	Present on leukocytes	Used to determine the type and level of differentiation of leukocytes involved in different types of leukemia and lymphoma

and most are not elevated in the early stages of malignancy. Hence, tumor markers have limited value as screening tests. Furthermore, they are not in themselves specific enough to permit a diagnosis of a malignancy, but once a malignancy has been diagnosed and shown to be associated with elevated levels of a tumor marker, the marker can be used to assess progress of the disease. Extremely elevated levels of a tumor marker can indicate a poor prognosis or the need for more aggressive treatment. Perhaps the greatest value of tumor markers is in monitoring therapy in people with widespread cancer. The level of most cancer markers tends to decrease with successful treatment and increase with recurrence or spread of the tumor.

Cytologic, Histologic, and Gene Profiling Methods

Histologic and cytologic studies are laboratory methods used to examine tissues and cells. Several sampling approaches are available including cytologic smears, tissue biopsies, and needle aspiration.[4]

Papanicolaou Test. The Pap test is a cytologic method that is used for detecting cancer cells. It consists of a microscopic examination of a properly prepared slide by a cytotechnologist or pathologist for the purpose of detecting the presence of abnormal cells. The usefulness of the Pap test relies on the fact that cancer cells lack the cohesive properties and intercellular junctions that are characteristic of normal tissue; without these characteristics, cancer cells tend to exfoliate and become mixed with secretions surrounding the tumor growth. Although the Pap test is widely used as a screening test for cervical cancer, it can be performed on other body secretions, including nipple drainage, pleural or peritoneal fluid, and gastric washings.

Tissue Biopsy. Tissue biopsy involves the removal of a tissue specimen for microscopic study. It is of critical importance in designing the treatment plan should cancer cells be found. Biopsies are obtained in a number of ways, including needle biopsy; endoscopic methods, such as bronchoscopy or cystoscopy, which involve the passage of an endoscope through an orifice and into the involved structure; and laparoscopic methods. In some instances, a surgical incision is made from which biopsy specimens are obtained. Excisional biopsies are those in which the entire tumor is removed. The tumors usually are small, solid, palpable masses. If the tumor is too large to be completely removed, a wedge of tissue from the mass can be excised for examination. A quick frozen section may be done to determine the nature of a mass lesion or evaluate the margins of an excised tumor to ascertain that the entire neoplasm has been removed.[5]

Fine needle aspiration is another approach that is widely used. The procedure involves aspirating cells and attendant fluid with a small-bore needle. The method is most widely used for assessment of readily palpable lesions in sites such as the thyroid, breast, and lymph nodes. Modern imaging techniques have also enabled the method to be extended to deeper structures such as the pelvic lymph nodes and pancreas.

Immunohistochemistry. Immunohistochemistry involves the use of monoclonal antibodies to facilitate the identification of cell products or surface markers.[5] For example, certain anaplastic carcinomas, malignant lymphomas, melanomas, and sarcomas look very similar under the microscope, but must be accurately identified because their treatment and prognosis are quite different.

Immunohistochemistry can also be used to determine the site of origin of metastatic tumors. Many cancer patients present with metastasis. In cases in which the origin of the metastasis is obscure, immunochemical detection of tissue-specific or organ-specific antigens can often help to identify the tumor source. Immunochemistry can also be used to detect molecules that have prognostic or therapeutic significance. For example, detection of estrogen receptors on breast cancer cells is of prognostic and therapeutic significance because these tumors respond to antiestrogen therapy.

Microarray Technology. Microarray technology has the advantage of analyzing a large number of molecular changes in cancer cells to determine overall patterns of behavior that would not be available by conventional means. The techniques uses "gene chips" that can simultaneously perform miniature assays to detect and quantify the expression of large numbers of genes at the same time.[4] DNA arrays are now commercially available to assist in making clinical decisions regarding breast cancer treatment. In addition to identifying tumor types, microarrays have been used for predicting prognosis and response to therapy, examining tumor changes after therapy, and classifying hereditary tumors.[4]

Staging and Grading of Tumors

The two basic methods for classifying cancers are grading according to the histologic or cellular characteristics of the tumor and staging according to the clinical spread of the disease. Both methods are used to determine the course of the disease and aid in selecting an appropriate treatment or management plan.

Grading of tumors involves the microscopic examination of cancer cells to determine their level of differentiation and the number of mitoses. The closer the tumor cells resemble comparable normal tissue cells, both morphologically and functionally, the lower the grade. Accordingly, on a scale ranging from grade I to IV, grade I neoplasms are well differentiated and grade IV are poorly differentiated and display marked anaplasia.[4,5]

The *clinical staging* of cancers uses methods to determine the extent and spread of the disease. It is useful in determining the choice of treatment for individual patients, estimating prognosis, and comparing the results of different treatment regimens. The significant criteria used for staging that vary with different organs include the size of the primary tumor, its extent of local growth (whether within or outside the organ), lymph node involvement, and presence of distant metastasis.[4,5] This

assessment is based on clinical and radiographic examination (CT and MRI) and, in some cases, surgical exploration. Two methods of staging are currently in use: the TNM staging system, which was developed by the Union Internationale Contre Center (UICC), and the American Joint Committee (AJC) system.[4] In the TNM system, T1, T2, T3, and T4 describe the increasing size of the primary tumor; N0, N1, N2, and N3, advancing node involvement; and M0 or M1, the absence or presence of distant metastasis. In the AJC system, cancers are divided into stages 0 to IV incorporating the size of the primary lesions and the presence of nodal spread and distant metastasis.

Cancer Treatment

The goals of cancer treatment methods fall into three categories: curative, control, and palliative. The most common modalities are surgery, radiation, chemotherapy, hormonal therapy, and biotherapy. The treatment of cancer involves the use of a carefully planned program that combines the benefits of multiple treatment modalities and the expertise of an interdisciplinary team of specialists including medical, surgical, and radiation oncologists; clinical nurse specialists; nurse practitioners; pharmacists; and a variety of ancillary personnel.

Surgery

Surgery is used for diagnosis, staging of cancer, tumor removal, and palliation (i.e., relief of symptoms) when a cure cannot be achieved.[51] The type of surgery to be used is determined by the extent of the disease, the location and structures involved, the tumor growth rate and invasiveness, the surgical risk to the patient, and the quality of life the patient will experience after the surgery. If the tumor is small and has well-defined margins, the entire tumor often can be removed. If, however, the tumor is large or involves vital tissues, surgical removal may be difficult if not impossible.

Radiation Therapy

Radiation can be used as the primary method of treatment, as preoperative or postoperative treatment, with chemotherapy, or with chemotherapy and surgery.[52,53] It can also be used as a palliative treatment to reduce symptoms in persons with advanced cancers. It is effective in reducing the pain associated with bone metastasis and, in some cases, improves mobility. Radiation also is used to treat several oncologic emergencies, such as superior vena cava syndrome, spinal cord compression, bronchial obstruction, and hemorrhage.

Radiation therapy exerts its effects through ionizing radiation, which affects cells by direct ionization of molecules or, more commonly, by indirect ionization. Indirect ionization produced by x-rays or gamma rays causes cellular damage when these rays are absorbed into tissue and give up their energy by producing fast-moving electrons. These electrons interact with free or loosely bonded electrons of the absorber cells and subsequently produce free radicals that interact with critical cell components (see Chapter 2). It can immediately kill cells, delay or halt cell cycle progression, or, at dose levels commonly used in radiation therapy, cause damage to the cell nucleus, resulting in cell death after replication. Cell damage can be sublethal, in which case a single break in the strand can repair itself before the next radiation insult. Double-stranded breaks in DNA are generally believed to be the primary damage that leads to cell death. Cells with unrepaired DNA damage may continue to function until they undergo cell mitosis, at which time the genetic damage causes cell death.

The therapeutic effects of radiation therapy derive from the fact that the rapidly proliferating and poorly differentiated cells of a cancerous tumor are more likely to be injured by radiation therapy than are the more slowly proliferating cells of normal tissue. To some extent, however, radiation is injurious to all rapidly proliferating cells, including those of the bone marrow and the mucosal lining of the gastrointestinal tract. This results in many of the common adverse effects of radiation therapy, including infection, bleeding, and anemia due to loss of blood cells and nausea and vomiting due to loss of gastrointestinal cells. In addition to its lethal effects, radiation also produces sublethal injury. Recovery from sublethal doses of radiation occurs in the interval between the first dose of radiation and subsequent doses. This is why large total doses of radiation can be tolerated when they are divided into multiple smaller, fractionated doses. Normal tissue is usually able to recover from radiation damage more readily than is cancerous tissue.

Therapeutic radiation can be delivered in one of three ways: external beam or teletherapy, with beams generated by a linear accelerator or cobalt-60 machine at a distance and aimed at the tumor within patient; brachytherapy, in which a sealed radioactive source is placed close to or directly in the tumor site; and systemic therapy, in which radioisotopes with a short half-life are given by mouth or injected into the tumor site.[54]

Chemotherapy

Cancer chemotherapy has evolved as one of the major systemic treatment modalities.[55–57] Unlike surgery and radiation, cancer chemotherapy is a systemic treatment that enables drugs to reach the site of the tumor as well as distant sites. Chemotherapeutic drugs may be used as the primary form of treatment, or they may be used as part of a multimodal treatment plan. Chemotherapy is the primary treatment for most hematologic and some solid tumors, including choriocarcinoma, testicular cancer, acute and chronic leukemia, Burkitt lymphoma, Hodgkin disease, and multiple myeloma.

Most cancer drugs are more toxic to rapidly proliferating cells than to those incapable of replication or in phase G_0 of the cell cycle. Because of their mechanism of action, they are more effective against tumors with a high growth fraction. By the time many cancers reach a size that is clinically detectable, the growth fraction has decreased considerably. In this case, reduction in tumor size through the use of surgical debulking procedures or radiation therapy often causes tumor cells residing in G_0 to reenter the cell

cycle. Thus, surgery or radiation therapy may be used to increase the effectiveness of chemotherapy or chemotherapy may be given to patients with no overt evidence of residual disease after local treatment (e.g., surgical resection of a primary breast cancer).

For most chemotherapy drugs, the relationship between tumor cell survival and drug dose is exponential, with the number of cells surviving being proportional to drug dose, and the number of cells at risk for exposure being proportional to the destructive action of the drug. Exponential killing implies that a proportion or percentage of tumor cells is killed, rather than an absolute number (Fig. 7-10). This proportion is a constant percentage of the total number of cells. For this reason, multiple courses of treatment are needed if the tumor is to be eradicated.[55]

A major problem in cancer chemotherapy is the development of cellular resistance. Acquired resistance develops in a number of drug-sensitive tumor types.[57] Experimentally, drug resistance can be highly specific to a single agent and is usually based on genetic changes in a given tumor cell type. In other instances, a multidrug-resistant phenomenon affecting anticancer drugs with differing structures occurs. This type of resistance often involves the increased expression of transmembrane transporter genes involved in drug efflux.

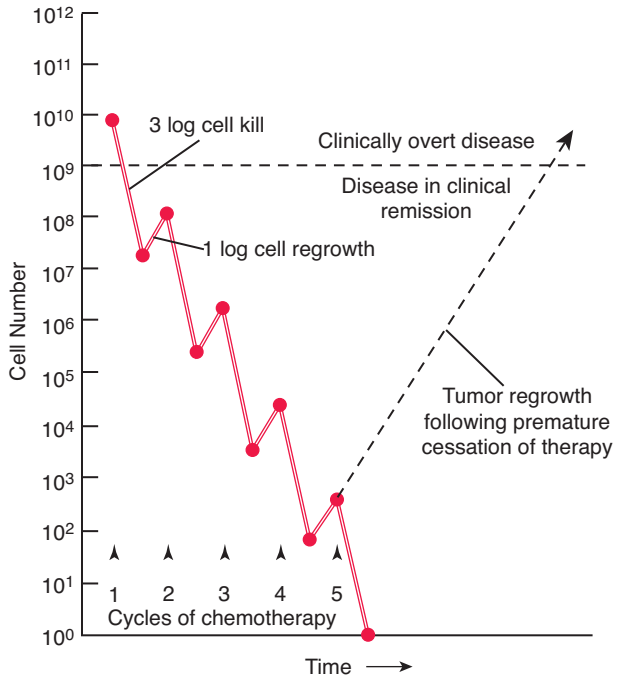


FIGURE 7-10. Relationship between tumor cell survival and administration of chemotherapy. The exponential relationship between drug dose and tumor cell survival dictates that a constant proportion, not number, of tumor cells is killed with each treatment cycle. In this example, each cycle of drug administration results in a 99.9% (3 log) cell kill, and 1 log of cell growth occurs between cycles. The *broken line* indicates what would occur if the last cycle of therapy were omitted: despite complete clinical remission of disease, the tumor ultimately would recur. (From Cooper M.R., Cooper M.R. [2001]. Basis for current major therapies for cancer: Systemic therapy. In Lenhard R.E., Osteen R.T., Gansler T. [Eds.], *The American Cancer Society's clinical oncology* [p. 181]. Atlanta: American Cancer Society.)

Cancer chemotherapy drugs may be classified as either cell cycle specific or cell cycle nonspecific. Drugs are *cell cycle specific* if they exert their action during a specific phase of the cell cycle. For example, methotrexate, an antimetabolite, acts by interfering with DNA synthesis and thereby interrupts the S phase of the cell cycle. *Cell cycle–nonspecific* drugs exert their effects throughout all phases of the cell cycle. The alkylating agents, which are cell cycle nonspecific, act by disrupting DNA when cells are in the resting state as well as when they are dividing. The site of action of chemotherapeutic drugs varies. Chemotherapy drugs that have similar structures and effects on cell function usually are grouped together, and these drugs usually have similar side effect profiles. Because chemotherapy drugs differ in their mechanisms of action, cell cycle–specific and cell cycle–nonspecific agents are often combined to treat cancer.

Combination chemotherapy has been found to be more effective than treatment with a single drug. With this method, several drugs with different mechanisms of action, metabolic pathways, times of onset of action and recovery, side effects, and onset of side effects are used. Drugs used in combinations are individually effective against the tumor and synergistic with each other. The maximum possible drug doses usually are used to ensure the maximum cell killing. Routes of administration and dosage schedules are carefully designed to ensure optimal delivery of the active forms of the drugs to the tumor during the sensitive phase of the cell cycle.

Chemotherapy Side Effects. Unfortunately, chemotherapeutic drugs affect both cancer cells and the rapidly proliferating cells of normal tissue, producing undesirable side effects. Some side effects appear immediately or after a few days (acute), some within a few weeks (intermediate), and others months to years after chemotherapy administration (long term).

Most chemotherapeutic drugs suppress bone marrow function and formation of blood cells, leading to anemia, neutropenia, and thrombocytopenia. With neutropenia, there is risk for developing serious infections, whereas thrombocytopenia increases the risk for bleeding. The availability of hematopoietic growth factors (e.g., granulocyte colony-stimulating factor [G-CSF]; erythropoietin, which stimulates red blood production; and IL-11, which stimulates platelet production) has shortened the period of myelosuppression, thereby reducing the need for hospitalizations due to infection and decreasing the need for blood products.

Anorexia, nausea, and vomiting are common problems associated with cancer chemotherapy.[57] The severity of the vomiting is related to the emetic potential of the particular drug. These symptoms can occur within minutes or hours of drug administration and are thought to be due to stimulation of the chemoreceptor trigger zone in the medulla that stimulates vomiting (see Chapter 28). The chemoreceptor trigger zone responds to the level of chemicals circulating in the blood. The acute symptoms usually subside within 24 to 48 hours and often can be relieved by

antiemetic drugs. The pharmacologic approaches to prevent chemotherapy-induced nausea and vomiting have greatly improved over several decades. The development of serotonin (5-HT_3) receptor antagonists has facilitated the use of highly emetic chemotherapy drugs by more effectively reducing the nausea and vomiting induced by these drugs.

Alopecia or hair loss results from impaired proliferation of the hair follicles and is a side effect of a number of cancer drugs; it usually is temporary, and the hair tends to regrow when treatment is stopped. The rapidly proliferating structures of the reproductive system are particularly sensitive to the action of cancer drugs. Women may experience changes in menstrual flow or have amenorrhea. Men may have a decreased sperm count (i.e., oligospermia) or absence of sperm (i.e., azoospermia). Many chemotherapeutic agents also may have teratogenic or mutagenic effects leading to fetal abnormalities.[57]

Chemotherapy drugs are toxic to all cells. Because they are potentially mutagenic, carcinogenic, and teratogenic, special care is required when handling or administering the drugs. Drugs, drug containers, and administration equipment require special disposal as hazardous waste.[58]

Hormone and Antihormone Therapy

Hormonal therapy consists of administration of drugs designed to negatively alter the hormonal environment of cancer cells. It is used for cancers that are responsive to or dependent on hormones for growth.[59] The actions of hormones and antihormones depend on the presence of specific receptors in the tumor. Among the tumors that are known to be responsive to hormonal manipulation are those of the breast, prostate, and endometrium. Other cancers, such as Kaposi sarcoma and renal, liver, ovarian, and pancreatic cancer, are also responsive to hormonal manipulation, but to a lesser degree. The theory behind the majority of hormone-based cancer treatments is to deprive the cancer cells of the hormonal signals that otherwise would stimulate them to divide.

The therapeutic options for altering the hormonal environment in the woman with breast cancer or the man with prostate cancer include surgical and pharmacologic measures. Surgery involves the removal of the organ responsible for the hormone production that is stimulating the target tissue (e.g., ovaries in women or testes in men). Pharmacologic methods focus largely on reducing circulating hormone levels or changing the hormone receptors so that they no longer respond to the hormone. Pharmacologic suppression of circulating hormone levels can be effected through pituitary desensitization as with the administration of androgens or through the administration of *gonadotropin-releasing hormone* (GnRH) analogs that act at the level of the hypothalamus to inhibit gonadotropin production and release. Another class of drugs, the *aromatase inhibitors*, is used to treat breast cancer; these drugs act by interrupting the biochemical processes that convert the adrenal androgen androstenedione to estrone.[60]

Hormone receptor function can be altered by the administration of pharmacologic doses of exogenous hormones that act by producing a decrease in hormone receptors or by antihormone drugs (antiestrogens and antiandrogens) that bind to hormone receptors, making them inaccessible to hormone stimulation. Initially, patients often respond favorably to hormonal treatments, but eventually the cancer becomes resistant to hormonal manipulation, and other approaches must be sought to control the disease.

Biotherapy

Biotherapy involves the use of immunotherapy and biologic response modifiers as a means of changing the person's immune response to cancer.[57,61] The major mechanisms by which biotherapy exerts its effects are modification of host responses and modification of tumor cell biology.

Immunotherapy. Immunotherapy techniques include active and passive, or adoptive, immunotherapy. *Active immunotherapy* involves nonspecific techniques such as bacille Calmette-Guérin (BCG). BCG is an attenuated strain of the bacterium that causes bovine tuberculosis. It acts as a nonspecific stimulant of the immune system and is instilled into the bladder as a means of treating superficial bladder cancer.

Passive or *adoptive immunotherapy* involves the transfer of cultured immune cells into a tumor-bearing host. Early research efforts with adoptive immunotherapy involved the transfer of sensitized NK cells or T lymphocytes, combined with cytokines to the tumor-bearing host, in an attempt to augment the host's immune response. However, randomized clinical trials demonstrated no benefit from the addition of the cellular component beyond the benefit from the cytokine alone. Further research has focused on using antigen-presenting dendritic cells as delivery vehicles for tumor antigens. Dendritic cells are efficient at activating not only $CD4^+$ helper cells and $CD8^+$ killer T cells, but also B cells and innate effectors such as NK cells.[61]

Biologic Response Modifiers. The biologic response modifiers include cytokines (e.g., interferons and interleukins) and monoclonal antibodies. The *interferons* appear to inhibit viral replication and also may be involved in inhibiting tumor protein synthesis, prolonging the cell cycle, and increasing the percentage of cells in the G_0 phase. Interferons stimulate NK cells and T-lymphocyte killer cells. There are three major types of interferons, alpha (α), beta (β), and gamma (γ), with members of each group differing in terms of their cell surface receptors.[62] Interferon-γ has been approved for the treatment of hairy cell leukemia, AIDS-related Kaposi sarcoma, and chronic myelogenous leukemia, and as adjuvant therapy for patients at high risk for recurrent melanoma.[62] Interferon-α has been used to treat some solid tumors (e.g., renal cell carcinoma, colorectal cancer, carcinoid tumors, ovarian cancer) and hematologic neoplasms (e.g., B-cell and T-cell lymphomas, cutaneous T-cell lymphoma, and multiple myeloma).[62] Research now is focusing on combining interferons with other forms of

cancer therapy and establishing optimal doses and treatment protocols.

The *interleukins* (ILs) are cytokines that provide communication between cells by binding to receptor sites on the cell surface membranes of the target cells. Of the 18 known interleukins (see Chapter 15), IL-2 has been the most widely studied. A recombinant human IL-2 (rIL-2, aldesleukin) has been approved by the U.S. Food and Drug Administration (FDA) and is currently being used for the treatment of metastatic renal cell carcinoma and metastatic melanoma.[63]

Monoclonal antibodies (MoAbs) are highly specific antibodies (e.g., immunoglobulin G [IgG], which is the most commonly used immunoglobulin) derived from cloned cells or hybridomas.[64,65] Scientists have developed methods for producing large quantities of these MoAbs that are specific for tumor cells. For an MoAb to be therapeutic as a cancer treatment modality, a specific target antigen should be present on cancer cells only. MoABs can be combined with a toxin, chemotherapy drug, or radioisotope as a means of targeting its action to tumor cells.

Targeted Therapy

Researchers have been working diligently to produce drugs that selectively attack malignant cells while leaving normal cells unharmed.[66] The characteristics and capabilities of cancer cells have been used to establish a framework for the development of such targeted therapies, including those that disrupt molecular signaling pathways, inhibit angiogenesis, and harness the body's immune system. The first targeted therapies were the monoclonal antibodies. Researchers are now working to design drugs that can disrupt molecular signaling pathways such as those that use the protein tyrosine kinases. The protein tyrosine kinases are intrinsic components of the signaling pathways for growth factors involved in the proliferation of lymphocytes and other cell types. Imatinib mesylate is a protein tyrosine kinase inhibitor indicated in the treatment of chronic myeloid leukemia (see Chapter 11). Angiogenesis is also being explored as a target for targeted cancer therapy.[66] One of the more newly developed antiangiogenic agents, bevacizumab, targets and blocks vascular endothelial growth factor (VEGF), which is released by many cancers to stimulate proliferation of new blood vessels.

In summary, the methods used in the diagnosis of cancer vary with the type of cancer and its location. Because many cancers are curable if diagnosed early, health care practices designed to promote early detection are important. Histologic studies are done in the laboratory using cells or tissue specimens. There are two basic methods of classifying tumors: grading according to the histologic or tissue characteristics and clinical staging according to spread of the disease. The TNM system for clinical staging of cancer uses tumor size, lymph node involvement, and presence of metastasis.

Treatment plans that use more than one type of therapy, often in combination, are providing cures for a number of cancers that a few decades ago had a poor prognosis, and are increasing the life expectancy in other types of cancer. Surgical procedures are more precise and less invasive, preserving organ function and resulting in better quality-of-life outcomes. Newer radiation equipment and novel radiation techniques permit greater and more controlled destruction of cancer cells while sparing normal tissues. Cancer chemotherapy has evolved as one of the major systemic treatment modalities for cancer. Unlike surgery and radiation, chemotherapy is a treatment that enables drugs to reach the site of the tumor as well as other distant sites. Other systemic agents include hormonal and molecularly targeted agents that block specific enzymes and growth factors involved in cancer cell growth.

Childhood Cancers

Cancer in children is relatively rare, accounting for about 1% of all malignancies in the United States and Canada.[1,2] Despite progressively improved 5-year survival rates, from 56% in 1974 to 75% in 2000, cancer remains the second leading cause of death among children between 1 to 14 years in the United States.[1] Leukemia (discussed in Chapter 11) accounts for 30% of the cases of childhood cancer and one third of the expected deaths.[1] Other forms of cancer that occur in children include non-Hodgkin and Hodgkin lymphoma (discussed in Chapter 11) and bone cancers (osteosarcoma and Ewing sarcoma, discussed in Chapter 43).

Two young girls with acute lymphocytic leukemia are receiving chemotherapy. (From National Cancer Institute Visuals Online. Available: http://www.visualsonline.cancer.gov.)

Incidence and Types of Childhood Cancers

The spectrum of cancers that affect children differs markedly from those that affect adults. Although most

adult cancers are of epithelial cell origin (e.g., lung cancer, breast cancer, colorectal cancers), childhood cancers usually involve the hematopoietic system, nervous system, soft tissues, bone, and kidneys.[67,68] Histologically, many of the childhood cancers tend to have "a more primitive (embryonal) rather than pleomorphic-anaplastic microscopic appearance, are often characterized by sheets of cells, with small round nuclei, and frequently exhibit features of organogenesis specific to the site of origin."[4]

The incidence of childhood cancers is greatest during the first years of life, decreases during middle childhood, and then increases during puberty and adolescence.[68] During the first 2 years of life, embryonal tumors such as neuroblastoma, retinoblastoma, and Wilms tumor are among the most common types of tumors. Acute lymphatic leukemia has a peak incidence in children 2 to 5 years of age. As children age, especially after they pass puberty, bone malignancies, lymphoma, gonadal germ cell tumors (testicular and ovarian carcinomas), and various carcinomas such as thyroid cancer and malignant melanoma increase in incidence.

A number of the tumors of infancy and early childhood are embryonal in origin, meaning that they exhibit features of organogenesis similar to that of embryonic development. Because of this characteristic, these tumors are frequently designated with the suffix "*-blastoma*" (e.g., nephroblastoma [Wilms tumor], retinoblastoma, neuroblastoma).[4] Wilms tumor (discussed in Chapter 25) and neuroblastoma are particularly illustrative of this type of childhood tumor.

Biology of Childhood Cancers

As with adult cancers, there probably is no one cause of childhood cancer. Although a number of genetic conditions are associated with childhood cancer, such conditions are relatively rare, suggesting an interaction between genetic susceptibility and environmental exposures. The most notable heritable conditions that impart susceptibility to childhood cancer include Down syndrome (20- to 30-fold increased risk of acute lymphoblastic leukemia),[1] neurofibromatosis (NF) type 1 (neurofibromas, optic gliomas, brain tumors), NF type 2 (acoustic neuroma, meningiomas), xeroderma pigmentosum (skin cancer), ataxia-telangiectasia (lymphoma, leukemia), and the Beckman-Wiedemann syndrome (Wilms tumor).[4,68]

While constituting only a small percentage of childhood cancers, the biology of a number of these tumors illustrates several important biologic aspects of neoplasms, such as the two-hit theory of recessive tumor-suppressor genes (e.g., RB gene mutation in retinoblastoma); defects in DNA repair; and the histologic similarities between embryonic organogenesis and oncogenesis. Syndromes associated with defects in DNA repair include xeroderma pigmentosa, in which there is increased risk of skin cancers owing to defects in repair of DNA damaged by ultraviolet light. The development of childhood cancers has also been linked to genomic imprinting, which is characterized by selective inactivation of one of the two alleles of a certain gene (discussed in Chapter 5).[67] The inactivation is determined by whether the gene is inherited from the mother or father. For example, normally the maternal allele for the insulin-like growth factor-2 (IGF-2) gene is inactivated (imprinted). The Beckwith-Wiedemann syndrome is an overgrowth syndrome characterized by organomegaly, macroglossia (enlargement of the tongue), hemihypertrophy (muscular or osseous hypertrophy of one side of the body or face), renal abnormalities, and enlarged adrenal cells.[4,67] The syndrome, which reflects changes in the imprinting of IGF-2 genes located on chromosome 11, is also associated with increased risk of Wilms tumor, hepatoblastoma, rhabdomyosarcoma, and adrenal cortical carcinoma.

Diagnosis and Treatment

Because many childhood cancers are curable, early detection is imperative. In addition, there are several types of cancers for which less therapy is indicated than for more advanced disease. Therefore, early detection often minimizes the amount and duration of treatment required for cure.

Unfortunately, there are no early warning signs or screening tests for cancer in children. Prolonged fever, persistent lymphadenopathy, unexplained weight loss, growing masses (especially in association with weight loss), and abnormalities of central nervous system function should be viewed as warning signs of cancer in children. Because these signs and symptoms of cancer are often similar to those of common childhood diseases, they are frequently attributed to other causes.[67]

Diagnosis of childhood cancers involves many of the same methods that are used in adults. Histologic examination is usually an essential part of the diagnostic procedure. Accurate disease staging is especially beneficial in childhood cancers, in which the potential benefits of treatment must be carefully weighed against potential long-term treatment effects.

The treatment of childhood cancers is complex and continuously evolving. It usually involves appropriate multidisciplinary and multimodal therapy, as well as the evaluation for recurrent disease and late effects of the disease and therapies used in its treatment. The treatment program should include specialized teams of health care providers.[67]

Several modalities are frequently used in the treatment of childhood cancer, with chemotherapy being the most widely used, followed, in order of use, by surgery, radiotherapy, and biologic agent therapy. Chemotherapy is more widely used in treatment of children with cancer than in adults because children better tolerate the acute adverse effects, and in general, pediatric tumors are more responsive to chemotherapy than adult cancers.[67] Radiation therapy is generally used sparingly in children because they are more vulnerable to the late adverse effects. As with care of adults, adequate pain management is critical.

Survivors of Childhood and Adolescent Cancers

With improvement in treatment methods, the number of children who survive childhood cancer is continuing to

increase.[69,70] As a result of cancer treatment, almost 80% of children and adolescents with a diagnosis of cancer become long-term survivors.[1] Unfortunately, radiation and chemotherapy may produce late sequelae, such as impaired growth, neurologic dysfunction, hormonal dysfunction, cardiomyopathy, pulmonary fibrosis, and risk for second malignancies. There is a special risk of second cancers in children with the retinoblastoma gene. Thus, one of the growing challenges is providing appropriate health care to survivors of childhood and adolescent cancers.

Children reaching adulthood after cancer therapy may have reduced physical stature because of the therapy they received, particularly radiation, which retards the growth of normal tissues along with cancer tissue. The younger the age and the higher the radiation dose, the greater the deviation from normal growth.

There is concern about the effect that CNS radiation has on cognition and hormones that are controlled by the hypothalamic-pituitary axis. Children younger than 6 years of age at the time of radiation and those receiving the highest radiation doses are most likely to have subsequent cognitive difficulties.[69] Growth hormone deficiency in adults is associated with increased prevalence of dyslipidemia, insulin resistance, and cardiovascular mortality. Moderate doses of cranial radiation therapy (CRT) are also associated with obesity, particularly in female patients.[69] For many years, whole-brain radiation or cranial radiation was the primary method of preventing CNS relapse in children with acute lymphocytic leukemia. Because of cognitive dysfunction associated with CRT, other methods of CNS prophylaxis are now being used.

Delayed sexual maturation in both boys and girls can result from irradiation of the gonads. Delayed sexual maturation also is related to the treatment of children with alkylating agents. Cranial irradiation may result in premature menarche in girls, with subsequent early closure of the epiphyses and a reduction in final growth achieved. Data related to fertility and health of the offspring of childhood cancer survivors is just becoming available.

Vital organs such as the heart and lungs may be affected by cancer treatment. Children who received anthracyclines (i.e., doxorubicin or daunorubicin) may be at risk for developing cardiomyopathy and congestive heart failure. Pulmonary irradiation may cause lung dysfunction and restrictive lung disease. Drugs such as bleomycin, methotrexate, and busulfan also can cause lung disease.

In summary, although most adult cancers are of epithelial cell origin, most childhood cancers usually involve the hematopoietic system, nervous system, or connective tissue. Heritable forms of cancer tend to have an earlier age of onset, a higher frequency of multifocal lesions in a single organ, and bilateral involvement of paired organs or multiple primary tumors. The early diagnosis of childhood cancers often is overlooked because the signs and symptoms mimic those of other childhood diseases. With improvement in treatment methods, the number of children who survive childhood cancer is continuing to increase. As these children approach adulthood, there is continued concern that the life-saving therapy they received during childhood may produce late effects, such as impaired growth, cognitive dysfunction, hormonal dysfunction, cardiomyopathy, pulmonary fibrosis, and risk for second malignancies.

REVIEW EXERCISES

1. A 30-year-old woman has experienced heavy menstrual bleeding and is told she has a uterine tumor called a *leiomyoma*. She is worried she has cancer.

A. What is the difference between a leiomyoma and leiomyosarcoma?
B. How would you go about explaining the difference to her?

2. Among the characteristics of cancer cells are the lack of cell differentiation, impaired cell–cell adhesion, and loss of anchorage dependence.

A. Explain how each of these characteristics contributes to the usefulness of the Pap smear as a screening test for cervical cancer.

3. A 12-year-old boy is seen in the pediatric cancer clinic with osteosarcoma. His medical history reveals that his father had been successfully treated for retinoblastoma as an infant.

A. Relate the genetics of the RB gene and "two hit" hypothesis to the development of osteosarcoma in this boy.

4. A 48-year-old man presents at his health care clinic with complaints of leg weakness. He is a heavy smoker and has had a productive cough for years. Subsequent diagnostic tests reveal he has a small cell lung cancer with brain metastasis. His proposed plan of treatment includes chemotherapy and radiation therapy.

A. What is the probable cause of the leg weakness and is it related to the lung cancer?
B. Relate this man's smoking history to the development of lung cancer.
C. Explain the mechanism of cancer metastasis.
D. Explain the mechanisms whereby chemotherapy and irradiation are able to destroy cancer cells while having less or no effect on normal cells.

5. A 17-year-old girl is seen by a guidance counselor at her high school because of problems in keeping up with assignments in her math and science courses. She tells the counselor that she had leukemia when she was 2 years old and was given radiation treatment to her brain. She confides that she has always had more trouble with learning than her classmates and thinks it might be due to the radiation. She also relates that she is shorter than her classmates and this has been bothering her.

A. Explain the relationship between cranial radiation therapy and decreased cognitive function and short stature.

B. What other neuroendocrine problems might this girl have as a result of the radiation treatment?

REFERENCES

1. American Cancer Society. (2009). *Global cancer facts & figures 2007*. Atlanta: American Cancer Society.
2. Jemel A., Seigel R., Ward E. (2010). Cancer Statistics, 2009. *CA: A Cancer Journal for Clinicians* 59, 225–249.
3. Marrett L., De P., Deyer D., et al. (2009). Canadian cancer statistics 2009. Canadian Cancer Society.
4. Striker T.P., Kumanr V. (2010). Neoplasia. In Kumar V., Abbas A., Fausto N., et al. *Robbins and Cotran pathologic basis of disease* (8th ed., pp 259–330). Philadelphia: Saunders Elsevier.
5. Giordano A., DeFalco G., Rubin E., et al. (2008). Neoplasia. In Rubin R., Strayer D.S. *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 137–176). Philadelphia: Lippincott Williams & Wilkins.
6. Loeb K.R., Loeb L.A. (1999). Genetic instability and the mutator phenotype. Studies in ulcerative colitis. *American Journal of Pathology* 154, 1621–1626.
7. Damjanov I. (2006). *Pathophysiology for the health professions* (pp. 70–96). Philadelphia: Elsevier Saunders.
8. Alberts B., Johnson A., Lewis J., et al. (2008). *The cell* (5th ed., pp. 1133–1139, 1175–1176, 1230–1240). New York: Garland Science.
9. Wang L. (2004). Molecular signaling regulating anchorage-independence growth in cancer cells. *Mount Sinai Journal of Medicine* 71(6), 361–367.
10. Carruba G., Webber M.M., Quader S.T.A., et al. (2002). Regulation of cell-to-cell communication in non-tumorigenic and malignant human prostate epithelial cells. *Prostate* 50, 73–82.
11. Yaeger T.E., Brady L.W. (2001). Basis for current major therapies in cancer. In Lenhard R.E., Osteen R.T., Gansler T. (Eds.), *The American Cancer Society's clinical oncology* (pp. 159–229). Atlanta: American Cancer Society.
12. Marutsuka T., Shimada S., Shiomori K., et al. (2003). Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: An ultrarapid detection system for intra peritoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. *Clinical Cancer Research* 9, 678–685.
13. Tobler N.E., Detmar M. (2006). Tumor and lymph node lymphangiogenesis—Impact on cancer metastasis. *Journal of Leukocyte Biology* 8, 691–696.
14. Chen S.L., Iddings D.M., Scheri R., et al. (2006). Lymphatic mapping and sentinel node analysis: Current concepts and applications. *CA: A Cancer Journal for Clinicians* 56, 292–307.
15. Stetler-Stevenson W.G. (2005). Molecular biology of cancer: Invasion and metastasis. In DeVita V.T. Jr., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles and practice of oncology* (7th ed., pp. 113–126). Philadelphia: Lippincott Williams & Wilkins.
16. Ruffini P.A., Morandi P., Altundag K., et al. (2007). Manipulating the chemokine-chemokine receptor network to treat cancer. *Cancer* 109(12), 2392–2404.
17. Kakinuma T., Twang S.T. (2006). Chemokines, chemokine receptors, and cancer metastasis. *Journal of Leukocyte Biology* 79, 639–651.
18. Crocce C.M. (2008). Oncogenes and cancer. *New England Journal of Medicine* 358(5), 502–511.
19. Zhou B.P., Hung M.C. (2003). Dysregulation of cellular signaling by HER2/neu in breast cancer. *Seminars in Oncology* 30 (5 Suppl 16), 38–48.
20. Kumar V., Abbas A.K., Fausto N., et al. (2008). *Robbins basic pathology* (8th ed., p. 137). Philadelphia: Saunders Elsevier.
21. Esteller M. (2008). Epigenetics in cancer. *New England Journal of Medicine* 358(11), 1148–1159.
22. Baylin S.B. (2005). DNA methylation and gene silencing in cancer. *Nature Clinical Practice Oncology* 2, S4–S11.
23. Schulze-Bergkamen H., Krammer P.H. (2004). Apoptosis in cancer—Implications for therapy. *Seminars in Oncology* 31, 90–119.
24. Mooi W.J., Peeper D.S. (2006). Oncogene-induced cell senescence—Halting the road to cancer. *New England Journal of Medicine* 355(10), 1037–1046.
25. Kerbel R.S. (2008). Tumor angiogenesis. *New England Journal of Medicine* 358(19), 2039.
26. Boccaccio C., Comoglio P.M. (2006). Invasive growth: A *MET*-driven genetic programme for cancer and stem cells. *Nature Reviews Cancer* 6, 637–645.
27. Ceschi M., Gutzwiller F., Mody H., et al. (2007). Epidemiology and pathophysiology of obesity as a cause of cancer. *Swiss Medical Weekly* 137, 50–56.
28. Finn O.J. (2008). Cancer immunology. *New England Journal of Medicine* 358(25), 2704–2715.
29. Burnett F.M. (1967). Immunologic aspects of malignant disease. *Lancet* 1, 1171.
30. Willett, W.C. (2001). Cancer prevention: Diet and chemopreventive agents. In Devita V.T., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles & practice of oncology* (6th ed., pp. 561–614). Philadelphia: Lippincott Williams & Wilkins.
31. Seitz H.K., Stickel F. (2007). Molecular mechanisms of alcohol-mediated carcinogenesis. *Nature Reviews Cancer* 7, 599–612.
32. Jablon S., Kato H. (1972). Studies of the mortality of A-bomb survivors: 5. Radiation dose and mortality, 1950–1970. *Radiation Research* 50, 649–698.
33. Liao J.B. (2006). Viruses and human cancer. *Yale Journal of Biology and Medicine* 79, 115–122.
34. Centers for Disease Control and Prevention. *HPV information for young women*. [Online]. Available at: http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-young-women.htm. Accessed May, 12, 2010.
35. Rugo H.S. (2009). Cancer. In McPhee S.J., Papadakis M.A., Tierney L.M. Jr. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 1486–1487). New York: McGraw-Hill.
36. Knight K., Wade S., Balducci L. (2004). Prevalence and outcomes of anemia in cancer: A systematic review of the literature. *American Journal of Medicine* 116(7A), 11S–26S.
37. Hurter B., Bush N.J. (2007). Cancer-related anemia: Clinical review and management update. *Clinical Journal of Oncology Nursing* 11(3), 349–359.
38. Imui A. (2002). Cancer anorexia-cachexia syndrome: Current issues in research and management. *CA: A Cancer Journal for Clinicians* 52(2), 72–91.

39. Gordon J.N., Green S.R., Goggin P.M. (2005). Cancer cachexia. *Quarterly Journal of Medicine* 98, 779–788.
40. Tisdale M.J. (2005). Molecular pathways leading to cancer cachexia. *Physiology* 20, 340–348.
41. Patrick D.L., Ferketich S.L., Harris J.J., et al. (2003). National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15–17, 2002. *Journal of the National Cancer Institute* 95(15), 1110–1117.
42. Ryan J.L., Carroll J.K., Ryan E.P., et al. (2007). Mechanisms of cancer-related fatigue. *Oncologist* 12(Suppl 1), 1–S22.
43. Hofman M., Ryan J.L., Comar D., et al. (2007). Cancer-related fatigue: The scale of the problem. *Oncologist* 12(Suppl 1), 4–10.
44. Arnold S.M., Lieberman F.S., Foon K.A. (2005). Paraneoplastic syndromes. In DeVita V.T. Jr., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles and practice of oncology* (7th ed., pp. 2191–2210). Philadelphia: Lippincott Williams & Wilkins.
45. Rosenthal P.E. (2001). Paraneoplastic and endocrine syndromes. In Lenhard R.E., Osteen R.T., Gansler T. (Eds.), *The American Cancer Society's clinical oncology* (pp. 721–732). Atlanta: American Cancer Society.
46. Shoback D., Funk J. (2004). Humoral manifestations of malignancy. In Greenspan F.S., Gardner D.G. (Eds.), *Basic and clinical endocrinology* (7th ed., pp. 814–841). New York: McGraw-Hill.
47. Darnell R.B., Posner J.B. (2003). Paraneoplastic syndromes involving the nervous system. *New England Journal of Medicine* 349(16), 1543–1554.
48. Miser W.F. (2007). Cancer screening in the primary care setting. *Primary Care Clinics in Office Practice* 34, 137–167.
49. Smith R.A., Eyre H.J. (2007). Cancer screening in the United States, 2007: A review of current guidelines. *CA: A Cancer Journal for Clinicians* 57, 90–104.
50. Pfiefer J.D., Wick M.R. (2001). Pathologic evaluation of neoplastic diseases. In Lenhard R.E., Osteen R.T., Gansler T. (Eds.), *The American Cancer Society's clinical oncology* (pp. 123–147). Atlanta: American Cancer Society.
51. Rosenberg S.A. (2001). Cancer management: Principles of surgical oncology. In DeVita V.T. Jr., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles and practice of oncology* (6th ed., pp. 253–264). Philadelphia: Lippincott Williams & Wilkins.
52. Jeremic B. (2004). Radiation therapy. *Hematology/Oncology Clinics of North America* 18, 1–12.
53. Hahn S.M., Gladstein E. (2005). Principles of radiation therapy. In Kasper D.L., Fauci A.S., Longo D.L., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 482–489). New York: McGraw-Hill.
54. Willers H., Held K.D. (2006). Introduction to clinical radiation biology. *Hematology/Oncology Clinics of North America* 20, 1–24.
55. Cooper M.R., Cooper M.R. (2001). Basis for current major therapies for cancer: Systemic therapy. In Lenhard R.E., Osteen R.T., Gansler T. (Eds.), *The American Cancer Society's clinical oncology* (pp. 175–215). Atlanta: American Cancer Society.
56. Chu E., Sartorelli A.C. (2007). Cancer chemotherapy. In Katzung B.G. (Eds.), *Basic and clinical pharmacology* (10th ed., pp. 878–907). New York. McGraw-Hill.
57. Sausville E.A., Longo D.L. (2005). Principles of cancer treatment: Surgery, chemotherapy, and biologic therapy. In Kasper D.L., Fauci A.S., Longo D.L., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 464–482). New York: McGraw-Hill.
58. Polovich M. (2003). *Safe handling of hazardous drugs*. Pittsburgh: Oncology Nursing Society.
59. Hawkins R. (2002). Hormone therapy in cancer. *Oncology Nursing Update*s 9(3), 1–16.
60. Altundag K., Ibrahim N.K. (2006). Aromatase inhibitors in breast cancer: An overview. *Oncologist* 11, 553–562.
61. Reiger P.T. (2001). Biotherapy: An overview. In Reiger P.T. (Ed.), *Biotherapy: A comprehensive overview* (2nd ed., pp. 3–37). Sudbury, MA: Jones and Bartlett.
62. Kirkwood J.M. (2001). Interferons. In DeVita V.T. Jr., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles and practice of oncology* (7th ed., pp. 461–471). Philadelphia: Lippincott Williams & Wilkins.
63. Mier J.W., Atkins M.B. (2001). Interleukin-2. In DeVita V.T. Jr., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles and practice of oncology* (7th ed., pp. 471–478). Philadelphia: Lippincott Williams & Wilkins.
64. Schmidt K.V., Wood B.A. (2003). Trends in cancer therapy: Role of monoclonal antibodies. *Seminars in Oncology Nursing* 19(3), 169–179.
65. Von Mehren M., Adams G.P., Weiner L.M. (2003). Monoclonal antibody therapy for cancer. *Annual Review of Medicine* 54, 343–369.
66. Sharkey R.M., Goldenberg D.M. (2006). Targeted therapy of cancer: New prospects for antibodies and immunoconjugates. *CA: A Cancer Journal for Clinicians* 56, 226–243.
67. Behrman R.E., Kliegman R.M., Jensen H.B. (Eds.). (2004). *Nelson textbook of pediatrics* (17th ed., pp. 1679–1693). Philadelphia: W.B. Saunders.
68. Ries L.A.G., Smith M.A., Gurney J.G., et al. (Eds.). (1999). *Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995*. Bethesda MD: National Cancer Institute. [Online] Available: http://seer.cancer.gov/publications/childhood/. Accessed December 31, 2008.
69. Oeffinger K.C., Mertens A.C., Sklar C.A., et al. (2006). Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine* 355, 1572–1582.
70. Oeffinger K.C., Hudson M.M. (2004). Long-term complications following childhood and adolescent cancer: Foundations for providing risk-based health care for survivors. *CA: A Cancer Journal for Clinicians* 54, 208–236.

UNIT 2

Integrative Body Functions

Composition and Compartmental Distribution of Body Fluids
- *Introductory Concepts*
  - Dissociation of Electrolytes
  - Diffusion and Osmosis
- *Compartmental Distribution of Body Fluids*
- *Capillary/Interstitial Fluid Exchange*
  - Edema
  - Third-Space Accumulation

Sodium and Water Balance
- *Regulation of Sodium and Water Balance*
  - Regulation of Water Balance
  - Regulation of Sodium Balance
  - Mechanisms of Water and Sodium Balance
- *Disorders of Thirst and Antidiuretic Hormone*
  - Disorders of Thirst
  - Disorders of Antidiuretic Hormone
- *Disorders of Water and Sodium Balance*
  - Isotonic Fluid Volume Deficit
  - Isotonic Fluid Volume Excess
  - Hyponatremia
  - Hypernatremia

Potassium Balance
- *Regulation of Potassium Balance*
  - Mechanisms of Regulation
- *Disorders of Potassium Balance*
  - Hypokalemia
  - Hyperkalemia

Calcium and Magnesium Balance
- *Disorders of Parathyroid Function*
  - Hypoparathyroidism
  - Hyperparathyroidism
- *Disorders of Calcium Balance*
  - Regulation of Calcium Balance
  - Hypocalcemia
  - Hypercalcemia
- *Disorders of Magnesium Balance*
  - Regulation of Magnesium Balance
  - Hypomagnesemia
  - Hypermagnesemia

Acid-Base Balance
- *Introductory Concepts*
  - Acid-Base Chemistry
  - Acid and Base Production
  - Calculation of pH
- *Regulation of pH*
  - Chemical Buffer Systems
  - Respiratory Control Mechanisms
  - Renal Control Mechanisms
- *Laboratory Tests*
- *Disorders of Acid-Base Balance*
  - Metabolic Versus Respiratory Acid-Base Disorders
  - Primary Versus Compensatory Changes in pH
  - Metabolic Acidosis
  - Metabolic Alkalosis
  - Respiratory Acidosis
  - Respiratory Alkalosis

Chapter 8

Disorders of Fluid, Electrolyte, and Acid-Base Balance

Fluids and electrolytes are present in body cells, in the tissue spaces between the cells, and in the blood that fills the vascular compartment. Body fluids transport gases, nutrients, and wastes; help generate the electrical activity needed to power body functions; take part in the transforming of food into energy; and otherwise maintain the overall function of the body. Although fluid volume and composition remain relatively constant in the presence of a wide range of changes in intake and output, conditions such as environmental stresses and disease can impair intake, increase losses, and otherwise interfere with mechanisms that regulate fluid volume, composition, and distribution.

This chapter is divided into five sections: composition and compartmental distribution of body fluids, disorders of sodium and water balance, disorders of potassium balance, disorders of calcium and magnesium balance, and disorders of acid-base balance.

Composition and Compartmental Distribution of Body Fluids

Body fluids are distributed between the intracellular and extracellular fluid compartments.[1,2] The *intracellular fluid (ICF) compartment* consists of fluid contained

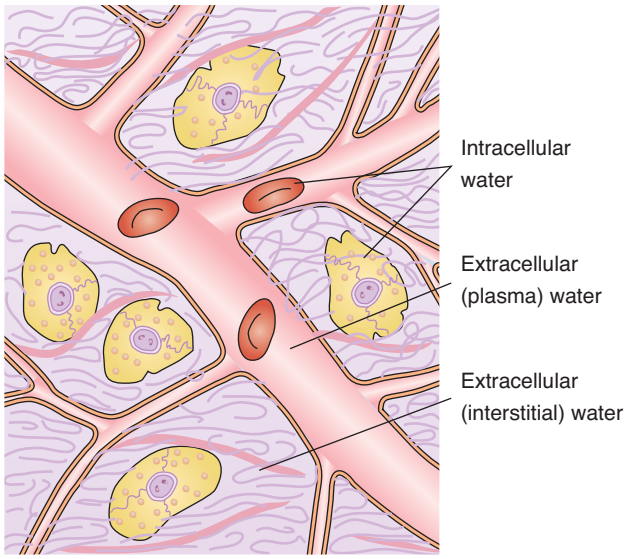


FIGURE 8-1. Distribution of body water. The extracellular space includes the vascular compartment and the interstitial spaces.

within all of the billions of cells in the body. It contains approximately two thirds of the body water in healthy adults, and is the larger of the two compartments. The remaining one third of body water is in the *extracellular fluid (ECF) compartment*, which contains all the fluids outside the cells, including that in the interstitial or tissue spaces and blood vessels (Fig. 8-1).

The composition of the ICF and ECF are strikingly different. The ECF, including the plasma and interstitial fluids, contains large amounts of sodium and chloride, moderate amounts of bicarbonate, but only small quantities of potassium, magnesium, calcium, and phosphate. In contrast to the ECF, the ICF contains almost no calcium; small amounts of sodium, chloride, bicarbonate, and phosphate; moderate amounts of magnesium; and large amounts of potassium (Table 8-1). Although blood levels usually are representative of the total body levels of an electrolyte, this is not always the case, particularly with potassium, which is approximately 28 times more concentrated inside the cell than outside. It is the ECF levels of electrolytes in the blood or blood plasma that are measured clinically (this text uses the term *serum* rather than *plasma* in reference to laboratory values of electrolytes).

The cell membrane serves as the primary barrier to the movement of substances between the ECF and ICF compartments (see Chapter 1). Lipid-soluble substances (e.g., oxygen [O_2] and carbon dioxide [CO_2]), which dissolve in the lipid bilayer of the cell membrane, pass directly through the membrane, whereas many ions (e.g., sodium [Na^+] and potassium [K^+]) rely on transport mechanisms such as the Na^+/K^+-adenosine triphosphatase (ATPase) pump that is located in the cell membrane for movement across the membrane. The Na^+/K^+-ATPase pump utilizes adenosine triphosphate (ATP) and the enzyme ATPase for the maintenance of the ion concentration gradients across the membrane. Water crosses the cell membrane by osmosis using special transmembrane protein channels called *aquaporins*.

Introductory Concepts

Dissociation of Electrolytes

Electrolytes are substances that dissociate in solution to form charged particles, or *ions*. For example, a sodium chloride (NaCl) molecule dissociates to form a positively charged Na^+ and a negatively charged Cl^- ion. Particles that do not dissociate into ions such as glucose and urea are called *nonelectrolytes*. Positively charged ions are called *cations* because they are attracted to the cathode of a wet electric cell, and negatively charged ions are called *anions* because they are attracted to the anode. The ions found in body fluids carry one charge (i.e., monovalent ion) or two charges (i.e., divalent ion). Because of their attraction forces, positively charged cations are always accompanied by negatively charged anions. Thus, all body

TABLE 8-1 Concentrations of Extracellular and Intracellular Electrolytes in Adults

	Extracellular Concentration*		Intracellular Concentration*	
Electrolyte	***Conventional Units***	***SI Units***	***Conventional Units***	***SI Units***
Sodium	135–145 mEq/L	135–145 mmol/L	10–14 mEq/L	10–14 mmol/L
Potassium	3.5–5.0 mEq/L	3.5–5.0 mmol/L	140–150 mEq/L	140–150 mmol/L
Chloride	98–106 mEq/L	98–106 mmol/L	3–4 mEq/L	3–4 mmol/L
Bicarbonate	24–31 mEq/L	24–31 mmol/L	7–10 mEq/L	7–10 mmol/L
Calcium	8.5–10.5 mg/dL	2.1–2.6 mmol/L	<1 mg/dL	<0.25 mmol/L
Phosphorus	2.5–4.5 mg/dL	0.8–1.45 mmol/L	4 mEq/kg†	75 mmol/L
Magnesium	1.8–3.0 mg/dL	0.75–1.25 mmol/L	variable†	variable†

*Values may vary among laboratories, depending on the method of analysis used.

†Values vary among various tissues and with nutritional status.

fluids contain equal amounts of anions and cations. However, cations and anions may be exchanged for one another, providing they carry the same charge. For example, a positively charged hydrogen ion (H^+) may be exchanged for a positively charged K^+ and a negatively charged bicarbonate ion (HCO_3^-) may be exchanged for a negatively charged chloride ion (Cl^-).

Diffusion and Osmosis

Diffusion is the movement of charged or uncharged particles along a concentration gradient. All molecules and ions, including water and dissolved molecules, are in constant random motion. It is the motion of these particles, each colliding with one another, that supplies the energy for diffusion. Because there are more molecules in constant motion in a concentrated solution, particles move from an area of higher concentration to one of lower concentration. The concentrations of electrolytes and solutes can be expressed in several ways, for example, milligrams per deciliter (mg/dL), milliequivalents per liter (mEq/L), or millimoles per liter (mmol/L).

Despite the remarkable difference in the concentration of individual solutes in the ICF and ECF, the total concentration gradient is the same in both compartments because of the osmotic movement of water. Osmosis is the movement of water across a semipermeable membrane (i.e., one that is permeable to water but impermeable to most solutes).[1,2] As with solute particles, water diffuses down its concentration gradient, moving from the side of the membrane with greater concentration of water and lesser concentration of solute particles to the side with lesser concentration of water and greater concentration of solute particles (Fig. 8-2). As water moves across the semipermeable membrane, it generates a pressure called the *osmotic pressure*. The magnitude of the osmotic pressure represents the hydrostatic pressure (measured in millimeters of mercury [mm Hg]) needed to oppose the movement of water across the membrane.

The osmotic activity that nondiffusible particles exert in pulling water from one side of the semipermeable membrane to the other is measured by a unit called an *osmole*. The osmole is derived from the gram molecular weight of a substance (i.e., 1 gram molecular weight of a nondiffusible and nonionizable substance is equal to 1 osmole). In the clinical setting, osmotic activity usually is expressed in milliosmoles (one thousandth of an osmole) per liter. Each nondiffusible particle, large or small, is equally effective in its ability to pull water through a semipermeable membrane. Thus, it is the

Box 8-1 Measurement Units

Laboratory measurements of electrolytes in body fluids are expressed as a concentration or amount of solute in a given volume of fluid, such as milligrams per deciliter (mg/dL), milliequivalents per liter (mEq/L), or millimoles per liter (mmol/L).

The use of *milligrams (mg) per deciliter* expresses the weight of the solute in one tenth of a liter (dL). The concentration of electrolytes, such as calcium, phosphate, and magnesium, is often expressed in mg/dL.

The *milliequivalent* is used to express the charge equivalency for a given weight of an electrolyte: 1 mEq of sodium has the same number of charges as 1 mEq of chloride, regardless of molecular weight. The number of milliequivalents of an electrolyte in a liter of solution can be derived from the following equation:

$$\text{mEq} = \frac{\text{mg/100 mL} \times 10 \times \text{valence}}{\text{atomic weight}}$$

The Système Internationale (SI) units express electrolyte concentration in *millimoles per liter* (mmol/L). A millimole is one thousandth of a mole, or the molecular weight of a substance expressed in milligrams. The number of millimoles of an electrolyte in a liter of solution can be calculated using the following equation:

$$\text{mmol/L} = \frac{\text{mEq/L}}{\text{valence}}$$

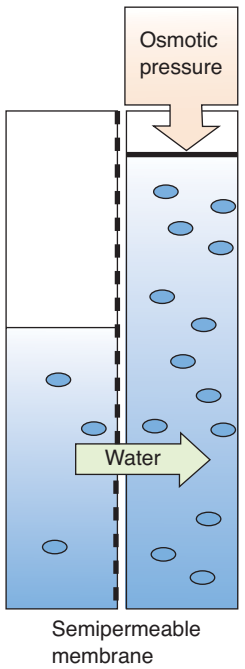


FIGURE 8-2. Movement of water across a semipermeable membrane. Water moves from the side that has fewer nondiffusible particles to the side that has more. The osmotic pressure is equal to the hydrostatic pressure needed to oppose water movement across the membrane.

number, rather than the size, of the nondiffusible particles that determines the osmotic activity of a solution.

The osmotic activity of a solution may be expressed in terms of either its osmolarity or osmolality. *Osmolarity* refers to the osmolar concentration in 1 L of solution (mOsm/L) and *osmolality* to the osmolar concentration in 1 kg of water (mOsm/kg of H_2O).[2] Osmolarity is usually used when referring to fluids outside the body and osmolality for describing fluids inside the body. Because 1 L of water weighs 1 kg, the terms *osmolarity* and *osmolality* are often used interchangeably.

Serum osmolality, which is largely determined by Na^+ and its attendant anions (Cl^- and HCO_3^-), normally ranges between 275 and 295 mOsm/kg. Blood urea nitrogen (BUN) and glucose, which also are osmotically active, account for less than 5% of the total osmotic pressure in the extracellular compartment. However, this can change, such as when blood glucose levels are elevated in persons with diabetes mellitus or when BUN levels change rapidly in persons with chronic kidney disease.

The term *tonicity* refers to the tension or effect that the effective osmotic pressure of a solution with impermeable solutes exerts on cell size because of water movement across the cell membrane.[2] Solutions to which body cells are exposed can be classified as isotonic, hypotonic, or hypertonic depending on whether they cause cells to swell or shrink (Fig. 8-3). Cells placed in an isotonic solution, which has the same effective osmolality as the ICF (i.e., 280 mOsm/L), neither shrink nor swell. An example of an isotonic solution is 0.9% sodium chloride. When cells are placed in a hypotonic solution, which has a lower effective osmolality than the ICF, they swell as water moves into the cell, and when they are placed in a hypertonic solution, which has a greater effective osmolality than the ICF, they shrink as water is pulled out of the cell.

Compartmental Distribution of Body Fluids

Body water, which constitutes a high percentage of body weight, is distributed between the ICF and ECF compartments. In the adult, the fluid in the ICF compartment constitutes approximately 40% of body weight and that in the ECF approximately 20% of body weight (Fig. 8-4).[1–4]

The fluid in the ECF compartment is further divided into two major subdivisions: the plasma compartment, which constitutes approximately 5% of body weight, and the interstitial fluid compartment, which constitutes approximately 14% of body weight (Fig. 8-4). The fluid in the interstitial compartment acts as a transport vehicle for gases, nutrients, wastes, and other materials that move between the vascular compartment and body cells. The interstitial fluid compartment also provides a reservoir from which vascular volume can be maintained during periods of hemorrhage or loss of vascular volume. A tissue gel, which is a spongelike material composed of large quantities of mucopolysaccharides, fills the tissue spaces and aids in even distribution of interstitial fluid. Normally, most of the fluid in the interstitium is in gel form. The tissue gel is supported by collagen fibers that hold the gel in place. The tissue gel, which has a firmer consistency than water, opposes the outflow of water from the capillaries and prevents the accumulation of free water in the interstitial spaces.

A third, usually minor, subdivision of the ECF compartment is the transcellular compartment. It includes the cerebrospinal fluid and fluid contained in the various body spaces, such as the peritoneal, pleural, and pericardial cavities, and joint spaces. Normally, only about 1% of ECF is in the transcellular space. This amount can increase considerably in conditions such as ascites, in

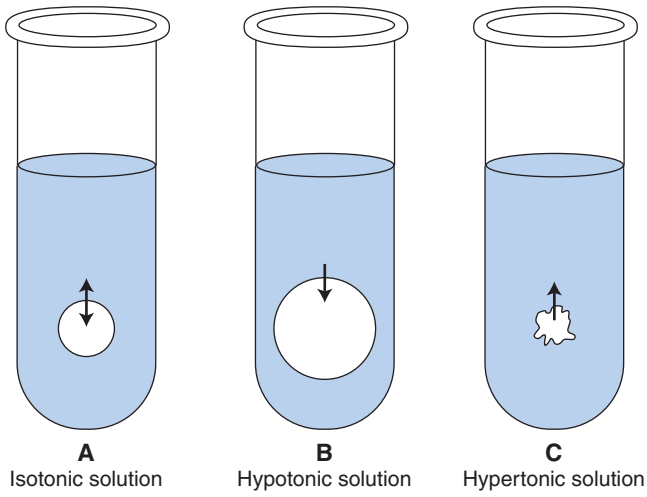


FIGURE 8-3. Tonicity: Red cells undergo no change in size in isotonic solutions **(A)**. They increase in size in hypotonic solutions **(B)** and decrease in size in hypertonic solutions **(C)**.

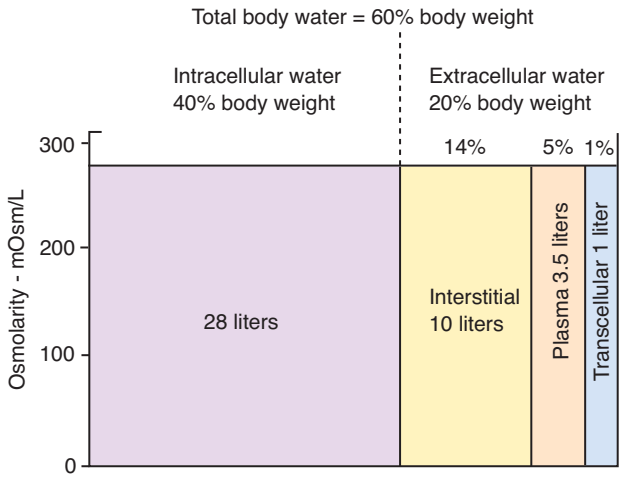


FIGURE 8-4. Approximate size of body compartments in a 70-kg adult.

which large amounts of fluid are sequestered in the peritoneal cavity. When the transcellular fluid compartment becomes considerably enlarged, it is referred to as a *third space,* because this fluid is not readily available for exchange with the rest of the ECF.

Capillary/Interstitial Fluid Exchange

The transfer of water between the vascular and interstitial compartments occurs at the capillary level. There are four main forces that control the movement of water between the capillary and interstitial spaces: (1) the capillary filtration pressure, which *pushes* water out of the capillary into the interstitial spaces; (2) the capillary colloidal osmotic pressure, which *pulls* water back into the capillary; (3) the interstitial or tissue hydrostatic pressure, which *opposes* the movement of water out of the capillary; and (4) the interstitial colloidal osmotic pressure, which *pulls* water out of the capillary into the interstitial spaces.[1–3,5] Normally, the combination of these four forces is such that only a small excess of fluid remains in the interstitial compartment. This excess fluid is removed from the interstitium by the lymphatic system and returned to the systemic circulation.

Capillary filtration refers to the movement of water through capillary pores because of a mechanical, rather than an osmotic, force. The capillary filtration pressure (about 30 to 40 mm Hg at the arterial end, 10 to 15 mm Hg at the venous end, and 25 mm Hg in the middle), sometimes called the *capillary hydrostatic pressure,* is the pressure pushing water out of the capillary into the interstitial spaces. It reflects the arterial and venous pressures, the precapillary (arterioles) and postcapillary (venules) resistances, and the force of gravity.[2] A rise in arterial or venous pressure increases capillary pressures throughout the body, whereas the force of gravity increases the capillary pressure in dependent parts of the body. In a person who is standing absolutely still, the weight of blood in the vascular column causes an increase of 1 mm Hg in pressure for every 13.6 mm of distance from the heart.[2] This pressure results from the weight of water and is therefore called *hydrostatic pressure*. In the adult who is standing absolutely still, the pressure in the veins of the feet can reach 90 mm Hg.

The *capillary colloidal osmotic pressure* (about 28 mm Hg) is the osmotic pressure generated by the plasma proteins that are too large to pass through the pores of the capillary wall.[2] The term *colloidal osmotic pressure* differentiates this type of osmotic pressure from the osmotic pressure that develops at the cell membrane from the presence of electrolytes and nonelectrolytes. Because plasma proteins do not normally penetrate the capillary pores and because their concentration is greater in the plasma than in the interstitial fluids, it is capillary colloidal osmotic pressure that pulls fluids back into the capillary.

The interstitial fluid pressure (about –3 mm Hg) and interstitial colloidal osmotic pressure (about 8 mm Hg) contribute to movement of water into and out of the interstitial spaces.[2] The interstitial hydrostatic fluid pressure, which is normally negative, contributes to the outward movement of water into the interstitial spaces. The interstitial colloidal osmotic pressure, which reflects the small amount of plasma proteins that normally escape into the interstitial spaces from the capillary, also pulls water out of the capillary into the tissue spaces.

The lymphatic system represents an accessory route whereby fluid from the interstitial spaces can return to the circulation. More importantly, the lymphatic system provides a means for removing plasma proteins and osmotically active particulate matter from the tissue spaces, neither of which can be reabsorbed into the capillaries.

Edema

Edema can be defined as palpable swelling produced by an increase in interstitial fluid volume. Edema does not become evident until the interstitial volume has been increased by 2.5 to 3 L.[3] The physiologic mechanisms that contribute to edema formation include factors that (1) increase the capillary filtration pressure, (2) decrease the capillary colloidal osmotic pressure, (3) increase capillary permeability, or (4) produce obstruction to lymph flow. The causes of edema are summarized in Chart 8-1.

Increased Capillary Filtration Pressure. As the capillary filtration pressure rises, the movement of vascular fluid into the interstitial spaces increases. Among the factors that increase capillary pressure are (1) increased arterial pressure or decreased resistance to flow through the precapillary sphincters, (2) an increase in venous pressure or increased resistance to outflow at the postcapillary sphincter, and (3) capillary distention due to increased vascular volume.

Edema can be either localized or generalized. The localized edema that occurs with urticaria (i.e., hives) or other allergic or inflammatory conditions results from the release of histamine and other inflammatory mediators that cause dilation of the precapillary sphincters and arterioles that supply the swollen lesions. Thrombophlebitis obstructs venous flow, producing an elevation of venous pressure and edema of the affected part, usually one of the lower extremities.

Generalized edema (termed *anasarca*) is generally the result of increased vascular volume. The swelling of hands and feet that occurs in healthy persons during hot weather is an example of edema that is caused by the vasodilation of superficial blood vessels along with sodium and water retention. Generalized edema is common in conditions such as congestive heart failure that produce fluid retention and venous congestion. In right-sided heart failure, blood dams up throughout the entire venous system, causing organ congestion and edema of the dependent extremities (see Chapter 20).

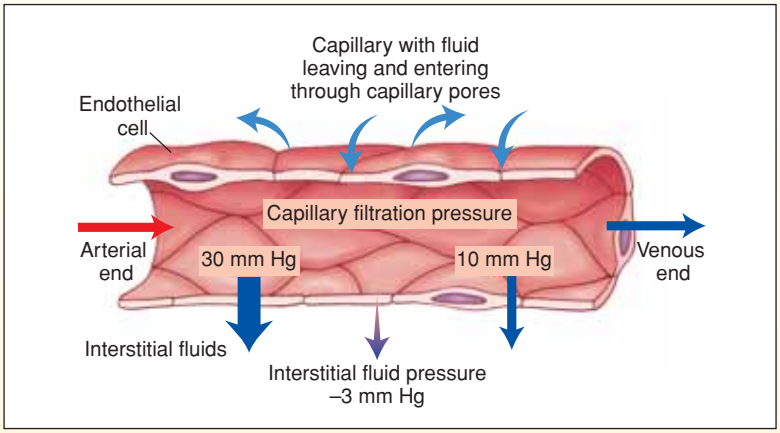
Because of the effects of gravity, edema resulting from increased capillary pressure commonly causes fluid to accumulate in the dependent parts of the body, a condition

UNDERSTANDING → Capillary Fluid Exchange

Movement of fluid between the vascular compartment and the interstitial fluid compartment surrounding the body cells occurs at the capillary level. The direction and amount of fluid that flows across the capillary wall are determined by: (1) the hydrostatic pressure of the two compartments, (2) the colloidal osmotic pressures of the two compartments, and (3) the removal of excess fluid and osmotically active particles from the interstitial spaces by the lymphatic system.

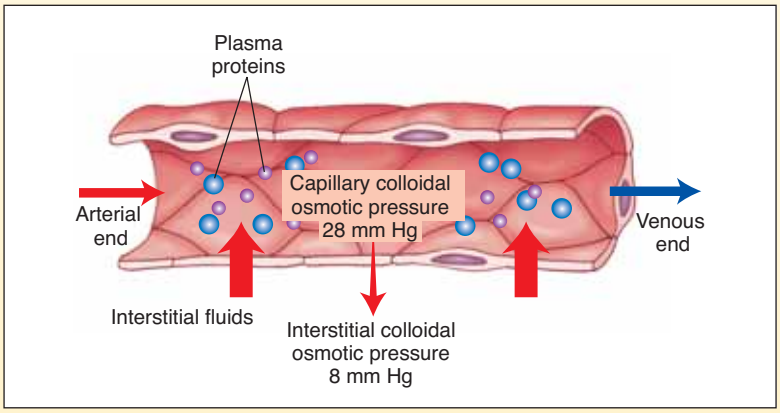
1

Hydrostatic Pressure. The hydrostatic pressure is the pushing force exerted by a fluid. Inside the capillaries, the hydrostatic pressure is the same as the capillary filtration pressure, about 30 mm Hg at the arterial end and 10 mm Hg at the venous end. The interstitial fluid pressure is the force of fluid in the interstitial spaces pushing against the outside of the capillary wall. Evidence suggests that the interstitial pressure is slightly negative (−3 mm Hg), contributing to the outward movement of fluid from the capillary.



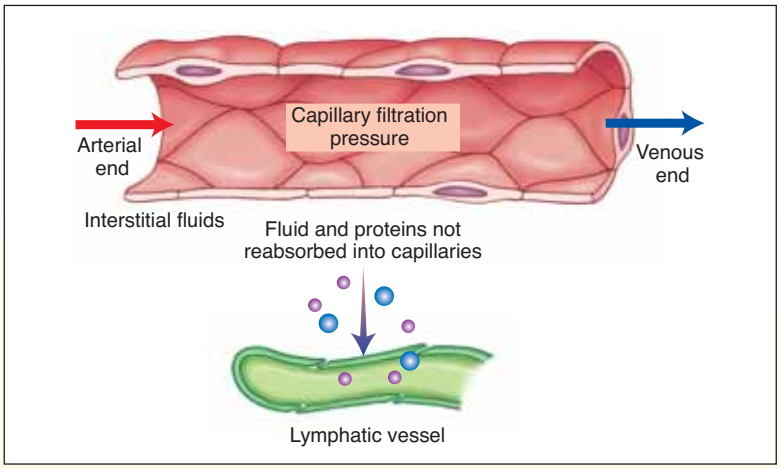
2

Colloidal Osmotic Pressure. The colloidal osmotic pressure is the pulling force created by the presence of evenly dispersed particles, such as the plasma proteins, that cannot pass through the pores of the capillary membrane. The capillary colloidal osmotic pressure is normally about 28 mm Hg throughout the length of the capillary bed. The interstitial colloidal osmotic pressure (about 8 mm Hg) represents the pulling pressure exerted by the small amounts of plasma proteins that leak through the pores of the capillary wall into the interstitial spaces. The capillary colloidal osmotic pressure, which is greater than both the hydrostatic pressure at the venous end of the capillary and the interstitial colloidal osmotic pressure, is largely responsible for the movement of fluid back into the capillary.



3

Lymph Drainage. The lymphatic system represents an accessory system by which fluid can be returned to the circulatory system. Normally the forces moving fluid out of the capillary into the interstitium are greater than those returning fluid to the capillary. Any excess fluids and osmotically active plasma proteins that may have leaked into the interstitium are picked up by vessels of the lymphatic system and returned to the circulation. Without the function of the lymphatic system, excessive amounts of fluid would accumulate in the interstitial spaces.



referred to as *dependent edema*. For example, edema of the ankles and feet becomes more pronounced during prolonged periods of standing.

Decreased Capillary Colloidal Osmotic Pressure. Plasma proteins exert the osmotic force needed to pull fluid back into the capillary from the tissue spaces. The plasma proteins constitute a mixture of proteins, including albumin, globulins, and fibrinogen. Albumin, the smallest of the plasma proteins, has a molecular weight of 69,000; globulins have molecular weights of approximately 140,000; and fibrinogen has a molecular weight of 400,000.[2] Because of its lower molecular weight, 1 g of albumin has approximately twice as many osmotically active molecules as 1 g of globulin and almost six times as many osmotically active molecules as 1 g of fibrinogen. Also, the concentration of albumin (approximately 4.5 g/dL) is greater than that of the globulins (2.5 g/dL) and fibrinogen (0.3 mg/dL).

Edema caused by decreased capillary colloidal osmotic pressure usually is the result of inadequate production or abnormal loss of plasma proteins, mainly albumin. The plasma proteins are synthesized in the liver. In persons with severe liver failure, the impaired synthesis of albumin results in a decrease in colloidal osmotic pressure. In starvation and malnutrition, edema develops because there is a lack of amino acids for plasma protein synthesis. The most common site of plasma protein loss is the kidney. In kidney diseases such as glomerulonephritis, the glomerular capillaries become permeable to the plasma proteins, particularly albumin, which is the smallest of the proteins (see Chapter 25). When this occurs, large amounts of albumin are filtered out of the blood and lost in the urine. An excessive loss of plasma proteins also occurs when large areas of skin are injured or destroyed. Edema is a common problem during the early stages of a burn, resulting from capillary injury and loss of plasma proteins.[6]

Because the plasma proteins are evenly distributed throughout the body and are not affected by the force of gravity, edema that is caused by a decrease in capillary colloidal osmotic pressure tends to produce generalized edema rather than dependent edema. There is swelling of the face as well as the legs and feet.

Increased Capillary Permeability. When the capillary pores become enlarged or the integrity of the capillary wall is damaged, capillary permeability is increased. When this occurs, plasma proteins and other osmotically active particles leak into the interstitial spaces, increasing the tissue colloidal osmotic pressure and thereby contributing to the accumulation of interstitial fluid. Among the conditions that increase capillary permeability are burn injury, capillary congestion, inflammation, and immune responses.

Obstruction of Lymphatic Flow. Osmotically active plasma proteins and other large particles that cannot be reabsorbed through the pores in the capillary membrane rely on the lymphatic system for movement back into the circulatory system. Edema due to impaired lymph flow is commonly referred to as *lymphedema*. Malignant involvement of lymph structures and removal of lymph nodes at the time of cancer surgery are common causes of lymphedema. Another cause of lymphedema is infection and trauma involving the lymphatic channels and lymph nodes.

CHART 8-1 Causes of Edema

Increased Capillary Pressure

Increased vascular volume
- Heart failure
- Kidney disease
- Premenstrual sodium retention
- Pregnancy
- Environmental heat stress
- Thiazolidinedione (e.g., pioglitazone, rosiglitazone) therapy

Venous obstruction
- Liver disease with portal vein obstruction
- Acute pulmonary edema
- Venous thrombosis (thrombophlebitis)

Decreased arteriolar resistance
- Calcium channel–blocking drug responses

Decreased Colloidal Osmotic Pressure

Increased loss of plasma proteins
- Protein-losing kidney diseases
- Extensive burns

Decreased production of plasma proteins
- Liver disease
- Starvation, malnutrition

Increased Capillary Permeability

Inflammation
Allergic reactions (e.g., hives, angioneurotic edema)
Malignancy (e.g., ascites, pleural effusion)
Tissue injury and burns

Obstruction of Lymphatic Flow

Malignant obstruction of lymphatic structures
Surgical removal of lymph nodes

Manifestations. The effects of edema are determined largely by its location. Edema of the brain, larynx, or lungs is an acute, life-threatening condition. Although not life threatening, edema may interfere with movement, limiting joint motion. Swelling of the ankles and feet often is insidious in onset and may or may not be associated with disease. At the tissue level, edema increases the distance for diffusion of oxygen, nutrients, and wastes. Edematous tissues usually are more susceptible to injury and development of ischemic tissue damage, including pressure ulcers. Edema can also compress blood vessels. For example, the skin of a severely swollen finger can act as a tourniquet, shutting off the blood flow to the finger. Edema can also be disfiguring, causing psychological effects and disturbances in self-concept. It can also create problems with obtaining proper-fitting clothing and shoes.

Pitting edema occurs when the accumulation of interstitial fluid exceeds the absorptive capacity of the tissue gel. In this form of edema, the tissue water becomes mobile and can be translocated with pressure exerted by a finger. *Nonpitting edema* usually reflects a condition in which plasma proteins have accumulated in the tissue spaces and coagulated. It is seen most commonly in areas of localized infection or trauma. The area often is firm and discolored. *Brawny edema* is a type of nonpitting edema in which the skin thickens and hardens.

Assessment and Treatment. Methods for assessing edema include daily weight, visual assessment, measurement of the affected part, and application of finger pressure to assess for pitting edema. Daily weight measurements taken at the same time each day with the same amount of clothing provides a useful index of water gain (1 L of water weighs 2.2 pounds) due to edema. Visual inspection and measurement of the circumference of an extremity can also be used to assess the degree of swelling. This is particularly useful when swelling is due to thrombophlebitis. Finger pressure can be used to assess the degree of pitting edema. If an indentation remains after the finger has been removed, pitting edema is identified. It is evaluated on a scale of +1 (minimal) to +4 (severe) (Fig. 8-5).

Distinguishing lymphedema from other forms of edema can be challenging, especially early in its course. *Papillomatosis*, a characteristic honeycomb appearance of the skin due to dilated lymph vessels that are enveloped in fibrotic tissue, distinguishes lymphedema from other edemas. Computed tomography (CT) or magnetic resonance imaging (MRI) may be used to confirm the diagnosis.[7]

Treatment of edema usually is directed toward maintaining life when the swelling involves vital structures, correcting or controlling the cause, and preventing tissue injury. Edema of the lower extremities may respond to simple measures such as elevating the feet. Diuretic therapy commonly is used to treat edema associated with an increase in ECF volume. Serum albumin levels can be measured, and albumin may be administered intravenously to raise the plasma colloidal osmotic pressure when edema is caused by hypoalbuminemia.

Elastic support stockings and sleeves increase interstitial fluid pressure and resistance to outward movement of fluid from the capillary into the tissue spaces. These support devices typically are prescribed for patients with conditions such as lymphatic or venous obstruction and

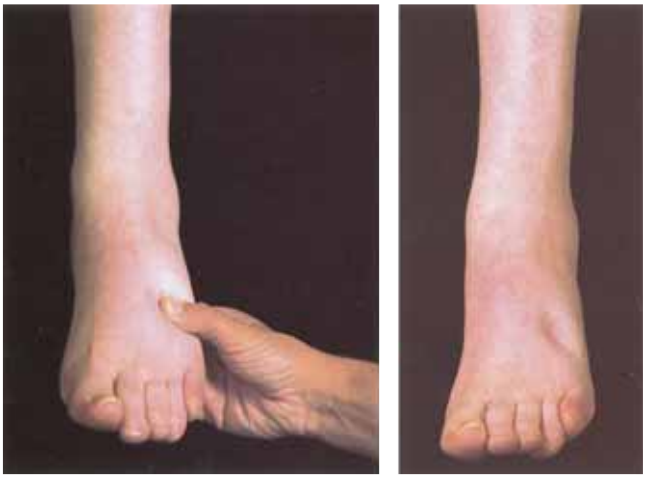


FIGURE 8-5. 3+ pitting edema of the left foot. (Used with permission from Bates B. [1995]. *Bates' guide to physical examination and history taking* [6th ed., p. 438]. Philadelphia: Lippincott Williams & Wilkins.)

are most efficient if applied before the tissue spaces have filled with fluid—in the morning, for example, before the effects of gravity have caused fluid to move into the ankles. Moderate to severe lymphedema is usually treated with light-pressure massage designed to increase lymph flow by encouraging opening and closing of lymph vessel valves; compression garments or pneumatic compression pumps; range-of-motion exercises; and scrupulous skin care to prevent infection.[7]

Third-Space Accumulation

Third spacing represents the loss or trapping of ECF into the transcellular space. The serous cavities are part of the transcellular compartment (i.e., third space) located in strategic body areas where there is continual movement of body structures—the pericardial sac, the peritoneal cavity, and the pleural cavity. The exchange of ECF between the capillaries, the interstitial spaces, and the transcellular space of the serous cavity uses the same mechanisms as capillaries elsewhere in the body. The serous cavities are closely linked with lymphatic drainage systems. The milking action of the moving structures, such as the lungs, continually forces fluid and plasma proteins back into the circulation, keeping these cavities empty. Any obstruction to lymph flow causes fluid accumulation in the serous cavities. As with edema fluid, third-space fluids represent an accumulation or trapping of body fluids that contribute to body weight but not to fluid reserve or function.

The prefix *hydro-* may be used to indicate the presence of excessive fluid, as in *hydrothorax*, which means excessive fluid in the pleural cavity. The accumulation of fluid in the peritoneal cavity is called *ascites*. The transudation of fluid into the serous cavities is also referred to as *effusion*. Effusion can contain blood, plasma proteins, inflammatory cells (i.e., pus), and extracellular fluid.

In summary, body fluids, which contain water and electrolytes, are distributed between the ICF and ECF compartments of the body. Two thirds of body fluids are contained in the body cells of the ICF compartment, and one third is contained in the vascular system, interstitial spaces, and third-space areas of the ECF compartment. The ICF has high concentrations of potassium, calcium, phosphate, and magnesium, and the ECF has high concentrations of sodium, chloride, and bicarbonate. *Diffusion* is the movement of electrolytes and nonelectrolytes down a concentration gradient and across the cell membranes separating the ICF and ECF compartments. Water crosses the cell membrane by *osmosis,* using special protein channels called *aquaporins*. Water moves from the side of the membrane having a lesser number of particles and greater concentration of water to the side having a greater number of particles and lesser concentration of water. The osmotic tension or effect that a solution exerts on cell volume in terms of causing the cell to swell or shrink is called *tonicity*.

Edema represents an increase in interstitial fluid volume. The physiologic mechanisms that contribute to the development of edema include factors that increase capillary filtration pressure, decrease capillary colloidal osmotic pressure, increase capillary permeability, or obstruct lymphatic flow. The effect that edema exerts on body function is determined by its location. Edema of the brain, larynx, or lungs is an acute, life-threatening situation, whereas swelling of the ankles and feet can be a normal discomfort that accompanies hot weather. Fluid can also accumulate in the transcellular compartment—the joint spaces, the pericardial sac, the peritoneal cavity, and the pleural cavity. Because this fluid is not easily exchanged with the rest of the ECF, it is often referred to as *third-space fluid*.

Sodium and Water Balance

Regulation of Sodium and Water Balance

The distribution of body fluids between the ICF and ECF compartments relies on the concentration of ECF sodium and water. Water provides approximately 90% to 93% of the volume of body fluids and sodium salts approximately 90% to 95% of ECF solutes. Normally, equivalent changes in sodium and water are such that the volume and osmolality of ECF are maintained within a normal range. Because it is the concentration of sodium (in milligrams per liter) that controls ECF osmolality, changes in sodium are usually accompanied by proportionate changes in water volume.

Regulation of Water Balance

Total body water (TBW) accounts for approximately 60% of body weight. Individual water content varies with the amount of adipose tissue, which is essentially water free (i.e., fat is approximately 10% water composition compared with skeletal muscle, which is 75%). In men, TBW approximates 60% of body weight during young adulthood and decreases to approximately 50% in old age; in young women it is approximately 50% and in elderly women approximately 40%.[8] Obesity produces further decreases in TBW, sometimes reducing these levels to values as low as 30% to 40% of body weight in adults (Fig. 8-6).

Infants normally have more TBW than older children or adults. TBW constitutes approximately 75% to 80% of body weight in full-term infants and is even greater in premature infants. In addition to having proportionately more body water than adults have, infants have relatively more water in their ECF compartment. Infants have more than half of their TBW in the ECF compartment, whereas adults have only approximately a third.[9] The greater ECF water content of an infant can be explained in terms of its higher metabolic rate, its larger surface area in relation to its body mass, and its inability to concentrate its urine because of immature kidney structures. Because ECF is

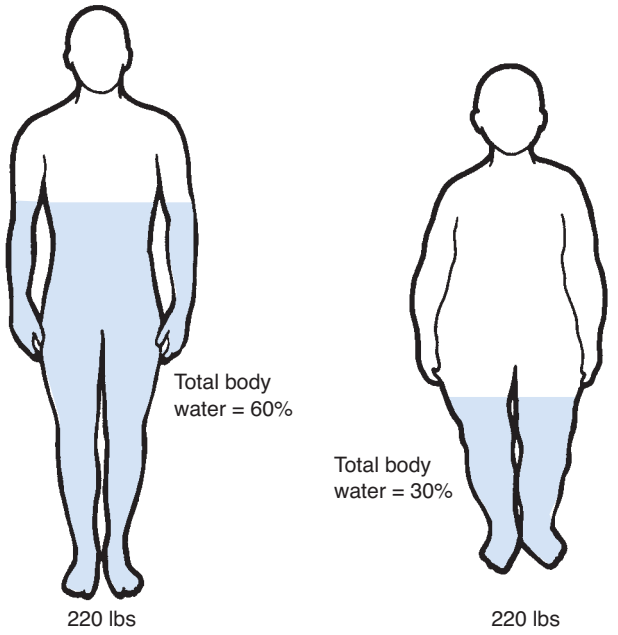


FIGURE 8-6. Body composition of a lean and an obese individual. (Adapted with permission from Statland H. [1963]. *Fluids and electrolytes in practice* [3rd ed.]. Philadelphia: J.B. Lippincott.)

more readily lost from the body, infants are more vulnerable to fluid deficit than are older children and adults. As an infant grows older, TBW decreases, and by the second year of life, the percentages and distribution of body water approach those of an adult.[9]

Gains and Losses. Regardless of age, all healthy persons require approximately 100 mL of water per 100 calories metabolized for dissolving and eliminating metabolic wastes. This means that a person who expends 1800 calories for energy requires approximately 1800 mL of water for metabolic purposes. The metabolic rate increases with fever, rising by approximately 12% for every 1°C (7% for every 1°F) increase in body temperature.[2] Fever also increases the respiratory rate, resulting in additional loss of water vapor through the lungs.

The main source of water gain is through oral intake and metabolism of nutrients. Water, including that obtained from liquids and solid foods, is absorbed from the gastrointestinal tract. Tube feedings and parenterally administered fluids are also a source of water gain. Metabolic processes also generate a small amount of water. The amount of water gained from these processes varies from 150 to 300 mL/day, depending on the metabolic rate.

Normally, the largest loss of water occurs through the kidneys, with lesser amounts being lost through the skin, lungs, and gastrointestinal tract. Even when oral or parenteral fluids are withheld, the kidneys continue to produce urine as a means of ridding the body of metabolic wastes. The urine output that is required to eliminate these wastes is called the *obligatory urine output*. Water losses that occur through the skin and lungs are referred to as *insensible water losses* because they occur without a person's awareness. Insensible water loss through the respiratory tract averages 300 to 400 mL/day.[2] The sources of body water gains and losses are summarized in Table 8-2.

TABLE 8-2 Sources of Body Water Gains and Losses in the Adult

Gains		Losses	
Oral intake		Urine	1500 mL
As water	1000 mL	Insensible losses	
In food	1300 mL	Lungs	300 mL
Water of oxidation	200 mL	Skin	500 mL
		Feces	200 mL
Total	2500 mL	Total	2500 mL

Regulation of Sodium Balance

Sodium is the most plentiful electrolyte in the ECF compartment with a concentration ranging from 135 to 145 mEq/L (135 to145 mmol/L). In contrast, only a small amount (10 to 14 mEq/L [10 to 14 mmol/L]) is located in the ICF compartment.

Sodium functions mainly in regulating the ECF volume. As the major cation in the ECF compartment, Na^+ and its attendant anions (Cl^- and HCO_3^-) account for approximately 90% to 95% of the osmotic activity in the ECF. Serum osmolality (normal range, 275 to 295 mOsm/kg) usually changes with changes in serum sodium concentration. Because sodium is part of the sodium bicarbonate molecule, it is important in regulating acid-base balance, and as a current-carrying ion, it contributes to the function of the nervous system and other excitable tissue.

Gains and Losses. Sodium normally enters the body through the gastrointestinal tract and is eliminated by the kidneys or lost from the gastrointestinal tract or skin. Sodium intake normally is derived from dietary sources. Body needs for sodium usually can be met by as little as 500 mg/day. Dietary intake, which frequently exceeds the amount needed by the body, is often influenced by culture and food preferences rather than need. As package labels indicate, many commercially prepared foods and soft drinks contain considerable amounts of sodium. Other sources of sodium are intravenous saline infusions and medications that contain sodium.

Most sodium losses occur through the kidney. The kidneys are extremely efficient in regulating sodium output, and when sodium intake is limited or conservation of sodium is needed, the kidneys are able to reabsorb almost all the Na^+ that has been filtered by the glomerulus. This results in essentially sodium-free urine. Conversely, urinary losses of sodium increase as intake increases.

Usually, less than 10% of sodium intake is lost through the gastrointestinal tract and skin. Although the sodium concentration of fluids in the upper part of the

gastrointestinal tract approaches that of the extracellular fluid, sodium is reabsorbed as the fluids move through the lower part of the bowel, so that the concentration of sodium in the stool is only approximately 40 mEq/L. Sodium losses increase with conditions such as vomiting, diarrhea, fistula drainage, and gastrointestinal suction that remove sodium from the stomach or small intestine.

Sodium leaves the skin by way of the sweat glands. Sweat is a hypotonic solution containing both sodium and chloride. Although sodium losses due to sweating are usually negligible, they can increase greatly during exercise and periods of exposure to a hot environment. A person who sweats profusely can lose up to 15 to 30 g of sodium each day for first few days of exposure to a hot environment. This amount usually drops to less than 3 to 5 g a day after 4 to 6 weeks of acclimatization.[2]

Mechanisms of Water and Sodium Regulation

The major factor regulating water and sodium balance is the maintenance of the *effective circulating volume* (also termed the *effective arterial blood volume*), which can be described as that portion of the ECF that fills the vascular compartment and is "effectively" perfusing the tissues.[1,10] A low effective circulating volume results in feedback mechanisms that produce an increase in renal sodium and water retention, and a high circulating volume results in feedback mechanisms that decrease sodium and water retention.

The effective circulating volume is monitored by a number of sensors that are located in both the vascular system and the kidney. These sensors are commonly referred to as *baroreceptors* because they respond to pressure-induced stretch of the vessel walls in which they are located.[1] There are baroreceptors located in the low-pressure side of the circulation (walls of the cardiac atria and large pulmonary vessels) that respond primarily to fullness of the circulation. Baroreceptors are also present in the high-pressure arterial side of the circulation (aortic arch and carotid sinus) that respond primarily to changes in the arterial pressure. The activity of both types of receptors regulates renal sodium and water elimination by modulating sympathetic nervous system outflow and antidiuretic hormone (ADH) secretion.[1] The *sympathetic nervous system* responds to changes in arterial pressure and blood volume by adjusting the glomerular filtration rate and thus the rate at which sodium is filtered from the blood. Sympathetic activity also regulates tubular reabsorption of sodium and renin release. ADH, which is secreted from the posterior pituitary glands, controls the permeability of the collecting tubules and ducts of the kidney to water, thereby regulating the amount of water that is lost in the urine. An additional mechanism that influences sodium excretion by the kidney is the *atrial natriuretic peptide* (ANP). ANP, which is released from the heart in response to atrial stretch and overfilling, increases the excretion of sodium by the distal and collecting tubules of the kidney (see Chapter 18).

Pressure-sensitive receptors in kidney, particularly in the afferent arterioles, respond directly to changes in arterial pressure through stimulation of the sympathetic nervous system and release of renin with activation of the renin-angiotensin-aldosterone system (RAAS).[11] The RAAS exerts its action through angiotensin II and aldosterone (see Chapter 18). Angiotensin II acts directly on the renal tubules to increase sodium reabsorption. It also acts to constrict renal blood vessels, thereby decreasing the glomerular filtration rate and slowing renal blood flow so that less sodium is filtered and more is reabsorbed. Angiotensin II is also a powerful regulator of *aldosterone*, a hormone secreted by the adrenal cortex. Aldosterone acts at the level of the cortical collecting tubules of the kidneys to increase sodium reabsorption while increasing potassium elimination.

Disorders of Thirst and Antidiuretic Hormone

There are two main physiologic mechanisms that contribute directly to the regulation of body water and indirectly to the regulation of sodium: thirst and ADH. Thirst is primarily a regulator of water intake and ADH a regulator of water output. Both mechanisms respond to changes in ECF osmolality and the effective circulating volume.

Disorders of Thirst

Like appetite and eating, thirst and drinking are two separate entities.[1,2,12] Thirst is the conscious sensation of the need to obtain and drink fluids high in water content. Drinking of water or other fluids often occurs as the result of habit or for reasons other than those related to thirst. Most people drink without being thirsty, and water is consumed before it is needed. As a result, thirst is basically an emergency response. It usually occurs only when the need for water has not been anticipated.

Thirst is controlled by the thirst center in the hypothalamus. There are two stimuli for true thirst based on water need: (1) cellular dehydration caused by an increase in ECF osmolality and (2) a decrease in blood volume, which may or may not be associated with a decrease in serum osmolality. Sensory neurons, called *osmoreceptors*, which are located in or near the thirst center in the hypothalamus, respond to changes in ECF osmolality by swelling or shrinking (Fig. 8-7). Thirst normally develops when there is as little as a 1% to 2% change in serum osmolality.[12] The previously described stretch receptors in the vascular system that monitor the effective circulating volume also aid in the regulation of thirst. Thirst is one of the earliest symptoms of hemorrhage and is often present before other signs of blood loss appear.

A third important stimulus for thirst is angiotensin II, which becomes increased in response to low blood volume and low blood pressure. The renin-angiotensin mechanism contributes to nonosmotic thirst. This system is considered a backup system for thirst should other systems fail. Because it is a backup system, it probably does not contribute to the regulation of normal thirst. However, elevated levels of angiotensin II may lead to thirst in conditions, such as chronic kidney disease and congestive heart failure, in which renin levels may be elevated.

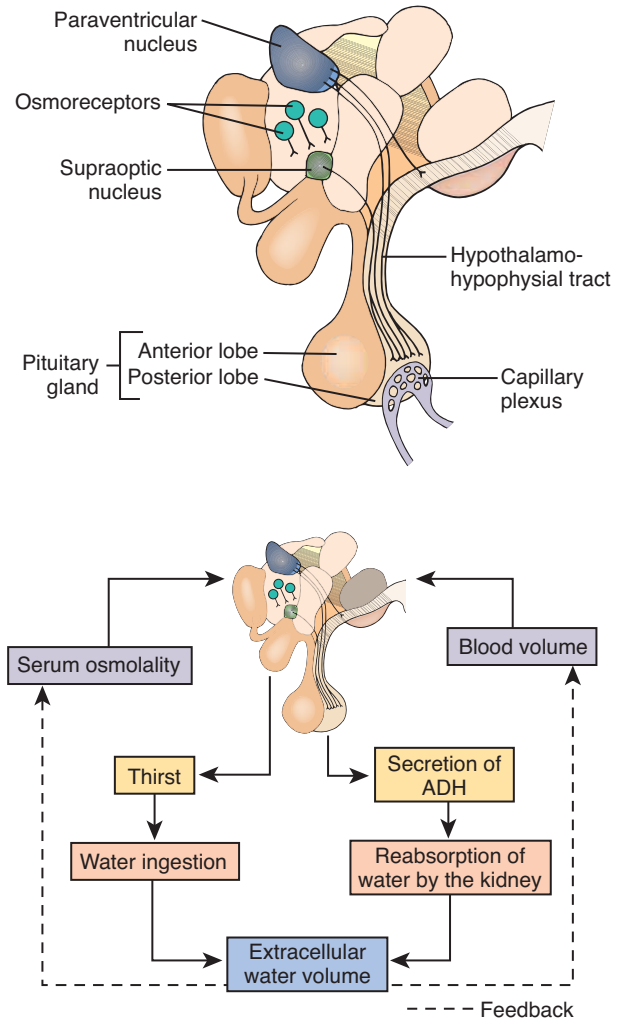


FIGURE 8-7. (*Top*) Sagittal section through the pituitary and anterior hypothalamus. Antidiuretic hormone (ADH) is formed primarily in the supraoptic nucleus and to a lesser extent in the paraventricular nucleus of the hypothalamus. It is then transported down the hypothalamohypophysial tract and stored in secretory granules in the posterior pituitary, where it can be released into the blood. (*Bottom*) Pathways for regulation of extracellular water volume by thirst and antidiuretic hormone.

Dryness of the mouth, such as the thirst a lecturer experiences during speaking, produces a sensation of thirst that is not necessarily associated with the body's hydration status. Thirst sensation also occurs in those who breathe through their mouths, such as smokers and persons with chronic respiratory disease or hyperventilation syndrome.

Hypodipsia. Hypodipsia represents a decrease in the ability to sense thirst. It is commonly associated with lesions in the area of the hypothalamus (e.g., head trauma, meningiomas, occult hydrocephalus, subarachnoid hemorrhage). There is also evidence that thirst is decreased and water intake reduced in elderly persons, despite higher serum sodium and osmolality levels.[13,14] The inability to perceive and respond to thirst is compounded in elderly persons who have had a stroke and may be further influenced by confusion, sensory deficits, and motor disturbances.

Polydipsia. Polydipsia, or excessive thirst, is normal when it accompanies conditions of water deficit. Increased thirst and drinking behavior can be classified into three categories: (1) symptomatic or true thirst, (2) inappropriate or false thirst that occurs despite normal levels of body water and serum osmolality, and (3) compulsive water drinking. *Symptomatic thirst* develops when there is a loss of body water and resolves after the loss has been replaced. Among the most common causes of symptomatic thirst are water losses associated with diarrhea, vomiting, diabetes mellitus, and diabetes insipidus. *Inappropriate* or *excessive thirst* may persist despite adequate hydration. It is a common complaint in persons with congestive heart failure and chronic kidney disease. Although the cause of thirst in these persons is unclear, it may result from increased angiotensin levels. Thirst is also a common complaint in persons with dry mouth caused by decreased salivary function or treatment with drugs with an anticholinergic action (e.g., antihistamines, atropine) that lead to decreased salivary flow.

Psychogenic polydipsia involves compulsive water drinking and is usually seen in persons with psychiatric disorders, most commonly schizophrenia. Persons with the disorder drink large amounts of water and excrete large amounts of urine. The cause of excessive water drinking in these persons is uncertain. It has been suggested that it may share the same pathology as the psychosis because persons with the disorder often increase their water drinking during periods of exacerbation of their psychotic symptoms.[15] The condition may be compounded by antipsychotic medications that increase ADH levels and interfere with water excretion by the kidneys. Cigarette smoking, which is common among persons with psychiatric disorders, also stimulates ADH secretion. Excessive water ingestion coupled with impaired water excretion (or rapid ingestion at a rate that exceeds renal excretion) in persons with psychogenic polydipsia can lead to water intoxication (see section on hyponatremia). Treatment usually consists of water restriction and behavioral measures aimed at decreasing water consumption. Measurements of body weight can be used to provide an estimate of water consumption.[16]

Disorders of Antidiuretic Hormone

The reabsorption of water by the kidneys is regulated by ADH, also known as *vasopressin*.[1,2,17] Because the human hormone contains arginine, it is often referred to as *arginine vasopressin* (AVP) to distinguish it from its analogs. ADH is a small peptide, nine amino acids in length, that is synthesized by cells in the supraoptic and paraventricular nuclei of the hypothalamus and then transported along a neural pathway (i.e., hypothalamic-hypophysial tract) to the posterior pituitary gland, where it is stored. When the supraoptic and paraventricular nuclei in the hypothalamus are stimulated by increased serum osmolality or other factors, nerve impulses travel down the hypothalamic-hypophysial tract to the posterior pituitary

gland, causing the stored ADH to be released into the circulation (see Fig. 8-7).

As with thirst, ADH levels are controlled by ECF volume and osmolality. Osmoreceptors in the hypothalamus sense changes in ECF osmolality and stimulate the production and release of ADH (Fig. 8-7). A small increase in serum osmolality of 1% is sufficient to cause ADH release. Likewise, stretch receptors that are sensitive to changes in blood pressure and the effective circulating volume contribute to the regulation of ADH release (i.e., nonosmotic ADH secretion). A blood volume decrease of 5% to 10% produces a maximal increase in ADH levels. As with many other homeostatic mechanisms, acute conditions produce greater changes in ADH levels than do chronic conditions.

ADH exerts its effects through three types of vasopressin (V) receptors—V_1, V_2, and V_3 receptors.[17] V_1 receptors, which are located in vascular smooth muscle, cause vasoconstriction—hence the name *vasopressin*. The distal and collecting tabules of the kidney express V_2 receptors, which mediate water retention. V_3 receptors are mainly found in the central nervous system (CNS), especially in the anterior pituitary gland, where their stimulation modulates corticotrophin release.[17] The V_2 receptors in the kidney are responsible for maintaining the osmolality of body fluids. ADH acts on the luminal membranes of the distal and collecting tubules to increase their permeability to water. In the presence of ADH, highly permeable water channels called *aquaporins* are inserted into the membrane.[17] The increased water permeability allows water to be reabsorbed from the tubular cells and makes the urine more concentrated or hyperosmotic (see understanding urine concentration, Chapter 24).

The abnormal synthesis and release of ADH occurs in a number of stress situations. Severe pain, nausea, trauma, surgery, certain anesthetic agents, and some narcotics (e.g., morphine and meperidine) increase ADH levels. Among the drugs that affect ADH are nicotine, which stimulates its release, and alcohol, which inhibits it. Two important conditions alter ADH levels: diabetes insipidus and the syndrome of inappropriate secretion of ADH.

Diabetes Insipidus. Diabetes insipidus (DI) is caused by a deficiency of or a decreased response to ADH.[18] Persons with DI are unable to concentrate their urine during periods of water restriction and they excrete large volumes of urine, usually 3 to 20 L/day, depending on the degree of ADH deficiency or renal insensitivity to ADH. This large urine output is accompanied by excessive thirst. As long as the thirst mechanism is normal and fluid is readily available, there is little or no alteration in the fluid levels of persons with DI. The danger arises when the condition develops in someone who is unable to communicate the need for water or is unable to secure the needed water. In such cases, inadequate fluid intake rapidly leads to increased serum osmolality and hypertonic dehydration.

There are two types of DI: neurogenic or central DI, which occurs because of a defect in the synthesis or release of ADH, and nephrogenic DI, which occurs because the kidneys do not respond to ADH.[18,19] In neurogenic DI, loss of 80% to 90% of ADH-secretory neurons is necessary before polyuria becomes evident. Most persons with neurogenic DI have an incomplete form of the disorder and retain some ability to concentrate their urine. Temporary neurogenic DI may follow traumatic head injury[20] or surgery near the hypothalamohypophysial tract. Nephrogenic DI is characterized by impairment of urine-concentrating ability and free-water conservation. It may occur as with the genetic loss of the ADH receptor,[19] lithium toxicity,[21] and electrolyte disorders such as potassium depletion or chronic hypercalcemia. Lithium and the electrolyte disorders are thought to interfere with the postreceptor actions of ADH on the permeability of the collecting ducts.

The manifestations of DI include complaints of intense thirst, especially with a craving for ice water, and polyuria, the volume of ingested fluids ranging from 2 to 20 L daily with corresponding large urine volumes. Partial DI usually presents with less intense thirst and should be suspected in persons with enuresis. DI may present with hypernatremia and dehydration, especially in persons without free access to water, or with damage to the hypothalamic thirst center and altered thirst sensation.

The management of central or neurogenic DI depends on the cause and severity of the disorder. Many persons with incomplete neurogenic DI maintain near-normal water balance when permitted to ingest water in response to thirst. Pharmacologic preparations of ADH are available for persons who cannot be managed by conservative measures. The preferred drug for treating chronic DI is desmopressin acetate (DDAVP). It usually is given orally, but is also available in parenteral and nasal forms. The oral antidiabetic agent chlorpropamide may be used to stimulate ADH release in partial neurogenic DI. It usually is reserved for special cases because of its ability to cause hypoglycemia. Both neurogenic and nephrogenic forms of DI respond partially to the thiazide diuretics (e.g., hydrochlorothiazide). These diuretics are thought to act by increasing sodium excretion by the kidneys, leading to ECF volume contraction, a decrease in the glomerular filtration rate (along with filtered load of sodium), and an increase in sodium and water reabsorption.[19]

Syndrome of Inappropriate Antidiuretic Hormone. The syndrome of inappropriate ADH (SIADH) results from a failure of the negative feedback system that regulates the release and inhibition of ADH.[22,23] In persons with this syndrome, ADH secretion continues even when serum osmolality is decreased, causing marked water retention and dilutional hyponatremia.

SIADH may occur as a transient condition, as in a stress situation, or as a chronic condition, resulting from disorders such as lung tumors. Stimuli such as surgery, pain, stress, and temperature changes are capable of stimulating ADH through the CNS. Drugs induce SIADH in different ways; some drugs are thought to increase hypothalamic production and release of ADH, and others are believed to act directly on the renal tubules to enhance the action of ADH. More chronic forms of SIADH may result from lung tumors, chest lesions, and CNS disorders.

Tumors, particularly bronchogenic carcinomas and cancers of the lymphoid tissue, prostate, and pancreas, are known to produce and release ADH independent of normal hypothalamic control mechanisms (examples of paraneoplastic conditions are described in Chapter 7). Other intrathoracic conditions, such as advanced tuberculosis, severe pneumonia, and positive-pressure breathing, also cause SIADH. The suggested mechanism for SIADH in positive-pressure ventilation is activation of baroreceptors (e.g., aortic baroreceptors, cardiopulmonary receptors) that respond to marked changes in intrathoracic pressure. Disease and injury to the CNS can cause direct pressure on or direct involvement of the hypothalamic–posterior pituitary structures. Examples include brain tumors, hydrocephalus, head injury, meningitis, and encephalitis. Human immunodeficiency virus (HIV) infection is an established cause of SIADH (e.g., related to associated infections, tumors, drugs, etc.).

The manifestations of SIADH are those of dilutional hyponatremia (to be discussed). Urine output decreases despite adequate or increased fluid intake. Urine osmolality is high and serum osmolality is low. Hematocrit and the serum sodium and BUN levels are all decreased because of the expansion of the ECF volume. The severity of symptoms is usually related to the extent of sodium depletion and water intoxication.[22,23]

The treatment of SIADH depends on its severity. In mild cases, treatment consists of fluid restriction. If fluid restriction is not sufficient, diuretics such as mannitol and furosemide (Lasix) may be given to promote diuresis and free-water clearance. Lithium and the antibiotic demeclocycline inhibit the action of ADH on the renal collecting ducts and sometimes are used in treating the disorder. In cases of severe water intoxication, a hypertonic (e.g., 3%) sodium chloride solution may be administered intravenously. The recently developed antagonists to the antidiuretic action of ADH (aquaretics) offer a new therapeutic approach to the treatment of euvolemic hyponatremia.[24] These agents (e.g., conivaptan) are specific ADH V_2 receptor antagonists and result in aquaresis (i.e., the electrolyte-sparing excretion of free water).

Disorders of Water and Sodium Balance

Disorders of water and sodium can be divided into two main categories: (1) isotonic contraction or expansion of the ECF volume brought about by proportionate changes in sodium and water, and (2) hypotonic dilution or hypertonic concentration of the ECF sodium concentration brought about by disproportionate changes in sodium and water (Fig. 8-8).

Isotonic disorders usually are confined to the ECF compartment, producing a contraction (fluid volume deficit) or expansion (fluid volume excess) of the interstitial and vascular fluids. Disorders of sodium concentration produce a change in the osmolality of the ECF with movement of water from the ECF compartment into the ICF compartment (hyponatremia) or from the ICF compartment into the ECF fluid compartment (hypernatremia).

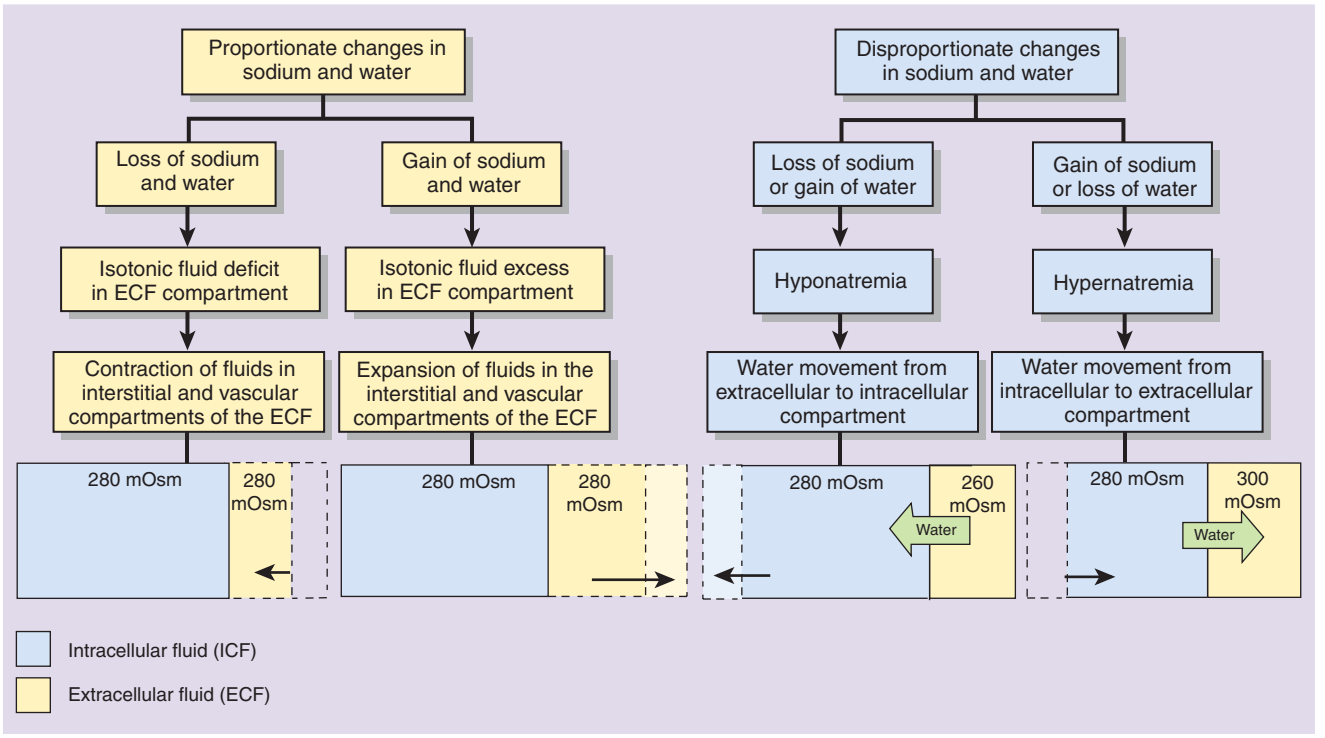


FIGURE 8-8. Effect of isotonic fluid excess and deficit and of hyponatremia and hypernatremia on movement of water between the extracellular fluid (ECF) and intracellular fluid (ICF) compartment.

Sodium and Water Balance

- It is the amount of water and its effect on sodium concentration in the ECF that serves to regulate the distribution of fluid between the ICF and the ECF compartments.
- Isotonic changes in body fluids that result from proportionate gains or losses of sodium and water are largely confined to the ECF compartment. Many of the manifestations of isotonic fluid deficit or excess reflect changes in vascular and interstitial fluid volume.
- Hyponatremia or hypernatremia that is brought about by disproportionate losses or gains in sodium or water exerts its effects on the ICF compartment, causing water to move in or out of body cells. Many of the manifestations of changes in sodium concentration reflect changes in the intracellular volume of cells, particularly those in the nervous system.

Isotonic Fluid Volume Deficit

Fluid volume deficit is characterized by a decrease in the ECF, including the circulating blood volume. The term *isotonic fluid volume deficit* is used to differentiate the type of fluid deficit in which there are proportionate losses in sodium and water from water deficit and the hyperosmolar state associated with hypernatremia.[25] Unless other fluid and electrolyte imbalances are present, the concentration of serum electrolytes remains essentially unchanged. When the effective circulating blood volume is compromised, the condition is often referred to as *hypovolemia*.

Isotonic fluid volume deficit results when water and electrolytes are lost in isotonic proportions. It is almost always caused by a loss of body fluids and is often accompanied by a decrease in fluid intake. This form of volume loss may follow a variety of disorders, including the loss of gastrointestinal fluids, as would be found in gastrointestinal suction, fistulas, drainage tube losses, and severe vomiting or diarrhea; polyuria, as occurs following osmotic diuresis or injudicious use of diuretic therapy; sweating due to fever and exercise; or endocrine disorders, such as adrenal insufficiency, in which reduced levels of aldosterone cause sodium to be lost in the urine (see Chapter 32). Third-space losses cause sequestering of ECF in the serous cavities, extracellular spaces in injured tissues, or lumen of the gut.

Manifestations. The manifestations of fluid volume deficit reflect a decrease in ECF volume. They include thirst, loss of body weight, signs of water conservation by the kidney, impaired temperature regulation, and signs of reduced interstitial and vascular volumes (Table 8-3).

A loss in fluid volume is accompanied by a decrease in body weight. One liter of water weighs 1 kg (2.2 lb). A mild ECF deficit exists when weight loss equals 2% of body weight. In a person who weighs 68 kg (150 lb), this percentage of weight loss equals 1.4 L of water. A moderate deficit equates to a 5% loss in weight and a severe deficit to an 8% or greater loss in weight.[9] To be accurate,

TABLE 8-3 Manifestations of Isotonic Fluid Volume Deficit and Excess

Fluid Volume Deficit	Fluid Volume Excess
Acute Weight Loss (% body weight)	***Acute Weight Gain (% body weight)***
Mild fluid volume deficit: 2%	Mild fluid volume excess: 2%
Moderate fluid volume deficit: 5%	Moderate fluid volume excess: 5%
Severe fluid volume deficit: >8%	Severe fluid volume excess: >8%
Signs of Compensatory Mechanisms	
Increased thirst	
Increased ADH: oliguria and high urine-specific gravity	
Decreased Interstitial Fluid Volume	***Increased Interstitial Fluid Volume***
Decreased skin and tissue turgor	Edema
Dry mucous membranes	
Sunken and soft eyeballs	
Depressed fontanel in infants	
Decreased Vascular Volume	***Increased Vascular Volume***
Postural hypotension	Full and bounding pulse
Weak, rapid pulse	Venous distention
Decreased vein filling	Pulmonary edema (severe excess)
Hypotension and shock (severe deficit)	Shortness of breath
	Crackles
	Dyspnea
	Cough

ADH, antidiuretic hormone.

weight must be measured at the same time each day with the person wearing the same amount of clothing. Because the ECF is trapped in the body in persons with third-space losses, their body weight may not decrease.

Thirst is a common symptom of fluid deficit, although it is not always present in early stages of isotonic fluid deficit. It develops as the effective circulatory volume decreases to a point sufficient to stimulate the thirst mechanism. Urine output decreases and urine osmolality and specific gravity increase as ADH levels rise because of a decrease in vascular volume. Although there is an isotonic loss of fluid from the vascular compartment, blood components such as red blood cells and BUN become more concentrated.

The fluid content of body tissues decreases as fluid is removed from the interstitial spaces. The eyes assume a sunken appearance and feel softer than normal as the fluid content in the anterior chamber of the eye is decreased. Fluids add resiliency to the skin and underlying tissues that is referred to as *tissue turgor*. Tissue turgor is assessed by pinching a fold of skin between the thumb and forefinger. The skin should immediately return to its original configuration when the fingers are released. A loss of 3% to 5% of body water in children causes the resiliency of the skin to be lost, and the tissue remains elevated for several seconds.[9] Decreased tissue turgor is less predictive of fluid deficit in older persons (>65 years) because of the loss of tissue elasticity. In infants, fluid deficit may be evidenced by depression of the anterior fontanel due to a decrease in cerebrospinal fluid.

Arterial and venous volumes decline during periods of fluid deficit, as does filling of the capillary circulation. As the volume in the arterial system declines, the blood pressure decreases, the heart rate increases, and the pulse becomes weak and thready. Postural hypotension (a drop in blood pressure on standing) is an early sign of fluid deficit. On the venous side of the circulation, the veins become less prominent. When volume depletion becomes severe, signs of hypovolemic shock and vascular collapse appear (see Chapter 20).

Diagnosis and Treatment. Diagnosis of fluid volume deficit is based on a history of conditions that predispose to sodium and water losses, weight loss, and observations of altered physiologic function indicative of decreased fluid volume. Intake and output measurements afford a means for assessing fluid balance. However, these measurements may not represent actual losses and gains, largely because accurate measurements of intake and output often are difficult to obtain and insensible losses are difficult to estimate.

Measurement of heart rate and blood pressure provides useful information about vascular volume. A simple test to determine venous refill time consists of compressing the distal end of a vein on the dorsal aspect of the hand when it is not in the dependent position. The vein is then emptied by "milking" the blood toward the heart. The vein should refill almost immediately when the occluding finger is removed. In the case of decreased venous volume, as occurs in fluid deficit, venous refill time increases. Capillary refill time is also increased. Capillary refill can be assessed by applying pressure to a fingernail for 5 seconds and then releasing the pressure and observing the time (normally 1 to 2 seconds) that it takes for the color to return to normal.[9]

Treatment of fluid volume deficit consists of fluid replacement and measures to correct the underlying cause. Usually, isotonic electrolyte solutions are used for fluid replacement. Acute hypovolemia and hypovolemic shock can cause renal damage; therefore, prompt assessment of the degree of fluid deficit and adequate measures to resolve the deficit and treat the underlying cause are essential.

Isotonic Fluid Volume Excess

Fluid volume excess represents an isotonic expansion of the ECF compartment with increases in both interstitial and vascular volumes. Although increased fluid volume is usually the result of a disease condition, this is not always true. For example, a compensatory isotonic expansion of body fluids can occur in healthy persons during hot weather as a mechanism for increasing body heat loss.

Isotonic fluid volume excess almost always results from an increase in total body sodium that is accompanied by a proportionate increase in body water. Although it can occur as the result of excessive sodium intake, it is most commonly caused by a decrease in sodium and water elimination by the kidney. Among the causes of decreased sodium and water elimination are disorders of renal function, heart failure, liver failure, and corticosteroid excess.

Heart failure (see Chapter 20) produces a decrease in the effective circulating volume and renal blood flow and a compensatory increase in sodium and water retention. Persons with severe congestive heart failure maintain a precarious balance between sodium and water intake and output. Even small increases in sodium intake can precipitate a state of fluid volume excess and a worsening of heart failure. A condition called *circulatory overload* results from an increase in blood volume; it can occur during infusion of intravenous fluids or transfusion of blood if the amount or rate of administration is excessive. Liver failure (e.g., cirrhosis of the liver) impairs aldosterone metabolism and decreases effective circulating volume and renal perfusion, leading to increased salt and water retention. The corticosteroid hormones increase sodium reabsorption by the kidneys. Persons taking corticosteroid medications and those with Cushing syndrome or disease (see Chapter 32) often have problems with sodium retention.

Manifestations. Isotonic fluid volume excess is manifested by an increase in interstitial and vascular fluids. It is characterized by weight gain over a short period of time. Mild fluid volume excess represents a 2% gain in weight; moderate fluid volume excess, a 5% gain in weight; and severe fluid volume excess, a gain of 8% or more in weight (see Table 8-3).[9] The presence of edema is characteristic of isotonic fluid excess. When the fluid excess accumulates gradually, as often happens

in debilitating diseases and starvation, edema may mask the loss of tissue mass. As vascular volume increases, central venous pressure increases, leading to distended neck veins, slow-emptying peripheral veins, a full and bounding pulse, and an increase in central venous pressure. The BUN and hematocrit may decrease as a result of dilution due to expansion of the plasma volume. When excess fluid accumulates in the lungs (i.e., pulmonary edema), there are complaints of shortness of breath and difficult breathing, respiratory crackles, and a productive cough. Ascites and pleural effusion may occur with severe fluid volume excess.

Diagnosis and Treatment. Diagnosis of fluid volume excess is usually based on a history of factors that predispose to sodium and water retention, weight gain, and manifestations such as edema and cardiovascular symptoms indicative of an expanded ECF volume.

The treatment of fluid volume excess focuses on providing a more favorable balance between sodium and water intake and output. A sodium-restricted diet is often prescribed as a means of decreasing extracellular sodium and water levels. Diuretic therapy is commonly used to increase sodium elimination. When there is a need for intravenous fluid administration or transfusion of blood components, the procedure requires careful monitoring to prevent fluid overload.

Hyponatremia

Hyponatremia is commonly defined as a serum sodium concentration of less than 135 mEq/L (135 mmol/L).[26–28] It is one of the most common electrolyte disorders seen in hospitalized patients and is also common in the outpatient population, particularly in the elderly. A number of age-related events make the elderly population more vulnerable to hyponatremia, including a decrease in renal function accompanied by limitations in sodium conservation. Although older people maintain body fluid homeostasis under most circumstances, the ability to withstand environmental, drug-related, and disease-associated stresses becomes progressively limited.

Because of the effects of osmotically active particles such as glucose, hyponatremia can present as a hypotonic or hypertonic state.[27–29] *Hypertonic (translocational) hyponatremia* results from an osmotic shift of water from the ICF to the ECF, such as occurs with hyperglycemia. In this situation, the sodium in the ECF becomes diluted as water moves out of body cells in response to the osmotic effects of the elevated blood glucose level. *Hypotonic (dilutional) hyponatremia,* by far the most common type of hyponatremia, is caused by water retention. It can be classified as hypovolemic, euvolemic, or hypervolemic based on accompanying ECF fluid volumes.[26–29] Diuretic therapy, which affects both sodium and water elimination, can cause either hypovolemic or euvolemic hyponatremia.

Hypovolemic hypotonic hyponatremia occurs when water and sodium is lost, but the loss of water far exceeds the associated loss of sodium and then only the water is replaced. Among the causes of hypovolemic hyponatremia is excessive sweating in hot weather, particularly during heavy exercise, which leads to loss of salt and water. Hyponatremia develops when water, rather than electrolyte-containing liquids, is used to replace fluids lost in sweating. Another potential cause of hypovolemic hypotonic hyponatremia is the loss of sodium from the gastrointestinal tract caused by frequent gastrointestinal irrigations with distilled water. Iso-osmotic fluid loss, such as occurs in vomiting or diarrhea, does not usually lower serum sodium levels unless these losses are replaced with disproportionate amounts of orally ingested or parenterally administered water. Gastrointestinal fluid loss and ingestion of excessively diluted formula are common causes of acute hyponatremia in infants and children. Hypovolemic hypotonic hyponatremia is also a common complication of adrenal insufficiency and is attributable to a decrease in aldosterone levels. A lack of aldosterone increases renal losses of sodium and a cortisol deficiency leads to increased release of ADH with water retention.

Euvolemic or *normovolemic hypotonic hyponatremia* represents retention of water with dilution of sodium while maintaining the ECF volume within a normal range. It is usually the result of SIADH. The risk of normovolemic hyponatremia is increased during the postoperative period. During this time ADH levels are often high, producing an increase in water reabsorption by the kidney (see SIADH). Although these elevated levels usually resolve in about 72 hours, they can persist for as long as 5 days. The hyponatremia becomes exaggerated when electrolyte-free fluids (e.g., 5% glucose in water) are used for intravenous fluid replacement.

Hypervolemic hypotonic hyponatremia is seen when hyponatremia is accompanied by edema-associated disorders such as decompensated heart failure, advanced liver disease, and renal disease. Although the total body sodium is increased in heart failure, the ECV is often sensed as inadequate by the baroreceptors (i.e., relative arterial underfilling), resulting in increased ADH levels (nonosmotic ADH secretion).[4] Abuse of methylenedioxymethylamine (MDMA), also know as "ecstasy," can lead to severe neurologic symptoms, including seizures, brain edema, and herniation due to severe hyponatremia. MDMA and its metabolites have been shown to produce enhanced release of ADH from the hypothalamus.[26]

Manifestations. The manifestations of hyponatremia depend on the rapidity of onset and the severity of the sodium dilution. The signs and symptoms may be acute (refers to onset within 48 hours), as in severe water intoxication, or more insidious in onset and less severe, as in chronic hyponatremia. Because of water movement, hyponatremia produces an increase in intracellular water, which is responsible for many of the clinical manifestations of the disorder (Table 8-4). Fingerprint edema is a sign of excess intracellular water. This phenomenon is demonstrated by pressing the finger firmly over the bony surface of the sternum for 15 to 30 seconds. When excess intracellular water is present, a fingerprint similar to that observed when pressing on a piece of modeling clay is seen.[9]

TABLE 8-4 Manifestations of Hyponatremia and Hypernatremia

Hyponatremia (Hypotonic)	Hypernatremia
Laboratory Values	***Laboratory Values***
Serum sodium <135 mEq/L (135 mmol/L)	Serum sodium >145 mEq/L (145 mmol/L)
Decreased serum osmolality	Increased serum osmolality
Dilutional decrease in blood components, including hematocrit, blood urea nitrogen (BUN)	Increased concentrations of blood components, including hematocrit, BUN
	Compensatory Mechanisms
	Increased thirst
	Increased ADH with oliguria and high urine-specific gravity
	Decreased Intracellular Fluid
	Dry skin and mucous membranes
	Decreased tissue turgor
	Decreased salivation and lacrimation
Hypo-osmolality and Movement of Water into Muscle, Neural, and Gastrointestinal Tract Tissue	***Hyperosmolality and Movement of Water out of Neural Tissue***
Muscle	Headache
Muscle cramps and weakness	Disorientation and agitation
Depressed deep tendon reflexes	Decreased reflexes
Central Nervous System	Seizures and coma (severe)
Headache	***Decreased Vascular Volume***
Disorientation	Weak, rapid pulse
Lethargy	Possible impaired temperature regulation with fever
Seizures and coma (severe)	Decreased blood pressure
Gastrointestinal Tract	Vascular collapse (severe)
Anorexia, nausea, vomiting	
Abdominal cramps, diarrhea	

ADH, antidiuretic hormone.

Muscle cramps, weakness, and fatigue reflect the effects of hyponatremia on skeletal muscle function and are often early signs of hyponatremia. These effects commonly are observed in persons with hyponatremia that occurs during heavy exercise in hot weather. Gastrointestinal manifestations such as nausea and vomiting, abdominal cramps, and diarrhea may also develop.

The cells of the brain and nervous system are the most seriously affected by increases in intracellular water. Symptoms include apathy, lethargy, and headache, which can progress to disorientation, confusion, gross motor weakness, and depression of deep tendon reflexes. Seizures and coma occur when serum sodium levels reach extremely low levels. These severe effects, which are caused by cerebral edema, may be irreversible. If the condition develops slowly, signs and symptoms do not usually develop until serum sodium levels approach 120 mEq/L (120 mmol/L) in severe hyponatremia.[28] The term *water intoxication* is often used to describe the neurologic effects of acute hypotonic hyponatremia.

Diagnosis and Treatment. Diagnosis of hyponatremia is based on laboratory reports of a decreased serum sodium concentration, serum and urine osmolality, and urine sodium concentration; assessment of the person's volume status; presence of conditions that predispose to sodium loss or water retention; and signs and symptoms indicative of the disorder.

The treatment of hyponatremia is determined by the underlying cause, severity, and rapidity of onset. When hyponatremia is caused by water intoxication, limiting water intake or discontinuing medications that contribute to SIADH may be sufficient. The administration of a saline solution orally or intravenously may be needed when hyponatremia is caused by sodium deficiency. Symptomatic hyponatremia (i.e., neurologic manifestations) is often treated with hypertonic saline solution and a loop diuretic, such as furosemide, to increase water elimination. This combination allows for correction of serum sodium levels while ridding the body of excess water. The ADH V_2 receptor antagonists may be used in the treatment of euvolemic hyponatremia.[30]

The treatment of severe hyponatremia varies dependent on the timing of the onset of the disorder. In acute severe hyponatremia (disorder onset in <48 hours), rapid treatment with a hypertonic saline (3% normal saline) solution is emergent.[28] When the onset of hyponatremia occurs after 48 hours, there is concern about the rapidity with which serum sodium levels are corrected. Cells, particularly those in the brain, tend to defend against changes in cell volume caused by changes in ECF osmolality by increasing or decreasing their concentration of organic osmolytes (organic molecules that don't cross the cell membrane).[3] In the case of prolonged water intoxication, brain cells reduce their concentration of osmolytes as a means of preventing an increase in cell volume. It takes

several days for brain cells to restore the osmolytes lost during hyponatremia. Thus, treatment measures that produce rapid changes in serum osmolality may cause a dramatic change in brain cell volume. One of the reported effects of rapid treatment of hyponatremia, called the *osmotic demyelination syndrome,* is characterized by destruction of the myelin sheath of the axons passing through the brain stem.[3,31,32] This syndrome can cause serious neurologic injury and sometimes death.

Hypernatremia

Hypernatremia implies a serum sodium level above 145 mEq/L (145 mmol/L) and a serum osmolality greater than 295 mOsm/kg. Because sodium is functionally an impermeable solute, it contributes to tonicity and induces movement of water across cell membranes. Hypernatremia is characterized by hypertonicity of extracellular fluids and almost always causes cellular dehydration.[33]

Causes. Hypernatremia represents a deficit of water in relation to the body's sodium stores. It can be caused by net loss of water or sodium gain. Net water loss can occur through the urine, gastrointestinal tract, lungs, or skin. A defect in thirst or inability to obtain or drink water can interfere with water replacement. Rapid ingestion or infusion of sodium with insufficient time or opportunity for water ingestion can produce a disproportionate gain in sodium.

Hypernatremia occurs when there is an excess loss of body fluids that have a lower than normal concentration of sodium so that water is lost in excess of sodium. This can result from increased losses from the respiratory tract during fever or strenuous exercise, from watery diarrhea, or when osmotically active tube feedings are given with inadequate amounts of water. With pure water loss, each body fluid compartment loses an equal percentage of its volume. Because approximately one third of the water is in the ECF compartment, compared with the two thirds in the ICF compartment, more actual water volume is lost from the ICF than the ECF compartment.

Normally, water deficit stimulates thirst and increases water intake. Therefore, hypernatremia is more likely to occur in infants and in persons who do not experience or cannot express their thirst or obtain water to drink. With hypodipsia, or impaired thirst, the need for fluid intake does not activate the thirst response. Hypodipsia is particularly prevalent among the elderly. In persons with diabetes insipidus, hypernatremia can develop when thirst is impaired or access to water is impeded.

The therapeutic administration of sodium-containing solutions may also cause hypernatremia. For example, the administration of sodium bicarbonate during cardiopulmonary resuscitation increases body sodium levels because the sodium concentration of each 50-mL ampule of 7.5% sodium bicarbonate contains 892 mEq of sodium.[9] Rarely, salt intake occurs rapidly, as in taking excess salt tablets or during near-drowning in salt water.

Manifestations. The clinical manifestations of hypernatremia caused by water loss are largely those of ECF loss and cellular dehydration (see Table 8-4). The severity of signs and symptoms is greatest when the increase in serum sodium is large and occurs rapidly. Body weight is decreased in proportion to the amount of water that has been lost. Because blood plasma is roughly 90% to 93% water, the concentrations of blood cells and other blood components increase as ECF water decreases.

Thirst is an early symptom of water deficit, occurring when water losses are equal to 0.5% of body water. Urine output is decreased and urine osmolality increased because of renal water-conserving mechanisms. Body temperature frequently is elevated, and the skin becomes warm and flushed. The vascular volume decreases, the pulse becomes rapid and thready, and the blood pressure drops. Hypernatremia produces an increase in serum osmolality and results in water being pulled out of body cells. As a result, the skin and mucous membranes become dry, and salivation and lacrimation are decreased. The mouth becomes dry and sticky, and the tongue becomes rough and fissured. Swallowing is difficult. The subcutaneous tissues assume a firm, rubbery texture. Most significantly, water is pulled out of the cells in the CNS, causing decreased reflexes, agitation, headache, and restlessness. Coma and seizures may develop as hypernatremia progresses.

Diagnosis and Treatment. The diagnosis of hypernatremia is based on history, physical examination findings indicative of dehydration, and results of laboratory tests. Treatment includes measures to treat the underlying cause of the disorder and fluid replacement therapy to treat the accompanying dehydration. Replacement fluids can be given orally or intravenously. Oral glucose–electrolyte replacement solutions are widely available in grocery stores and pharmacies for use in the treatment of diarrhea and other dehydrating disorders in infants and young children (see Chapter 29).[34] Oral replacement therapy is less expensive than intravenous therapy and has a lower complication rate. Intravenous therapy may be required for children and adults with severe dehydration.

One of the serious aspects of fluid volume deficit is dehydration of brain and nerve cells. Serum osmolality should be corrected slowly in cases of chronic hypernatremia. As discussed previously, brain cells mobilize organic osmolytes to protect against changes in cell volume.[3] If hypernatremia is corrected too rapidly before the osmolytes have had a chance to dissipate, the plasma may become relatively hypotonic in relation to brain cell osmolality. When this occurs, water moves into the brain cells, causing cerebral edema and potentially severe neurologic impairment.

In summary, body fluids are distributed between the ICF and ECF compartments. Regulation of fluid volume, solute concentration, and distribution between the two compartments depends on water and sodium balance. Water provides approximately 90% to 93% of fluid volume and sodium salts approximately 90% to 95% of extracellular solutes. Both water and sodium are absorbed from the gastrointestinal tract and eliminated by the kidneys. The main regulator of water and sodium is the maintenance of the effective circulating blood

volume, monitored by stretch receptors in the vascular system, which exert their effect through ADH and the sympathetic nervous system, and those in the kidney, which exert their effects through the sympathetic nervous system and the renin-angiotensin-aldosterone system. Body water and serum osmolality are also regulated by thirst, which controls water intake, and ADH, which controls urine concentration and renal output.

Isotonic fluid disorders result from contraction or expansion of ECF volume brought about by proportionate changes in sodium and water. *Isotonic fluid volume deficit* is characterized by a decrease in ECF volume. It causes thirst, decreased vascular volume and circulatory function, decreased urine output, and increased urine specific gravity. *Isotonic fluid volume excess* is characterized by an increase in ECF volume. It is manifested by signs of increased vascular volume and edema.

Alterations in extracellular sodium concentration are brought about by a disproportionate gain (hyponatremia) or loss (hypernatremia) of water. As the major cation in the ECF compartment, sodium controls the ECF osmolality and its effect on cell volume. Hyponatremia can present as a *hypertonic (translocational) hyponatremia,* in which water moves out of the cell in response to elevated blood glucose levels, or as a *hypotonic (dilutional) hyponatremia,* which is caused by retention of water by the body in excess of sodium. Hypotonic hyponatremia, which can present as a hypovolemic, euvolemic, or hypervolemic state, is characterized by water being pulled into the cell from the ECF compartment, causing cells to swell. It is manifested by muscle cramps and weakness; nausea, vomiting, abdominal cramps, and diarrhea; and CNS signs such as headache, lethargy, depression of deep tendon reflexes, and, in severe cases, seizure and coma.

Hypernatremia represents a disproportionate loss of body water in relation to sodium. It is characterized by intracellular water being pulled into the ECF compartment, causing cells to shrink. It is manifested by thirst and decreased urine output; dry mouth and decreased tissue turgor; signs of decreased vascular volume (tachycardia, weak and thready pulse); and CNS signs, such as decreased reflexes, agitation, headache, and, in severe cases, seizures and coma.

Potassium Balance

Potassium is the second most abundant cation in the body and the major cation in the ICF compartment. Approximately 98% of body potassium is contained within body cells, with an intracellular concentration of 140 to 150 mEq/L (140 to 150 mmol/L). The potassium content of the ECF (3.5 to 5.0 mEq/L [3.5 to 5.0 mmol/L]) is considerably less. Because potassium is an intracellular ion, total body stores of potassium are related to body size and muscle mass. In adults, total body potassium is approximately 50 mEq/kg of body weight.[35] Approximately 65% to 75% of potassium is in muscle.[36,37] Thus, total body potassium content declines with age, mainly as a result of a decrease in muscle mass.

Regulation of Potassium Balance

Potassium balance is strongly influenced by dietary intake and urine output. In healthy persons, potassium balance usually can be maintained by a daily dietary intake of 50 to 100 mEq. Additional amounts of potassium are needed during periods of trauma and stress. The kidneys are the main source of potassium loss. Approximately 80% to 90% of potassium losses occur in the urine, with the remainder being lost in stools or sweat.

Mechanisms of Regulation

Normally, the ECF concentration of potassium is precisely regulated at about 4.2 mEq/L (4.2 mmol/L). The precise control is necessary because many cell functions are sensitive to even small changes in ECF potassium levels. An increase in potassium of as small an amount as 0.3 to 0.4 mEq/L can cause serious cardiac arrhythmias and even death. Serum potassium levels are largely regulated through two mechanisms: (1) renal mechanisms that conserve or eliminate potassium and (2) a transcellular shift between the ICF and ECF compartments.

Renal Regulation. The major route for potassium elimination is the kidney. Unlike other electrolytes, the

Potassium Balance

- Potassium is mainly an intracellular ion with only a small, but vital, amount being present in the extracellular fluids.
- The distribution of potassium between the intracellular and extracellular compartments regulates electrical membrane potentials, controlling the excitability of nerve and muscle cells as well as contractility of skeletal, cardiac, and smooth muscle tissues.
- Because of its vital role in regulating neuromuscular excitability, potassium regulation must be extremely efficient. Even a 1% to 2% addition of potassium to the extracellular fluid compartment can elevate serum levels to dangerously high levels.
- Two major mechanisms function in the control of serum potassium: (1) renal mechanisms that conserve or eliminate potassium and (2) transcellular buffer systems that remove potassium from or release it into the serum as needed. Conditions that disrupt the function of either mechanism can result in a serious alteration in serum potassium levels.

regulation of potassium elimination is controlled by secretion from the blood into the tubular filtrate rather than through reabsorption from the tubular filtrate into the blood. Potassium is filtered in the glomerulus, reabsorbed along with sodium and water in the proximal tubule and with sodium and chloride in the thick ascending loop of Henle, and then secreted into the late distal and cortical collecting tubules for elimination in the urine. The latter mechanism serves to "fine-tune" the concentration of potassium in the ECF.

Aldosterone plays an essential role in regulating potassium elimination in the distal tubule of the kidney (see Chapter 24). In the presence of aldosterone, Na^+ is transported back into the blood and K^+ is secreted in the tubular filtrate for elimination in the urine. The rate of aldosterone secretion by the adrenal cortex is strongly controlled by serum potassium levels. For example, an increase of less than 1 mEq/L (1 mmol/L) of potassium causes aldosterone levels to triple.[2] The effect of serum potassium on aldosterone secretion is an example of the powerful feedback regulation of potassium elimination. There is also a potassium/hydrogen exchange mechanism in the cortical collecting tubules of the kidney. When serum potassium levels increase, K^+ is secreted into the urine and H^+ is reabsorbed into the blood, producing a decrease in pH and causing metabolic acidosis. Conversely, when potassium levels are low, K^+ is reabsorbed and H^+ is secreted in the urine, leading to metabolic alkalosis.

Extracellular–Intracellular Shifts. Normally, it takes 6 to 8 hours to eliminate 50% of potassium intake.[3] To avoid an increase in ECF potassium levels during this time, excess potassium is temporarily shifted into red blood cells and other cells such as those of muscle, liver, and bone. This movement is controlled by the function of the Na^+/K^+-ATPase membrane pump and the permeability of ion channels in the cell membrane.

Among the factors that alter the intracellular/extracellular distribution of potassium are serum osmolality, acid-base disorders, insulin, and β-adrenergic stimulation. Acute increases in serum osmolality cause water to leave the cell. The loss of cell water produces an increase in intracellular potassium, causing it to move out of the cell into the ECF. The H^+ and K^+ ions, which are positively charged, can be exchanged between the ICF and ECF in a cation shift (Fig. 8-9). In metabolic acidosis, for example, H^+ moves into body cells for buffering, causing K^+ to leave and move into the ECF. Both insulin and the catecholamines (e.g., epinephrine) increase cellular uptake of K^+ by increasing the activity of the Na^+/K^+-ATPase membrane pump.[3,37–39] Insulin produces an increase in cellular uptake of potassium after a meal. The catecholamines, particularly epinephrine, facilitate the movement of potassium into muscle tissue during periods of physiologic stress. β-Adrenergic agonist drugs, such as pseudoephedrine and albuterol, have a similar effect on potassium distribution.

Exercise can also produce compartmental shifts in potassium. Repeated muscle contraction releases potassium into the ECF. Although the increase usually is small with modest exercise, it can be considerable during exhaustive exercise. Even the repeated clenching and unclenching of the fist during a blood draw can cause potassium to move out of cells and artificially elevate serum potassium levels.

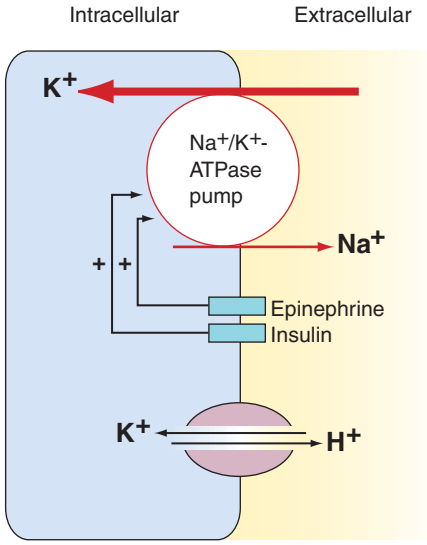


FIGURE 8-9. Mechanisms regulating transcellular shifts in potassium.

Disorders of Potassium Balance

As the major intracellular cation, potassium is critical to many body functions. It is involved in a wide range of body functions, including maintenance of the osmotic integrity of cells, acid-base balance, and the kidney's ability to concentrate urine. Potassium is necessary for growth and it contributes to the intricate chemical reactions that transform carbohydrates into energy, change glucose into glycogen, and convert amino acids to proteins. Potassium also plays a critical role in conducting nerve impulses and controlling the excitability of skeletal, cardiac, and smooth muscle. It does this by regulating the (1) resting membrane potential, (2) opening of the sodium channels that control the flow of current during the action potential, and (3) rate of membrane repolarization.[3] Changes in nerve and muscle excitability are particularly important in the heart, where alterations in serum potassium levels can produce serious cardiac arrhythmias and conduction defects.[38] Changes in serum potassium levels also affect the electrical activity of skeletal muscles and the smooth muscle in the blood vessels and gastrointestinal tract.

The *resting membrane potential* is determined by the ratio of ECF to ICF potassium concentration (see Chapter 1, Understanding Membrane Potentials). A *decrease* in the ECF potassium concentration (hypokalemia) causes the resting membrane potential to become more negative, moving it further from the threshold for excitation (Fig. 8-10). Thus, it takes a greater stimulus to reach the threshold potential and open the sodium channels that are

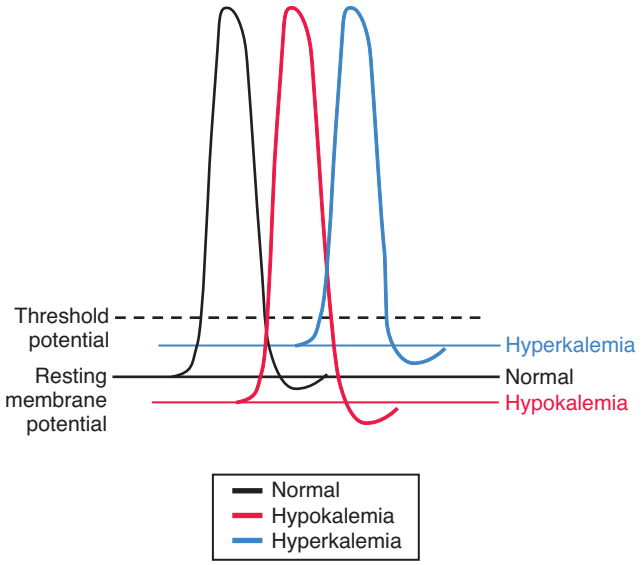


FIGURE 8-10. Effect of changes in serum hypokalemia (*red*) and hyperkalemia (*blue*) on the resting membrane potential in relation to the threshold potential.

responsible for the action potential. An *increase* in serum potassium (hyperkalemia) has the opposite effect; it causes the resting membrane potential to become more positive, moving it closer to the threshold. With severe hyperkalemia, the resting membrane potential approaches the threshold potential, causing sustained subthreshold depolarization with a resultant inactivation of the sodium channels and net decrease in excitability.[3] The *rate of repolarization* (return of the membrane potential toward its resting potential so it can undergo another action potential) also varies with serum potassium levels. It is more rapid in hyperkalemia and delayed in hypokalemia.

Hypokalemia

Hypokalemia refers to a decrease in serum potassium levels below 3.5 mEq/L (3.5 mmol/L). Because of transcellular shifts, temporary changes in serum levels can occur as the potassium moves between the ECF and ICF compartments.

Causes. The causes of potassium deficit can be grouped into three categories: (1) inadequate intake; (2) excessive gastrointestinal, renal, and skin losses; and (3) redistribution between the ICF and ECF compartments.

Inadequate intake is a frequent cause of hypokalemia. A potassium intake of at least 40 to 50 mEq (40 to 50 mmol)/day is needed to compensate for obligatory urine losses.[9] Insufficient dietary intake (typically <40 mEq [40 mmol]/day) may result from the inability to obtain or ingest food or from a diet that is low in potassium-containing foods. Potassium intake is often inadequate in persons on fad diets and those who have eating disorders. Elderly persons are particularly likely to have potassium deficits. Many have poor eating habits as a consequence of living alone; they may have limited income, which makes buying foods high in potassium difficult; they may have difficulty chewing many foods that have high potassium content because of poorly fitting dentures; or they may have problems with swallowing.

Excessive loss is the second cause of potassium deficit. Approximately 80% to 90% of potassium losses occur in the urine, with the remaining 10% to 20% being eliminated in the stool or through sweating. The kidneys lack the homeostatic mechanisms needed to conserve potassium during periods of insufficient intake. Excessive renal losses occur with diuretic therapy, metabolic alkalosis, magnesium depletion, trauma and stress, and an increase in aldosterone levels. Diuretic therapy, with the exception of potassium-sparing diuretics, is the most common cause of hypokalemia. Both thiazide and loop diuretics increase the loss of potassium in the urine.[36] Magnesium depletion, which often coexists with potassium depletion due to diuretic therapy, produces additional urinary losses. Renal losses of potassium are accentuated by aldosterone and cortisol. Primary aldosteronism, caused by either a tumor or hyperplasia of the cells of the adrenal cortex that secrete aldosterone, can produce severe losses of potassium (see Chapter 32).

Although potassium losses from the skin and the gastrointestinal tract usually are minimal, these losses can become excessive under certain conditions. For example, burns increase surface losses of potassium. Losses due to sweating increase in persons who are acclimated to a hot climate, partly because increased secretion of aldosterone during heat acclimatization increases the loss of potassium in urine and sweat. Gastrointestinal losses also can become excessive; this occurs with vomiting and diarrhea and when gastrointestinal suction is being used.

Hypokalemia can also be caused by *transcellular shifts* in potassium. Because of the large difference between extracellular and intracellular potassium levels, a redistribution of potassium from the ECF to the ICF compartment can produce marked decreases in the serum potassium (see Fig. 8-9). A wide variety of β_2-adrenergic agonist drugs (e.g., decongestants and bronchodilators) shift potassium into cells and cause transient hypokalemia.[39] Insulin also increases the movement of potassium into the cell. Because insulin increases the movement of glucose and potassium into cells, potassium deficit often develops during treatment of diabetic ketoacidosis.

Manifestations. The manifestations of hypokalemia include alterations in neuromuscular, gastrointestinal, renal, and cardiovascular function[40] (Table 8-5). These manifestations reflect the effects of hypokalemia on the electrical activity of excitable tissues such as those of the neuromuscular systems as well as the body's attempt to regulate ECF potassium levels within a more normal level. The signs and symptoms of potassium deficit seldom develop until serum potassium levels have fallen to less than 3.0 mEq/L (3.0 mmol/L). They are typically gradual in onset, and therefore the disorder may go undetected for some time.

The renal mechanisms that conserve potassium during hypokalemia interfere with the kidney's ability to concentrate urine. Urine output and plasma osmolality are increased, urine specific gravity is decreased, and complaints of polyuria, nocturia, and thirst are common. Metabolic alkalosis and renal chloride wasting are signs of severe hypokalemia.

TABLE 8-5 Manifestations of Hypokalemia and Hyperkalemia

Hypokalemia	Hyperkalemia
Laboratory Values	***Laboratory Values***
Serum potassium <3.5 mEq/L (3.5 mmol/L)	Serum potassium >5.0 mEq/L (5.0 mmol/L)
Thirst and Urine	
Increased thirst	
Inability to concentrate urine with polyuria and urine with low specific gravity	
Effects of Changes in Membrane Potentials on Neural and Muscle Function	***Effects of Changes in Membrane Potentials on Neural and Muscle Function***
Gastrointestinal	***Gastrointestinal***
Anorexia, nausea, vomiting	Nausea, vomiting
Abdominal distention	Intestinal cramps
Paralytic ileus (severe hypokalemia)	Diarrhea
Neuromuscular	***Neuromuscular***
Muscle weakness, flabbiness, fatigue	Weakness, dizziness
Muscle cramps and tenderness	Muscle cramps
Paresthesias	Paresthesias
Paralysis (severe hypokalemia)	Paralysis (severe hyperkalemia)
Central Nervous System	
Confusion, depression	
Cardiovascular	***Cardiovascular***
Postural hypotension	Electrocardiogram changes
Predisposition to digitalis toxicity	Risk of cardiac arrest with severe hyperkalemia
Electrocardiogram changes	
Cardiac arrhythmias	
Acid-Base Balance	
Metabolic alkalosis	

There are numerous signs and symptoms associated with gastrointestinal function, including anorexia, nausea, and vomiting. Atony of the gastrointestinal smooth muscle can cause constipation, abdominal distention, and, in severe hypokalemia, paralytic ileus. When gastrointestinal symptoms occur gradually and are not severe, they often impair potassium intake and exaggerate the condition.

The most serious effects of hypokalemia are those affecting the cardiovascular system. Most persons with serum potassium levels of less than 3.0 mEq/L (3.0 mmol/L) demonstrate electrocardiographic (ECG) changes typical of hypokalemia (Fig. 8-11). Hypokalemia produces a decrease in the resting membrane potential, causing prolongation of the PR interval. It also prolongs the rate of ventricular repolarization and lengthens the relative refractory period, causing a depression of the ST segment, flattening of the T wave, and appearance of a prominent U wave.[3,38] The U wave may be present on the normal ECG but should be of lower amplitude than the T wave. With hypokalemia, the amplitude of the T wave decreases as the U-wave amplitude increases. Although these ECG changes usually are not serious, they may predispose to reentry ventricular arrhythmias. Hypokalemia also increases the risk of digitalis toxicity in persons being treated with the drug and there is an increased risk of ventricular arrhythmias, particularly in persons with underlying heart disease. The dangers associated with digitalis toxicity are compounded in persons who are receiving diuretics that increase urinary losses of potassium.[38,40]

Complaints of weakness, fatigue, and muscle cramps, particularly during exercise, are common in moderate hypokalemia (serum potassium 3.0 to 2.5 mEq/L [3.0 to 2.5 mmol/L]). Muscle paralysis with life-threatening respiratory insufficiency can occur with severe hypokalemia (serum potassium <2.5 mEq/L). Leg muscles, particularly the quadriceps, are most prominently affected. Some persons complain of muscle tenderness and paresthesias rather than weakness. In chronic potassium deficiency, muscle atrophy may contribute to muscle weakness.

In a rare genetic condition called *hypokalemic familial periodic paralysis*, episodes of hypokalemia cause attacks of flaccid paralysis that last 6 to 48 hours if untreated.[3] The paralysis may be precipitated by situations that cause severe hypokalemia by producing an intracellular shift in potassium, such as ingestion of a high-carbohydrate meal or administration of insulin, epinephrine, or glucocorticoid drugs. The paralysis often can be reversed by potassium replacement therapy. A similar condition can occur with poorly controlled hyperthyroidism (thyrotoxic hypokalemic periodic paralysis), especially in Asian subjects. Treatment consists of potassium replacement and appropriate therapy for the underlying thyroid disorder.[41]

Diagnosis and Treatment. A diagnosis of hypokalemia is based on clinical manifestations and serum potassium

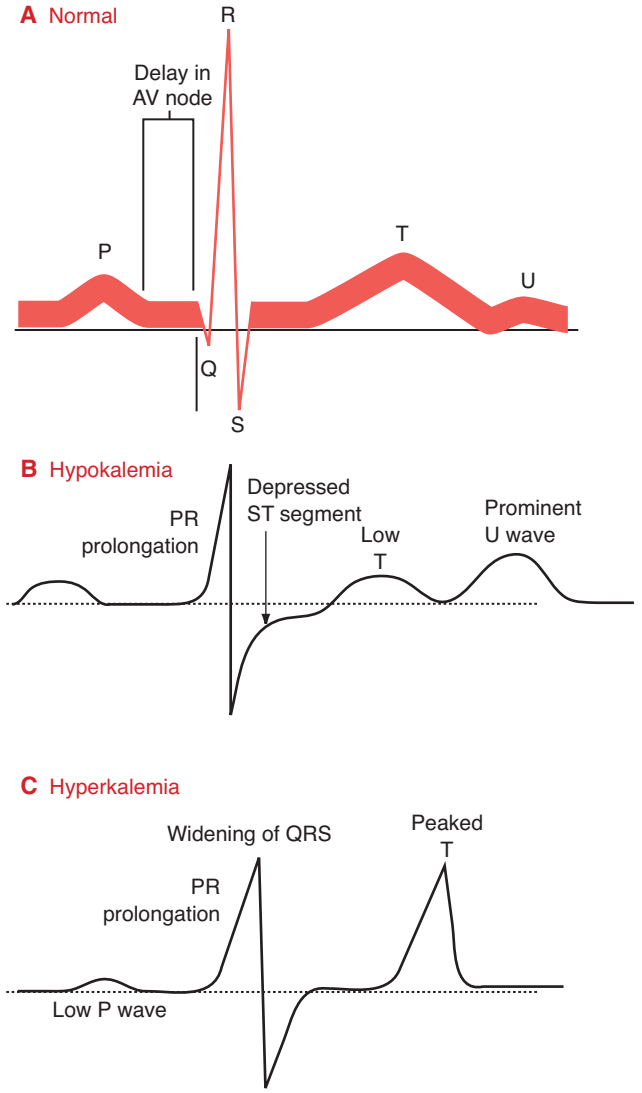


FIGURE 8-11. Comparison of the **(A)** normal electrocardiogram with electrocardiographic changes that occur with **(B)** hypokalemia and **(C)** hyperkalemia.

levels. When possible, hypokalemia caused by a potassium deficit is treated by increasing the intake of foods high in potassium content—meats, dried fruits, fruit juices (particularly orange juice), and bananas. Oral potassium supplements are prescribed for persons whose intake of potassium is insufficient in relation to losses. This is particularly true of persons who are receiving diuretic therapy and those who are taking digitalis.

Potassium may be given intravenously when the oral route is not tolerated or when rapid replacement is needed. Magnesium deficiency may impair potassium correction; in such cases, magnesium replacement is indicated.[3] The rapid infusion of a concentrated potassium solution can cause death from cardiac arrest. Health personnel who assume responsibility for administering intravenous solutions that contain potassium should be fully aware of all the precautions pertaining to their dilution and flow rate.

Hyperkalemia

Hyperkalemia refers to an increase in serum levels of potassium in excess of 5.0 mEq/L (5.0 mmol/L). It seldom occurs in healthy persons because the body is extremely effective in preventing excess potassium accumulation in the extracellular fluid.[3,42] A pseudohyperkalemia can occur secondary to release of potassium from intracellular stores after a blood sample has been collected, hemolysis of red blood cells from excessive agitation of a blood sample, traumatic venipuncture, or prolonged application of a tourniquet during venipuncture.[42]

Causes. The three major causes of potassium excess are (1) decreased renal elimination, (2) movement of potassium from the ICF to ECF compartment, and (3) excessively rapid rate of administration. The most common cause of serum potassium excess is decreased renal function. Chronic hyperkalemia is almost always associated with chronic kidney disease. Usually, the glomerular filtration rate must decline to less than 10 mL/minute before hyperkalemia develops. Some kidney disorders, such as sickle cell nephropathy, lead nephropathy, and systemic lupus nephritis, can selectively impair tubular secretion of potassium without causing kidney failure. Acidosis also increases ECF potassium concentration. Persons with acute kidney failure accompanied by lactic acidosis or ketoacidosis are at increased risk for the development of hyperkalemia. Correcting the acidosis usually helps to correct the condition.[3]

Aldosterone acts at the level of the distal tubular sodium/potassium exchange system to increase potassium excretion while facilitating sodium reabsorption. A decrease in aldosterone-mediated potassium elimination can result from adrenal insufficiency, depression of aldosterone release due to a decrease in renin or angiotensin II, or impaired ability of the kidneys to respond to aldosterone. Potassium-sparing diuretics can produce hyperkalemia by means of the latter mechanism. Because of their ability to decrease aldosterone levels, the angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers can also produce an increase in serum potassium levels.

The movement of potassium out of body cells into the ECF also can lead to elevated serum potassium levels. Acidosis tends to increase serum potassium levels in part by causing potassium to move from the ICF to the ECF. Although the mechanism responsible for this effect is not completely understood, one effect of increased hydrogen ion concentration is to decrease the activity of the Na^+/K^+-ATPase pump. Tissue injury also causes release of intracellular potassium into the ECF compartment. For example, burns and crushing injuries cause cell death and release of potassium into the extracellular fluids. The same injuries often diminish renal function, which contributes to the development of hyperkalemia. Transient hyperkalemia may be induced during extreme exercise or seizures, when muscle cells are permeable to potassium.

Potassium excess can also result from excessive oral ingestion or intravenous administration of potassium. Normally it is difficult to increase potassium intake to the point

of causing hyperkalemia when renal function is adequate and the aldosterone Na^+/K^+ exchange system is functioning. An exception to this rule is the intravenous route of administration. In some cases, severe and fatal incidents of hyperkalemia have occurred when intravenous potassium solutions were infused too rapidly. Because the kidneys control potassium elimination, the administration of intravenous solutions that contain potassium should not be initiated until urine output has been assessed and renal function has been deemed to be adequate.

Manifestations. The signs and symptoms of potassium excess are closely related to a decrease in neuromuscular excitability (see Table 8-5). The neuromuscular manifestations of potassium excess usually are absent until the serum concentration exceeds 6 mEq/L (6 mmol/L).[37] The first symptom associated with hyperkalemia typically is paresthesia. There may be complaints of generalized muscle weakness or dyspnea secondary to respiratory muscle weakness.

The most serious effect of hyperkalemia is on the heart. Hyperkalemia decreases membrane excitability, producing a delay in atrial and ventricular depolarization, and it increases the rate of ventricular repolarization.[3,38] As the serum potassium concentration rises, there is a characteristic sequence of changes in the ECG that are due to the effects of hyperkalemia on atrial and ventricular depolarization (represented by the P wave and QRS complex, respectively) and repolarization (represented by the T wave and QRS complex, respectively). The earliest ECG changes are peaked and narrowed T waves and a shortened QT interval, which reflect abnormally rapid repolarization (see Fig. 8-11). The alteration in T-wave configuration typically becomes prominent when the serum potassium concentration exceeds 6 mEq/L (6 mmol/L). If serum potassium levels continue to rise, delayed depolarization of the atria and ventricles produces further changes in the ECG. There is a prolongation of the PR interval, widening of the QRS complex with no change in its configuration, and decreased amplitude, widening, and eventual disappearance of the P wave. The heart rate may be slow. Ventricular fibrillation and cardiac arrest are terminal events. Detrimental effects of hyperkalemia on the heart are most pronounced when the serum potassium level rises rapidly.

Diagnosis and Treatment. Diagnosis of hyperkalemia is based on complete history, physical examination to detect muscle weakness and signs of volume depletion, serum potassium levels, and ECG findings. The history should include questions about dietary intake, use of potassium-sparing diuretics, history of kidney disease, and recurrent episodes of muscle weakness.

The treatment of potassium excess varies with the degree of increase in serum potassium and whether there are ECG and neuromuscular manifestations. On an emergent basis, calcium antagonizes the potassium-induced decrease in membrane excitability, restoring excitability toward normal.[40,41] The protective effect of calcium administration is usually short lived (15 to 30 minutes) and must be accompanied by other therapies to decrease the ECF potassium concentration. The redistribution of potassium from the ECF into the ICF compartment can be accomplished by the administration of sodium bicarbonate, β-agonists (e.g., nebulized albuterol), or insulin to rapidly decrease the ECF concentration.[41] Intravenous infusions of insulin and glucose may also be used for this purpose.[40,41]

Less emergent measures focus on decreasing or curtailing intake or absorption, increasing renal excretion, and increasing cellular uptake. Decreased intake can be achieved by restricting dietary sources of potassium. The major ingredient in most salt substitutes is potassium chloride, and such substitutes should not be given to patients with kidney problems. Increasing potassium output often is more difficult. Persons with kidney failure may require hemodialysis or peritoneal dialysis to reduce serum potassium levels.

In summary, as the major intracellular fluid (ICF) cation, potassium contributes to the maintenance of intracellular osmolality; plays a critical role in conducting nerve impulses and the excitability of skeletal, cardiac, and smooth muscle; and influences acid-base balance. Potassium is ingested in the diet and eliminated through the kidney. Because potassium is poorly conserved by the kidney, an adequate daily intake is needed. A transcellular shift can produce a redistribution of potassium between the extracellular fluid (ECF) and ICF compartments, causing blood levels to increase or decrease.

Hypokalemia represents a decrease in serum potassium levels to below 3.5 mEq/L (3.5 mmol/L). It can result from inadequate intake, excessive losses, or redistribution between the ICF and ECF compartments. The manifestations of potassium deficit include alterations in renal, skeletal muscle, gastrointestinal, and cardiovascular function, reflecting the crucial role of potassium in cell metabolism and neuromuscular function.

Hyperkalemia represents an increase in serum potassium to levels greater than 5.0 mEq/L (5.0 mmol/L). It seldom occurs in healthy persons because the body is extremely effective in preventing excess potassium accumulation in the ECF. The major causes of potassium excess are decreased elimination of potassium by the kidney, a transcellular shift in potassium from the ICF into the ECF compartment, and excessively rapid intravenous administration of potassium. The most serious effect of hyperkalemia is on the heart and development of serious and even fatal arrhythmias.

Calcium and Magnesium Balance

Calcium, phosphorous, and magnesium are the major divalent cations in the body. Approximately 99% of calcium, 85% of phosphorous, and 50% to 60% of magnesium are found in bone. Most of the remaining calcium

(approximately 1%), phosphorous (approximately 14%), and magnesium (approximately 40% to 50%) are located in the ICF. Only a small amount of the electrolyte form of calcium, phosphorous, and magnesium is present in ECF. The discussion in this chapter focuses on calcium homeostasis, parathyroid hormone disorders, and disorders of calcium and magnesium balance. Normal homeostatic mechanisms that regulate serum, intracellular, and bone deposition of calcium and phosphorous occur in three major organs—the intestine, kidney, and bone—principally through the complex integration of two hormones, parathyroid hormone (PTH) and vitamin D[43] (Fig. 8-12).

The main function of PTH is to maintain ECF calcium concentrations.[1,2,43] It does this by stimulating the release of calcium and phosphorous from bone into the ECF; increasing renal reabsorption of calcium and excretion of phosphorous; and enhancing the gastrointestinal absorption of calcium and phosphorous through its effects on vitamin D synthesis. Vitamin D, which is really a hormone, is synthesized by the skin and metabolized by the kidney to an active hormone, calcitriol. The active form of vitamin D has several effects on the intestines, kidneys, and bone that increase serum levels of calcium and phosphorous and contribute to their feedback regulation.[1,2,43] It stimulates the absorption of calcium, and to a lesser extent phosphorous, from the intestine; it increases calcium and phosphorous reabsorption by the renal tubules; and it inhibits PTH synthesis by the parathyroid glands. A third hormone, calcitonin, tends to decrease ECF calcium concentrations and, in general, has effects opposite those of PTH. However, the quantitative effects of calcitonin are far less than those of PTH. The role of PTH, vitamin D, and calcitonin on skeletal function is discussed further in Chapters 42 and 43.

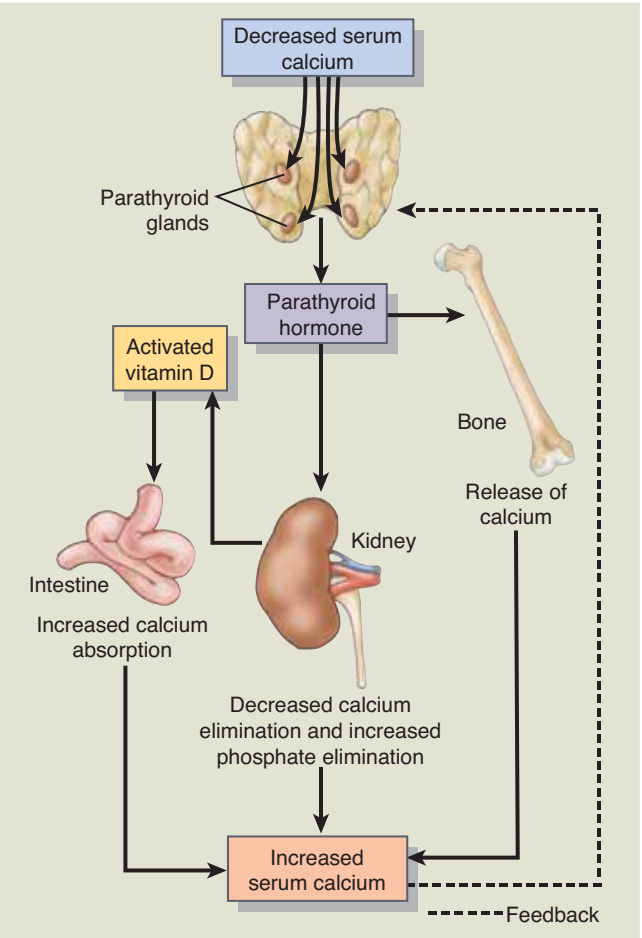


FIGURE 8-12. Regulation of serum calcium concentration by parathyroid hormone.

Disorders of Parathyroid Hormone

PTH, a major regulator of serum calcium and phosphorous, is secreted by the parathyroid glands. There are four parathyroid glands located on the dorsal surface of the thyroid gland. PTH is synthesized as a preprohormone in the parathyroid gland and cleaved first to a prohormone with 90 amino acids, then to the PTH with 84 amino acids, and finally packaged into secretory granules for release into the circulation. The dominant regulator of PTH secretion is the serum calcium concentration. A unique calcium receptor on the parathyroid cell membrane (extracellular calcium-sensing receptor) responds rapidly to changes in serum calcium levels.[43] When the serum calcium level is high, the secretion of PTH is inhibited, and serum calcium is deposited in the bones. When the level is low, PTH secretion is increased, and calcium is mobilized from the bones and released into the blood.

The synthesis and release of PTH from the parathyroid gland are also influenced by magnesium. Magnesium serves as a cofactor in the generation of cellular energy and is important in the function of second messenger systems. Magnesium's effects on the synthesis and release of PTH are thought to be mediated through these mechanisms. Because of its function in regulating PTH release, severe and prolonged hypomagnesemia can markedly inhibit PTH levels.

Hypoparathyroidism

Hypoparathyroidism reflects deficient PTH secretion, resulting in low serum levels of ionized calcium. PTH deficiency may occur because of a congenital absence of all of the parathyroid glands, as in DiGeorge syndrome (see Chapter 16), or because of an acquired disorder due to inadvertent removal or irreversible damage to the glands during thyroidectomy, parathyroidectomy, or radical neck dissection for cancer.[43,44] A transient form of PTH deficiency may occur after thyroid surgery owing to parathyroid gland suppression. Hypoparathyroidism also may have an autoimmune origin. Antiparathyroid antibodies have been detected in some persons with hypoparathyroidism, particularly those with multiple autoimmune disorders such as type 1 diabetes mellitus or Graves disease. Other causes of hypoparathyroidism include heavy metal damage such as occurs with Wilson disease and metastatic tumors. Functional impairment of parathyroid function occurs with magnesium deficiency. Correction of the hypomagnesemia results in rapid disappearance of the condition.

Manifestations. Manifestations of acute hypoparathyroidism, which result from a decrease in serum calcium,

include tetany with muscle cramps, carpopedal spasm, and convulsions (see section on hypocalcemia). Paresthesias, such as tingling of the circumoral area and in the hands and feet, are almost always present. Low calcium levels may cause prolongation of the QT interval, resistance to digitalis, hypotension, and refractory heart failure. Symptoms of chronic PTH deficiency include lethargy, an anxiety state, and personality changes. There may be blurring of vision because of cataracts, which develop over a number of years. Extrapyramidal signs, such as those seen with Parkinson disease, may occur because of calcification of the basal ganglia. Teeth may be defective if the disorder occurs during childhood.

Pseudohypoparathyroidism is a rare familial disorder characterized by target tissue resistance to PTH. It is characterized by hypocalcemia, increased parathyroid function, and a variety of congenital defects in the growth and development of the skeleton, including short stature and short metacarpal and metatarsal bones. There are variants in the disorder, with some persons having the pseudohypoparathyroidism along with the congenital defects and others having the congenital defects with normal calcium and phosphorous levels. The manifestations of the disorder are due primarily to chronic hypocalcemia.

Diagnosis and Treatment. Diagnosis of hypoparathyroidism is based on history, including a history of neck surgery; physical examination to assess for signs of neuromuscular irritability due to hypocalcemia (to be discussed); and laboratory measurements of serum total and ionized calcium, albumin, phosphorous, magnesium, vitamin D levels, and intact PTH (i.e., intact 84-amino-acid hormone).

The goals of therapy are to control symptoms while minimizing complications. Acute hypoparathyroid tetany is treated with intravenous calcium gluconate followed by oral administration of calcium salts and vitamin D. Magnesium supplementation is used when the disorder is caused by magnesium deficiency. Persons with chronic hypoparathyroidism are treated with oral calcium and vitamin D. Levels of serum calcium, phosphorous, and creatinine (to check kidney function) are monitored at regular intervals as a means of maintaining serum calcium within a slightly low but asymptomatic range.

Hyperparathyroidism

Hyperparathyroidism is caused by increased levels of PTH. Hyperparathyroidism can manifest as a primary disorder caused by hyperplasia (15%), an adenoma (85%), and rarely carcinoma of the parathyroid glands (<5%) or as a secondary disorder seen in persons with chronic renal failure or chronic malabsorption of calcium.[45–47] Parathyroid adenomas and hyperplasia can occur in several distinct familial diseases (including multiple endocrine neoplasia [MEN] types 1 and 2a).

Manifestations. Primary hyperparathyroidism is a leading cause of hypercalcemia in the outpatient department. It is seen more commonly after 50 years of age and is more common in women than men.[46] Primary hyperparathyroidism causes an elevation in ionized serum calcium and increased urinary excretion of both calcium and phosphorous. The increased urinary concentration of calcium and phosphorous provides the potential for development of kidney stones. Chronic bone resorption may produce diffuse demineralization, pathologic fractures, and cystic bone lesions. Signs and symptoms of the disorder are related to skeletal abnormalities, exposure of the kidney to high calcium levels, and elevated serum calcium levels (see hypercalcemia). At the present time, most patients with primary hyperparathyroidism manifest an asymptomatic disorder that is discovered in the course of routine biochemical testing. Although thought to be asymptomatic, these patents may experience nonspecific constitutional symptoms such as fatigue, weakness, anorexia, and bone pain.[47]

Secondary hyperparathyroidism involves hyperplasia of the parathyroid glands and occurs primarily in persons with chronic kidney disease.[46–48] In early stages of chronic kidney disease, an increase in PTH results from decreased serum calcium and activated vitamin D levels. As the disease progresses, there is a decrease in vitamin D and calcium receptors, making the parathyroid glands more resistant to feedback regulation by serum calcium and vitamin D levels. At this point, elevated phosphorous levels induce hyperplasia of the parathyroid glands independent of calcium and vitamin D levels. The bone disease seen in persons with secondary hyperparathyroidism due to chronic kidney disease is known as *renal osteodystrophy* (see Chapter 26).

Diagnosis and Treatment. Diagnostic procedures include serum calcium, intact PTH levels, and imaging studies of the parathyroid area. Treatment of hyperparathyroidism includes resolving the hypercalcemia with increased fluid intake. Parathyroidectomy may be indicated in persons with symptomatic primary hyperparathyroidism. Whenever possible, the underlying cause of secondary hyperparathyroidism should be removed. The goal of medical management is to normalize calcium levels. Calcitriol and other vitamin D analogs may be used to control parathyroid hyperplasia in chronic kidney disease. Persons with chronic kidney disease may also need phosphate binders to decrease hyperphosphatemia and prevent the skeletal disorders associated with the osteodystrophies[48] (see Chapter 26). Calcimimetic agents, which act through the calcium-sensing receptor in the parathyroid gland, may be used to decrease PTH production in primary and secondary hyperparathyroidism.[46,47]

Disorders of Calcium Balance

Calcium is the major divalent cation in the body. Approximately 99% of body calcium is found in bone, where it provides the strength and stability for the skeletal system and serves as an exchangeable source to maintain extracellular calcium levels. Most of the remaining calcium (approximately 1%) is located inside cells, and only approximately 0.1% to 0.2% (approximately 8.5 to 10.5 mg/dL [21 to 26 mmol/L]) of the remaining calcium is present in the ECF.

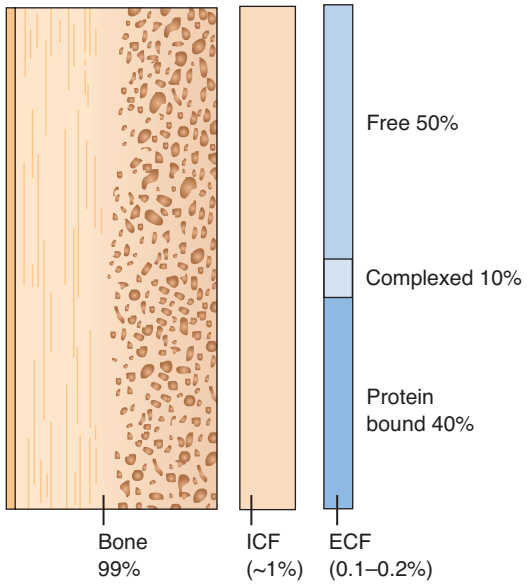


FIGURE 8-13. Distribution of body calcium between the bone and the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. The percentages of free, complexed, and protein-bound calcium in extracellular fluids are indicated.

Extracellular calcium exists in three forms: (1) protein bound, (2) complexed, and (3) ionized (Fig. 8-13). Approximately 40% of serum calcium is bound to plasma proteins, mostly albumin. Another 10% is complexed (i.e., chelated) with substances such as citrate, phosphorous, and sulfate.[1,2] This form is not ionized. The remaining 50% of serum calcium is present in the ionized form. Only the ionized form of calcium is free to leave the vascular compartment and participate in cellular functions. Since most of the protein-bound calcium combines with albumin, total serum calcium is significantly altered by serum albumin levels. As a general rule, a decrease in serum albumin of 1.0 g/dL below normal will decrease total calcium by 0.8 mg/dL.[9] Ionized calcium levels are inversely affected by the pH of the blood. For example, when the arterial pH increases in alkalosis, more calcium becomes bound to protein.[9,49] Although the total serum calcium remains unchanged, the ionized portion decreases.

Ionized calcium serves a number of functions. It participates in many enzyme reactions; exerts an important effect on membrane potentials and neuronal excitability; is necessary for contraction in skeletal, cardiac, and smooth muscle; participates in the release of hormones, neurotransmitters, and other chemical messengers; influences cardiac contractility and automaticity by way of slow calcium channels; and is essential for blood clotting. Calcium is required for all but the first two steps of the intrinsic pathway for blood coagulation. Because of its ability to bind calcium, citrate often is used to prevent clotting in blood that is to be used for transfusions.

Regulation of Calcium Balance

Calcium enters the body through the gastrointestinal tract, is absorbed from the intestine under the influence of vitamin D, is stored in bone, and is excreted by the kidney. The major sources of calcium are milk and milk products. Only 30% to 50% of dietary calcium is absorbed from the duodenum and upper jejunum; the remainder is eliminated in the stool. There is a calcium influx of approximately 150 mg/day into the intestine from the blood. Net absorption of calcium is equal to the amount that is absorbed from the intestine less the amount that moves into the intestine. Calcium balance can become negative when dietary intake (and calcium absorption) is less than intestinal secretion.

Calcium is stored in bone and excreted by the kidney. The ionized form of calcium is filtered from the plasma into the glomerulus and then selectively reabsorbed back into the blood. The distal convoluted tubule is an important regulatory site for controlling the amount of calcium that enters the urine. PTH and possibly vitamin D stimulate calcium reabsorption in this segment of the nephron. Thiazide diuretics, which exert their effects in the distal convoluted tubule, enhance calcium reabsorption. Another factor that influences calcium reabsorption by the kidney is the serum concentration of phosphorous. An increase in serum phosphorous stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with reduction in serum phosphorous levels.

Hypocalcemia

Hypocalcemia represents a total serum calcium level of less than 8.5 mg/dL (2.1 mmol/L) and an ionized calcium level of less than 4.6 mg/dL (1.2 mmol/L). A pseudohypocalcemia is caused by hypoalbuminemia. It results in a decrease in protein-bound, rather than ionized, calcium and usually is asymptomatic.[43] Thus, before a diagnosis of hypocalcemia can be made, the total calcium should be corrected for low albumin levels.

Causes. The most common causes of hypocalcemia are abnormal losses of calcium from the kidney, impaired ability to mobilize calcium from bone due to hypoparathyroidism, and increased protein binding or chelation such that greater proportions of calcium are in the nonionized form.[50]

Calcium Balance

- About 99% of body calcium is stored in bone; 1% is located inside cells; and 0.1% is found in the extracellular fluid.
- Extracellular fluid calcium levels are made up of free (ionized), complexed, and protein-bound fractions. Only the ionized Ca^{2+} plays an essential role in neuromuscular and cardiac excitability.
- Serum calcium levels are regulated by parathyroid hormone and by renal mechanisms in which serum levels of calcium and phosphate are reciprocally regulated to prevent the damaging deposition of calcium phosphate crystals in the soft tissues of the body.

An important cause of hypocalcemia is renal failure, in which decreased production of activated vitamin D and hyperphosphatemia both play a role (see Chapter 26). Because of the inverse relation between calcium and phosphate, serum calcium levels fall as phosphate levels rise in renal failure. Hypocalcemia and hyperphosphatemia occur when the glomerular filtration rate falls to less than 25 to 30 mL/minute (normal is 100 to 120 mL/minute).

The ability to mobilize calcium from bone depends on PTH levels. Decreased levels of PTH may result from the previously discussed primary or secondary forms of hypoparathyroidism. Suppression of PTH release may also occur when vitamin D levels are elevated. Magnesium deficiency also inhibits PTH release and impairs the action of PTH on bone resorption. This form of hypocalcemia is difficult to treat with calcium supplementation alone and requires correction of the magnesium deficiency. Hypocalcemia is also a common problem in acute pancreatitis in which fat necrosis and precipitation of calcium soaps produce a decrease in serum calcium.

Since only the ionized form of calcium is able to leave the capillary and participate in body functions, conditions that alter the ratio of protein-bound to ionized calcium can also produce signs of hypocalcemia. This can occur in situations where the increase in pH that occurs with alkalosis produces a decrease in ionized calcium. For example, hyperventilation sufficient to cause respiratory alkalosis can produce a decrease in ionized calcium sufficient to cause tetany. Free fatty acids also increase protein binding, causing a reduction in ionized calcium. Elevations in free fatty acids sufficient to alter calcium binding may occur during stressful situations that cause elevations of epinephrine, glucagon, growth hormone, and adrenocorticotropic hormone levels.

Manifestations. Hypocalcemia can manifest as an acute or chronic condition. Most persons with mild hypocalcemia are asymptomatic, whereas large or abrupt changes in ionized calcium lead to increased neuromuscular excitability and cardiovascular effects (Table 8-6).

Ionized calcium stabilizes neuromuscular excitability, thereby making nerve cells less sensitive to stimuli. Nerves exposed to low ionized calcium levels show decreased thresholds for excitation, repetitive responses to a single stimulus, and, in extreme cases, continuous activity. The severity of the manifestations depends on the underlying cause, rapidity of onset, accompanying electrolyte disorders, and extracellular pH. Increased neuromuscular excitability can manifest as paresthesias (i.e., tingling around the mouth and in the hands and feet), tetany (i.e., muscle spasms of the muscles of the face, hands, and feet), and, in severe hypocalcemia, laryngeal spasm and seizures.[43] Cardiovascular effects of acute hypocalcemia include hypotension, cardiac insufficiency, cardiac arrhythmias (particularly heart block and ventricular fibrillation), and failure to respond to drugs such as digitalis, norepinephrine, and dopamine that act through calcium-mediated mechanisms.[50]

TABLE 8-6 Manifestations of Hypocalcemia and Hypercalcemia

Hypocalcemia	Hypercalcemia
Laboratory	***Laboratory***
Serum calcium <8.5 mg/dL (2.1 mmol/L)	Serum calcium >10.5 mg/dL (2.6 mmol/L)
	Inability to Concentrate Urine and Exposure of Kidney to Increased Concentration of Calcium
	Polyuria
	Increased thirst
	Flank pain
	Signs of acute renal insufficiency
	Signs of kidney stones
Neural and Muscle Effects (Increased Excitability)	***Neural and Muscle Effects (Decreased Excitability)***
Paresthesias, especially numbness and tingling	Muscle weakness
Skeletal muscle cramps	Ataxia, loss of muscle tone
Abdominal muscle spasms and cramps	Lethargy
Hyperactive reflexes	Personality and behavioral changes
Carpopedal spasm	Stupor and coma
Tetany	
Laryngeal spasm	
Cardiovascular Effects	***Cardiovascular Effects***
Hypotension	Hypertension
Signs of cardiac insufficiency	Shortening of the QT interval
Decreased response to drugs that act by calcium-mediated mechanisms	Atrioventricular block
Prolongation of the QT interval predisposes to ventricular arrhythmias	
Skeletal Effects (Chronic Deficiency)	***Gastrointestinal Effects***
Osteomalacia	Anorexia
Bone pain	Nausea, vomiting
	Constipation

Diagnosis and Treatment. The diagnosis of hypocalcemia is initially based on serum calcium levels and signs of increased neuromuscular excitability. Chvostek and Trousseau tests can be used to assess for increased neuromuscular excitability that is associated with hypocalcemia (Fig. 8-14).[9] *Chvostek sign* is elicited by tapping the face just below the temple at the point where the facial nerve emerges. Tapping the face over the facial nerve causes spasm of the lip, nose, or face when the test result is positive. An inflated blood pressure cuff is used to test for *Trousseau sign*. The cuff is inflated 10 mm Hg above systolic blood pressure for 3 minutes. Contraction of the fingers and hands (i.e., carpopedal spasm) indicates the presence of tetany.

Acute hypocalcemia is an emergency situation, requiring prompt treatment. An intravenous infusion containing calcium (e.g., calcium gluconate, calcium chloride) is used when tetany or acute symptoms are present or anticipated because of a decrease in the serum calcium level.[43,50]

Chronic hypocalcemia is treated with oral intake of calcium. Oral calcium supplements of carbonate, gluconate, or lactate salts may be used.[43] Long-term treatment may require the use of vitamin D preparations, especially in persons with hypoparathyroidism and chronic kidney disease. The active form of vitamin D is administered when the liver or kidney mechanisms needed for hormone activation are impaired. Synthetic PTH (1–34) can be administered by subcutaneous injection as replacement therapy in hypoparathyroidism.

Hypercalcemia

Hypercalcemia represents a total serum calcium concentration greater than 10.5 mg/dL (2.6 mmol/L). Falsely elevated levels of calcium can result from prolonged drawing of blood with an excessively tight tourniquet. Increased serum albumin levels may also elevate the total serum calcium but not affect the ionized calcium.

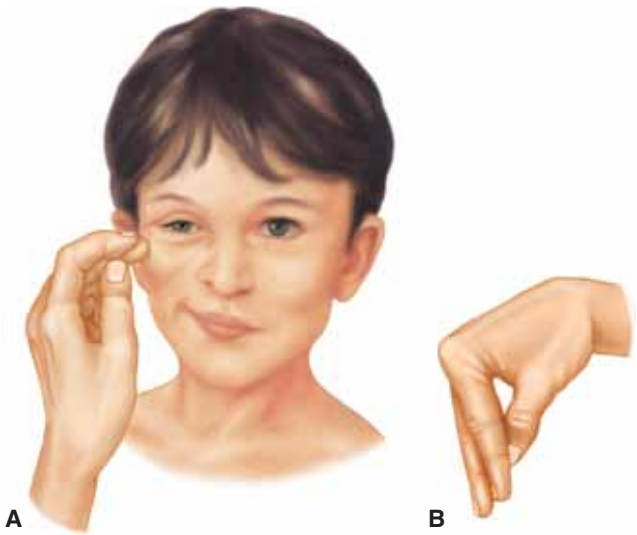


FIGURE 8-14. **(A)** The Chvostek sign: a contraction of the facial muscles elicited in response to a light tap over the facial nerve in front of ear. **(B)** The Trousseau sign: carpopedal spasm induced by inflating a blood pressure cuff above systolic blood pressure. (Adapted from Bullock B.A., Henze R.J. [2000]. *Focus on pathophysiology.* Philadelphia: Lippincott Williams & Wilkins.)

Causes. Hypercalcemia occurs when calcium movement into the circulation overwhelms calcium regulatory hormones or the ability of the kidney to remove excess calcium ions. The two most common causes of hypercalcemia are increased bone resorption due to neoplasms and hyperparathyroidism.[51] Hypercalcemia is a common complication of malignancy, occurring in approximately 20% to 30% of persons with advanced disease.[52] A number of malignant tumors, including carcinoma of the lungs, have been associated with hypercalcemia. Some tumors destroy the bone, while others produce humoral agents that stimulate bone resorption or inhibit bone formation.

Less common causes of hypercalcemia include prolonged immobilization, increased intestinal absorption of calcium, excessive doses of vitamin D, or the effects of drugs such as lithium and thiazide diuretics. Prolonged immobilization and lack of weight bearing cause demineralization of bone and release of calcium into the bloodstream. Intestinal absorption of calcium can be increased by excessive doses of vitamin D or as a result of a condition called the *milk-alkali syndrome*. The milk-alkali syndrome is caused by excessive ingestion of calcium (often in the form of milk) and absorbable antacids. Because of the availability of nonabsorbable antacids, the condition is seen less frequently than in the past, but it may occur in women who are overzealous in taking calcium preparations for osteoporosis prevention. Discontinuance of the antacid repairs the alkalosis and increases calcium elimination.

A variety of drugs elevate calcium levels. The use of lithium to treat bipolar disorders has been shown to cause hyperparathyroidism and hypercalcemia. The thiazide diuretics increase calcium reabsorption in the distal convoluted tubule of the kidney. Although the thiazide diuretics seldom cause hypercalcemia, they can unmask hypercalcemia from other causes such as underlying bone disease and conditions that increase bone resorption.

Manifestations. The signs and symptoms of calcium excess reflect a decrease in neural excitability, alterations in cardiac and smooth muscle function, and exposure of the kidneys to high concentrations of calcium (see Table 8-6). There may be a dulling of consciousness, stupor, weakness, and muscle flaccidity due to a decrease in neural excitability. Behavioral changes may range from subtle alterations in personality to acute psychoses. The heart responds to elevated levels of calcium with increased contractility and ventricular arrhythmias. Digitalis accentuates these responses. Gastrointestinal symptoms reflect a decrease in smooth muscle activity and include constipation, anorexia, nausea, and vomiting.

High calcium concentrations in the urine impair the ability of the kidneys to concentrate urine by interfering with the action of ADH (an example of nephrogenic DI).

This causes salt and water diuresis and an increased sensation of thirst. Hypercalciuria also predisposes to the development of renal calculi. Pancreatitis is another potential complication of hypercalcemia and is probably related to stones in the pancreatic ducts.

Hypercalcemic crisis describes an acute increase in the serum calcium level.[51] Malignant disease and hyperparathyroidism are the major causes of hypercalcemic crisis. In hypercalcemic crisis, polyuria, excessive thirst, volume depletion, fever, altered levels of consciousness, azotemia (i.e., nitrogenous wastes in the blood), and a disturbed mental state accompany other signs of calcium excess. Symptomatic hypercalcemia is associated with a high mortality rate; death often is caused by cardiac arrest.

Diagnosis and Treatment. The diagnosis of hypercalcemia is based on history, clinical manifestations, and serum calcium levels. Treatment of calcium excess usually is directed toward rehydration and use of measures to increase urinary excretion of calcium and inhibit release of calcium from bone.[51] Fluid replacement is needed in situations of volume depletion. The excretion of sodium is accompanied by calcium excretion. Diuretics and sodium chloride can be administered to increase urinary elimination of calcium after the ECF volume has been restored. Loop diuretics commonly are used rather than thiazide diuretics, which increase calcium reabsorption.

The initial lowering of calcium levels is followed by measures to inhibit bone reabsorption. Drugs that are used to inhibit calcium mobilization include bisphosphonates, calcitonin, and corticosteroids.[51] The bisphosphonates, which act mainly by inhibiting osteoclastic activity, provide a significant reduction in calcium levels with relatively few side effects. Calcitonin inhibits osteoclastic activity, thereby decreasing resorption. The corticosteroids inhibit the conversion of vitamin D to its active form and are used to treat hypercalcemia due to vitamin D toxicity and hematologic malignancies.

Disorders of Magnesium Balance

Magnesium is the second most abundant intracellular cation after potassium. Although the average adult has approximately 24 g of magnesium distributed throughout the body, only an estimated 2% is distributed in the ECF.[53–56] Approximately 20% to 30% of ECF magnesium is protein bound, and only a small fraction of ICF magnesium (15% to 30%) is exchangeable with the ECF. The normal serum concentration of magnesium is 1.8 to 2.6 mg/dL (0.75 to 1.1 mmol/L).

Only recently has the importance of magnesium to the overall function of the body been recognized. It is required for cellular energy metabolism, functioning of the Na^+/K^+-ATPase membrane pump, membrane stabilization, nerve conduction, and ion transport. Magnesium acts as a cofactor in many intracellular enzyme reactions, including the transfer of high-energy phosphate groups in the generation of ATP from adenosine diphosphate (ADP). It is essential to all reactions that require ATP, for every step related to replication and transcription of DNA, and for the translation of messenger RNA.[54]

Magnesium Balance

- Most of the body's magnesium is located within cells, where it functions in regulation of enzyme activity, generation of ATP, and calcium transport. Magnesium is necessary for parathyroid hormone function and hypomagnesemia is a common cause of hypocalcemia.
- Elimination of magnesium occurs mainly through the kidney, which adjusts urinary excretion as a means of maintaining serum magnesium levels. Diuretics tend to disrupt renal regulatory mechanisms and increase urinary losses of magnesium.
- There is an interdependency between intracellular concentrations of magnesium and potassium such that a decrease in one is accompanied by a decrease in the other. Magnesium deficiency contributes to cardiac arrhythmias that occur with hypokalemia.

Magnesium also participates in potassium and calcium channel activity. Potassium channels, including the acetylcholine-sensitive potassium channel, are dependent on adequate intracellular magnesium levels. Magnesium blocks the outward movement of potassium in cardiac cells; when magnesium levels are low, the channel permits outward flow of potassium, resulting in low levels of intracellular potassium with an accompanying risk for development of cardiac arrhythmias. Many calcium channels are also magnesium dependent. Higher ICF levels of magnesium inhibit calcium transport into the cell and its release from the sarcoplasmic reticulum. Thus, magnesium tends to act as a smooth muscle relaxant by altering calcium levels that are responsible for muscle contraction. Because of its smooth muscle relaxing effect, there has been a recent interest in the use of magnesium in the treatment of severe bronchial asthma.[57]

In addition, it has been suggested that magnesium may also have an anticonvulsant effect. The suggested mechanism of action is cerebral vasodilation and/or prevention of ischemic neuronal damage by blockade of *N*-methyl-D-aspartate (NMDA) receptors in the brain (see Chapter 37). Magnesium is the first-line drug in treatment of eclampsia in pregnant women.[57]

Regulation of Magnesium Balance

Magnesium is ingested in the diet, absorbed from the intestine, and excreted by the kidneys. Intestinal absorption is not closely regulated, and approximately 25% to 65% of dietary magnesium is absorbed. Magnesium is contained in all green vegetables, grains, nuts, meats, and seafood. Magnesium is also present in much of the groundwater in North America.

The kidney is the principal organ of magnesium regulation. The kidneys filter about 70% to 80% of the serum magnesium and excrete about 6%, although this amount can be influenced by other conditions and medications.[53] Magnesium is a unique electrolyte in that only approximately 12% to 20% of the filtered amount is reabsorbed in the proximal tubule.[56,57] The greatest quantity, approximately 70%, is passively reabsorbed in the thick ascending loop of Henle. The major driving force for magnesium absorption in the thick ascending loop of Henle is the positive voltage gradient created in the tubular lumen by the Na^+-K^+-$2Cl^-$ cotransport system (see Chapter 24). Inhibition of this transport system by loop diuretics lowers magnesium reabsorption. Active reabsorption of magnesium takes place in the distal convoluted tubule and accounts for about 10% of the filtered load. Magnesium reabsorption is stimulated by PTH and is decreased in the presence of increased serum levels of magnesium and calcium.

Hypomagnesemia

Magnesium deficiency refers to depletion of total body stores, while severe hypomagnesemia describes a low serum magnesium concentration of less than 1.8 mg/dL (0.75 mmol/L).[58] It is seen in conditions that limit intake or increase intestinal or renal losses, and it is a common finding in patients in emergency departments and critical care units.

Causes. Magnesium deficiency can result from insufficient intake, excessive losses, or movement between the ECF and ICF compartments. It can result from conditions that directly limit intake, such as malnutrition, starvation, or prolonged maintenance of magnesium-free parenteral nutrition. Other conditions, such as diarrhea, malabsorption syndromes, prolonged nasogastric suction, or laxative abuse, decrease intestinal absorption. Another common cause of magnesium deficiency is chronic alcoholism. Many factors contribute to hypomagnesemia in alcoholism, including low intake and gastrointestinal losses from diarrhea. The effects of hypomagnesemia are exaggerated by other electrolyte disorders, such as hypokalemia, hypocalcemia, and metabolic acidosis.

Although the kidneys are able to defend against hypermagnesemia, they are less able to conserve magnesium and prevent hypomagnesemia. Urine losses are increased in diabetic ketoacidosis, hyperparathyroidism, and hyperaldosteronism. Some drugs increase renal losses of magnesium, including both loop and thiazide diuretics, nephrotoxic drugs such as aminoglycoside antibiotics, cyclosporine, cisplatin, and amphotericin B.

Relative hypomagnesemia may also develop in conditions that promote movement of magnesium between the ECF and ICF compartments, including rapid administration of glucose, insulin-containing parenteral solutions, and alkalosis. Although transient, these conditions can cause serious alterations in body function.

Manifestations. Signs of magnesium deficiency are not usually apparent until the serum magnesium is less than 1.2 mEq/L (0.5 mmol/L). Many of the manifestations of magnesium deficit are due to related electrolyte disorders such as hypokalemia and hypocalcemia. Hypomagnesemia is characterized by an increase in neuromuscular excitability as evidenced by muscular weakness and tremors (Table 8-7). Other manifestations may include hyperactive deep tendon reflexes, paresthesias (i.e., numbness, pricking, tingling sensation), muscle fasciculations, and tetanic muscle contractions. A positive Chvostek or Trousseau sign may be present, especially if the abnormal serum magnesium level is associated with hypocalcemia. Because decreased serum magnesium increases irritability in nervous tissue, seizures may occur. Other manifestations may include ataxia, vertigo, disorientation, depression, and psychotic symptoms.

Cardiovascular manifestations include tachycardia, hypertension, and ventricular arrhythmias. There may be ECG changes such as widening of the QRS complex, appearance of peak T waves, prolongation of the PR interval, T-wave inversion, and appearance of U waves. Ventricular arrhythmias, particularly in the presence of digitalis, may be difficult to treat unless magnesium levels are normalized.

Magnesium deficiency often occurs in conjunction with hypocalcemia and hypokalemia, producing a number of related neurologic and cardiovascular manifestations.

TABLE 8-7 Manifestations of Hypomagnesemia and Hypermagnesemia

Hypomagnesemia	Hypermagnesemia
Laboratory Values	***Laboratory Values***
Serum magnesium <1.8 mg/dL (0.75 mmol/L)	Serum magnesium >2.6 mg/dL (1.1 mmol/L)
Neural and Muscle Effects	***Neural and Muscle Effects***
Personality changes	Lethargy
Athetoid or choreiform movements	Hyporeflexia
Nystagmus	Confusion
Tetany	Coma
Cardiovascular Effects	***Cardiovascular Effects***
Tachycardia	Hypotension
Hypertension	Cardiac arrhythmias
Cardiac arrhythmias	Cardiac arrest

Hypocalcemia is typical of severe hypomagnesemia. Most persons with hypomagnesemia-related hypocalcemia have decreased PTH levels, probably as a result of impaired magnesium-dependent mechanisms that control PTH release and synthesis. Hypokalemia is also a typical feature of hypomagnesemia. It leads to a reduction in intracellular potassium and impairs the ability of the kidneys to conserve potassium. When hypomagnesemia is present, hypokalemia is unresponsive to potassium replacement therapy.

Diagnosis and Treatment. The diagnosis of hypomagnesemia is based on clinical manifestations and laboratory findings. Treatment consists of magnesium replacement. The route of administration depends on the severity of the condition. Symptomatic, moderate to severe magnesium deficiency is treated by parenteral administration. Treatment must be continued for several days to replace stored and serum levels. In conditions of chronic intestinal or renal loss, maintenance support with oral magnesium may be required.

Magnesium often is used therapeutically to treat cardiac arrhythmia, myocardial infarct, angina, bronchial asthma, and pregnancy complicated by preeclampsia or eclampsia. Caution to prevent hypermagnesemia is essential; patients with any degree of chronic kidney disease must be carefully monitored to prevent magnesium excess.

Hypermagnesemia

Hypermagnesemia represents an increase in total body magnesium and a serum magnesium concentration in excess of 2.6 mg/dL (1.1 mmol/L). Because of the ability of the normal kidney to excrete magnesium, hypermagnesemia is rare.

Causes. When hypermagnesemia does occur, it usually is related to renal insufficiency and the injudicious use of magnesium-containing medications such as antacids, mineral supplements, or laxatives. The elderly are particularly at risk because they have age-related reductions in kidney function and tend to consume more magnesium-containing medications, including antacids and laxatives. Magnesium sulfate is used to treat toxemia of pregnancy and premature labor; in these cases, careful monitoring for signs of hypermagnesemia is essential.

Manifestations. The signs and symptoms occur only when serum magnesium levels exceed 4.8 mg/dL (2.0 mmol/L).[58] Because magnesium tends to suppress PTH secretion, hypocalcemia may accompany hypermagnesemia.

Hypermagnesemia affects neuromuscular and cardiovascular function (see Table 8-7). Increased levels of magnesium decrease acetylcholine release at the myoneural junction, causing hyporeflexia and muscle weakness. Cardiovascular effects are related to the calcium channel–blocking effects of magnesium. Blood pressure is decreased, and the ECG shows an increase in the PR interval, a shortening of the QT interval, T-wave abnormalities, and prolongation of the QRS and PR intervals. Severe hypermagnesemia is associated with muscle and respiratory paralysis, complete heart block, and cardiac arrest.

Diagnosis and Treatment. The diagnosis of hypermagnesemia is based on clinical manifestations and laboratory findings. The treatment of hypermagnesemia includes cessation of magnesium administration. Calcium is a direct antagonist of magnesium, and intravenous administration of calcium may be used. Peritoneal dialysis or hemodialysis may be required.

In summary, calcium, phosphorous, and magnesium are major divalent ions in the body. These divalent ions are directly or indirectly regulated by a number of factors including vitamin D and PTH. The major action of the activated form of vitamin D is to increase the absorption of calcium from the intestine. The main function of PTH is to maintain the calcium concentration of the ECF. It performs this function by promoting the release of calcium from the bone, increasing the activation of vitamin D as a means of enhancing intestinal absorption of calcium, and stimulating calcium conservation by the kidney while increasing phosphorous elimination. Hypoparathyroidism, which is characterized by hypocalcemia, reflects deficient PTH secretion, resulting in hypocalcemia. Hyperparathyroidism, which is caused by hypersecretion of PTH, is manifest by signs and symptoms related to skeletal abnormalities, exposure of the kidney to high calcium levels, and elevated serum calcium levels.

Calcium is a major divalent cation. Approximately 99% of body calcium is found in bone; less than 1% is found in the ECF compartment. The calcium in bone is in dynamic equilibrium with ECF calcium. Of the three forms of ECF calcium (i.e., protein bound, complexed, and ionized), only the ionized form can cross the cell membrane and contribute to cellular function. Ionized calcium has a number of functions. It contributes to neuromuscular function, plays a vital role in the blood clotting process, and participates in a number of enzyme reactions. Alterations in ionized calcium levels produce neural effects; neural excitability is increased in hypocalcemia and decreased in hypercalcemia.

Magnesium is the second most abundant ICF cation. It acts as a cofactor in many intracellular enzyme reactions and is required for cellular energy metabolism, functioning of the Na^+/K^+-ATPase membrane pump, nerve conduction, ion transport, and potassium and calcium channel activity. Hypomagnesemia impairs PTH release and the actions of PTH; it leads to a reduction in ICF potassium and impairs the ability of the kidney to conserve potassium. Cardiovascular manifestations include tachycardia, hypertension, and ventricular arrhythmias. Hypermagnesemia causes neuromuscular dysfunction with hyporeflexia, muscle weakness, and confusion.

Acid-Base Balance

Metabolic activities of the body require precise regulation of acid-base balance, which is reflected in the pH of the ECF. Membrane excitability, enzyme systems, and chemical reactions all depend on the pH being regulated within a narrow physiologic range to function in an optimal way. Many conditions, pathologic or otherwise, can alter acid-base balance.

Introductory Concepts

Normally, the concentration of body acids and bases is regulated so that the pH of extracellular body fluids is maintained within a very narrow range of 7.35 to 7.45. This balance is maintained through mechanisms that generate, buffer, and eliminate acids and bases.

Mechanisms of Acid-Base Balance

- The pH is determined by the ratio of the bicarbonate (HCO_3^-) base to the volatile carbonic acid ($H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$). At a normal pH of 7.4, the ratio is 20:1.
- The pH is regulated by extracellular (carbonic acid [H_2CO_3]/bicarbonate [HCO_3^-]) and intracellular (proteins) systems that buffer changes in pH that would otherwise occur because of the metabolic production of volatile (CO_2) and nonvolatile (i.e., sulfuric and phosphoric) acids.
- The respiratory system regulates the concentration of the volatile carbonic acid ($CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$) by changing the rate and depth of respiration.
- The kidneys regulate the plasma concentration of HCO_3^- by two processes: reabsorption of the filtered HCO_3^- and generation of new HCO_3^- or the elimination of H^+ ions that have been buffered by tubular systems (phosphate and ammonia) to maintain a luminal pH of at least 4.5.

Acid-Base Chemistry

An *acid* is a molecule that can dissociate and release a hydrogen ion (H^+) and a *base* is an ion or molecule that can accept or combine with H^+.[1–3] For example, hydrochloric acid (HCl) dissociates in water to form H^+ and Cl^- ions. The bicarbonate ion (HCO_3^-) is a base because it can combine with H^+ to form carbonic acid (H_2CO_3). Most of the body's acids and bases are weak acids and bases, the most important being H_2CO_3, which is a weak acid derived from carbon dioxide (CO_2), and *bicarbonate* HCO_3^-, which is a weak base.

The concentration of H^+ in body fluids is low compared with other ions. For example, the Na^+ is present at a concentration approximately 3.5 million times that of the H^+. Because it is cumbersome to work with such a small number, the H^+ concentration is commonly expressed in terms of the *pH*. Specifically, pH represents the negative logarithm ($\log_{10}$) of the H^+ concentration expressed in mEq/L. Thus, a pH value of 7.0 implies an H^+ concentration of 10^{-7} (0.0000001 mEq/L). Since the pH is inversely related to the H^+ concentration, a low pH indicates a high concentration of H^+ and a high pH a low concentration of H^+.

Acids and bases exist as buffer pairs or systems—a mixture of a weak acid and its conjugate base or a weak base and its conjugate acid. When an acid (HA) is added to water, it dissociates reversibly to form H^+ and its conjugate anion (A^-). The degree to which an acid dissociates and acts as an H^+ donor determines whether it is a strong or weak acid. *Strong acids*, such as sulfuric acid, dissociate completely, whereas *weak acids*, such as acetic acid, dissociate only to a limited extent. The same is true of a base and its ability to dissociate and accept a H^+.

Acid and Base Production

Acids are continuously generated as by-products of metabolic processes. Physiologically, these acids fall into two groups: the *volatile* H_2CO_3 *acid* and all other *nonvolatile* or *fixed acids*. Acids are continuously generated as by-products of metabolic processes (Fig. 8-15). The difference between the two types of acids arises because H_2CO_3 is in equilibrium with CO_2 ($H_2CO_3 \leftrightarrow CO_2 + H_2O$), which is volatile and leaves the body by way of the lungs. Therefore, the H_2CO_3 concentration is determined by the lungs and their capacity to exhale CO_2. The fixed or *nonvolatile acids* (e.g., sulfuric, hydrochloric, phosphoric) are not eliminated by the lungs. Instead, they are buffered by body proteins or extracellular buffers, such as HCO_3^-, and then eliminated by the kidney.

Carbon Dioxide and Bicarbonate Production. Carbon dioxide, which is the end product of aerobic metabolism, is transported in the circulation as a dissolved gas (i.e., PCO_2), as the bicarbonate ion (HCO_3^-), or as carbaminohemoglobin in CO_2 bound to hemoglobin (see understanding carbon dioxide transport). Collectively, dissolved CO_2 and HCO_3^- account for approximately 77% of the CO_2 that is transported in the extracellular fluid; the remaining CO_2 travels as carbaminohemoglobin.[2] Although CO_2 is a gas and not an acid, a small percentage of the gas combines with water to form H_2CO_3. The reaction that generates H_2CO_3 from CO_2 and water is catalyzed by an enzyme called *carbonic anhydrase*, which is present in large quantities in red blood cells, renal tubular cells, and other tissues in the body. The rate of the reaction between CO_2 and water is increased approximately 5000 times by the presence of carbonic anhydrase. Were it not for this enzyme, the reaction would occur too slowly to be of any significance.

Because it is almost impossible to measure H_2CO_3, CO_2 measurements are commonly used when calculating pH.

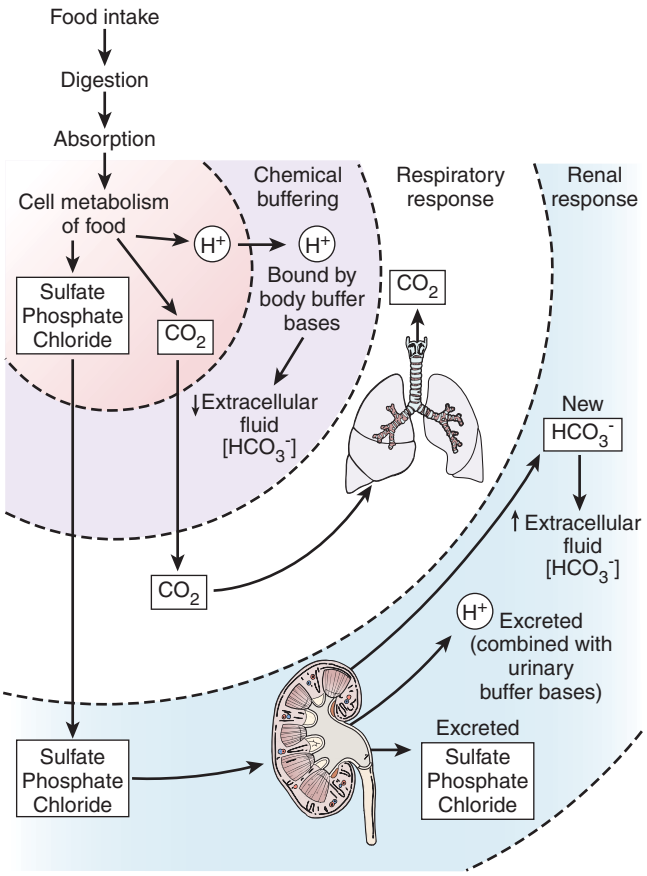


FIGURE 8-15. The maintenance of normal blood pH by chemical buffers, the respiratory system, and the kidneys. On a mixed diet, pH is threatened by the production of strong acids (sulfuric, hydrochloric, and phosphoric) mainly as the result of protein metabolism. These strong acids are buffered in the body by chemical buffer bases such as extracellular fluid (ECF) bicarbonate (HCO_3^-). The respiratory system disposes of carbon dioxide (CO_2). The kidney eliminates hydrogen ions (H^+) combined with urinary buffers and anions in the urine. At the same time, they add new HCO_3^- to the ECF to replace the HCO_3^- consumed in buffering strong acids. (From Rhoades R.A., Tanner G.A. [2003]. *Medical physiology* [2nd ed., p. 429]. Philadelphia: Lippincott Williams & Wilkins.)

The H_2CO_3 content of the blood can be calculated by multiplying the partial pressure of CO_2 (PCO_2) by its solubility coefficient, which is 0.03. This means that the concentration of H_2CO_3 in the arterial blood, which normally has a PCO_2 of approximately 40 mm Hg, is 1.20 mEq/L ($40 \times 0.03 = 1.20$), and that for venous blood, which normally has a PCO_2 of approximately 45 mm Hg, is 1.35 mEq/L.

Production of Fixed or Nonvolatile Acids and Bases. The metabolism of dietary proteins and other substances results in the generation of fixed or nonvolatile acids and bases.[3] Oxidation of the sulfur-containing amino acids (e.g., methionine, cysteine) results in the production of *sulfuric acid*; arginine and lysine, *hydrochloric acid*; and phosphorus-containing nucleic acids, *phosphoric acid*. Incomplete oxidation of glucose results in the formation of *lactic acid*, and incomplete oxidation of fats, the production of *ketoacids*. The major source of base is the metabolism of amino acids such as aspartate and glutamate and the metabolism of certain organic anions (e.g., citrate, lactate, acetate). Acid production normally exceeds base production, with the net effect being the addition of approximately 1 mmol/kg body weight of nonvolatile or fixed acid to the body each day.[3] Consumption of a vegetarian diet, which contains large amounts of organic anions, results in the net production of base.

Calculation of pH

The serum pH can be calculated using an equation called the *Henderson-Hasselbalch equation*. This equation uses the dissociation constant for the bicarbonate buffer system (6.1) and the HCO_3^--to-PCO_2 (used as a measure of H_2CO_3) ratio (Fig. 8-16). Because the ratio is used, a change in HCO_3^- will have little or no effect on pH as long as there is an accompanying change in PCO_2. Likewise, a change in PCO_2 will have little effect on pH as long as there is an accompanying change in HCO_3^-.

Regulation of pH

The pH of body fluids is regulated by three major mechanisms: (1) chemical buffer systems in body fluids, which immediately combine with excess acids or bases to prevent large changes in pH; (2) the lungs, which control the elimination of CO_2; and (3) the kidneys, which eliminate H^+ and both reabsorb and generate HCO_3^- (see Fig. 8-15).

Chemical Buffer Systems

The moment-by-moment regulation of pH depends on chemical buffer systems of the ICF and ECF. As previously discussed, a *buffer system* consists of a weak base and conjugate acid pair. In the process of preventing large changes in pH, the system trades a strong acid for a weak acid or a strong base for a weak base. The three major buffer systems that protect the pH of body fluids are the bicarbonate buffer system, the transcellular hydrogen-potassium exchange system, and body proteins.[1–3] Bone provides an additional buffering of body acids. These buffer systems are immediately available to combine with excess acids or bases and prevent large changes in pH from occurring during the time it takes for the respiratory and renal mechanisms to become effective.

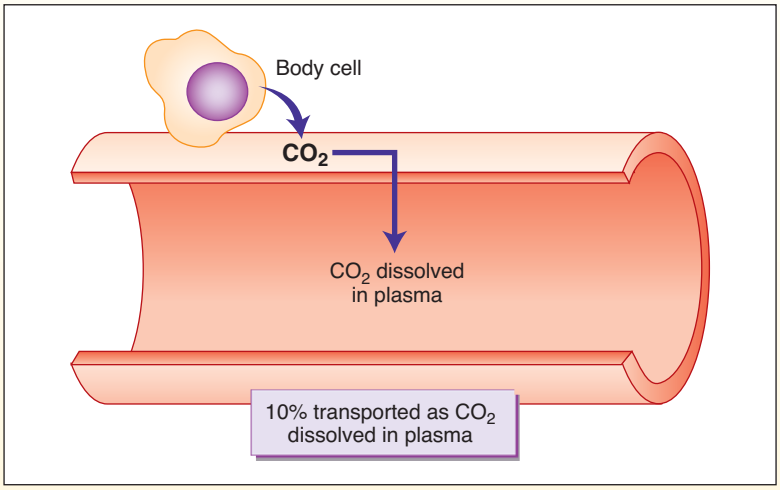
The *bicarbonate buffer system*, which is the principal ECF buffer, uses H_2CO_3 as its weak acid and a bicarbonate salt such as sodium bicarbonate ($NaHCO_3$) as its weak base. It substitutes the weak H_2CO_3 for a strong acid such as hydrochloric acid ($HCL + NaHCO_3 \leftrightarrow H_2CO_3 + NaCl$) or the weak bicarbonate base for a strong base such as sodium hydroxide ($NaOH + H_2CO_3 \leftrightarrow NaHCO_3 + H_2O$). The bicarbonate buffer system is a particularly efficient system because its components can be readily added or removed from the body.[59,60] Metabolism provides an ample supply of CO_2, which can replace any H_2CO_3 that is lost when excess base is added, and CO_2 can be readily eliminated when excess acid is

UNDERSTANDING → Carbon Dioxide Transport

Body metabolism results in a continuous production of carbon dioxide (CO_2). As CO_2 is formed during the metabolic process, it diffuses out of body cells into the tissue spaces and then into the circulation. It is transported in the circulation in three forms: (1) dissolved in the plasma, (2) as bicarbonate, and (3) attached to hemoglobin.

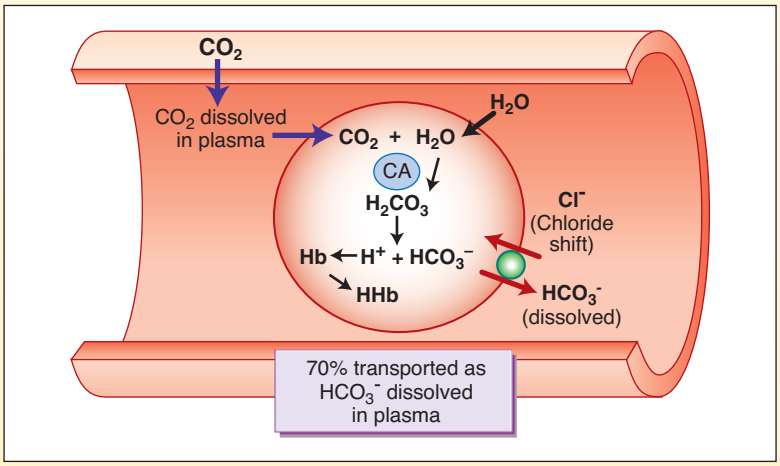
1

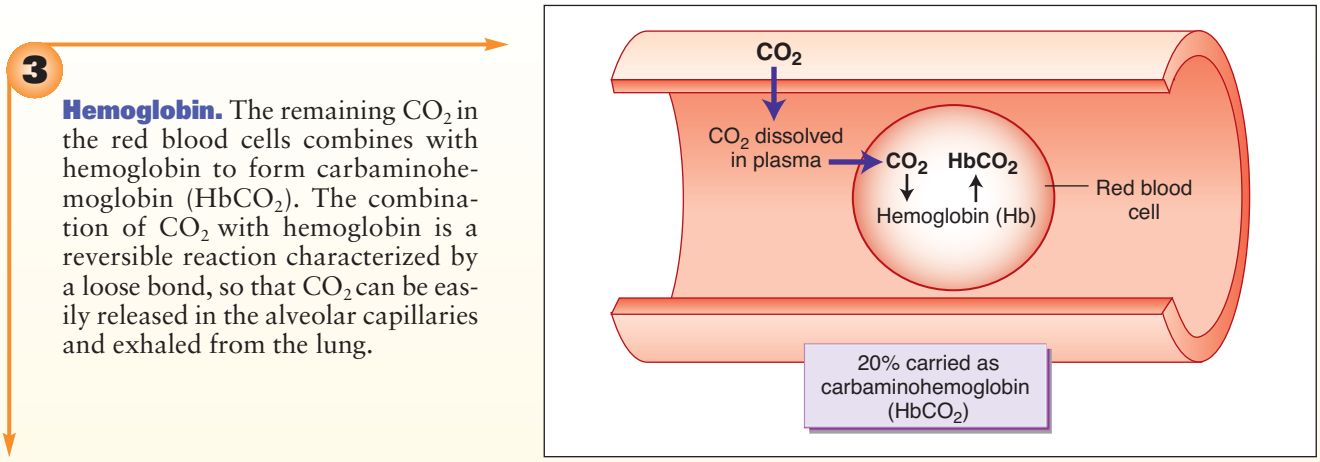
Plasma. A small portion (about 10%) of the CO_2 that is produced by body cells is transported in the dissolved state to the lungs and then exhaled. The amount of dissolved CO_2 that can be carried in plasma is determined by the partial pressure of the gas (PCO_2) and its solubility coefficient (0.03 mL/100 mL plasma for each 1 mm Hg PCO_2). Thus, each 100 mL of arterial blood with a PCO_2 of 40 mm Hg would contain 1.2 mL of dissolved CO_2. It is the carbonic acid (H_2CO_3) formed from hydration of dissolved CO_2 that contributes to the pH of the blood.



2

Bicarbonate. Carbon dioxide in excess of that which can be carried in the plasma moves into the red blood cells, where the enzyme carbonic anhydrase (CA) catalyzes its conversion to carbonic acid (H_2CO_3). The H_2CO_3, in turn, dissociates into hydrogen (H^+) and bicarbonate (HCO_3^-) ions. The H^+ combines with hemoglobin and the HCO_3^- diffuses into plasma, where it participates in acid-base regulation. The movement of HCO_3^- into the plasma is made possible by a special transport system on the red blood cell membrane in which HCO_3^- ions are exchanged for chloride ions (Cl^-).





added. Likewise, the kidney can conserve or form new HCO_3^- when excess acid is added, and it can excrete HCO_3^- when excess base is added.

The *transcellular hydrogen/potassium exchange system* provides another important system for regulation of acid-base balance. Both H^+ and K^+ are positively charged, and both ions move freely between the ICF and ECF compartments (see Fig. 8-9). When excess H^+ is present in the ECF, it moves into the ICF in exchange for K^+, and when excess K^+ is present in the ECF, it moves into the ICF in exchange for H^+. Thus, alterations in potassium levels can affect acid-base balance, and changes in acid-base balance can influence potassium levels. Potassium shifts tend to be more pronounced in metabolic acidosis than in respiratory acidosis.[1,60]

Proteins are the largest buffer system in the body. Proteins are *amphoteric*, meaning that they can function either as acids or bases. They contain many ionizable groups that can release or bind H^+. The protein buffers are largely located in cells, and H^+ ions and CO_2 diffuse across cell membranes for buffering by intracellular proteins. Albumin and plasma globulins are the major protein buffers in the vascular compartment.

Bone represents an additional source of acid-base buffering.[3] Excess H^+ ions can be exchanged for Na^+ and K^+ on the bone surface, and dissolution of bone minerals with release of compounds such as sodium bicarbonate ($NaHCO_3$) and calcium carbonate ($CaCO_3$) into the ECF can be used for buffering excess acids. It has been estimated that as much as 40% of buffering of an acute acid load takes place in bone. The role of bone buffers is even greater in the presence of chronic acidosis. The consequences of bone buffering include demineralization of bone and predisposition to development of kidney stones due to increased urinary excretion of calcium. Persons with chronic kidney disease are at particular risk for reduction in bone calcium due to acid retention.

Respiratory Control Mechanisms

The second line of defense against acid-base disturbances is the control of CO_2 by the lungs. Increased ventilation decreases PCO_2, while decreased ventilation increases PCO_2. Chemoreceptors in the brain stem and the peripheral chemoreceptors in the carotid and aortic bodies sense changes in the PCO_2 and pH of the blood and alter the ventilatory rate. The respiratory control of pH is rapid, occurring within minutes, and is maximal within 12 to 24 hours.[3] Although the respiratory response is rapid, it does not completely return the pH to normal. It is only about 50% to 75% effective as a buffer system.[59]

Renal Control Mechanisms

The kidneys regulate the pH of the ECF through three major mechanisms: (1) elimination of H^+ in the urine, (2) reabsorption of filtered HCO_3^-, and (3) production of new bicarbonate.[1–3,5] The renal mechanisms for regulating acid-base balance cannot adjust the pH within minutes, as respiratory mechanisms can, but they continue to function for days until the pH has returned to normal or the near-normal range.

Hydrogen/Bicarbonate Exchange. The hydrogen/bicarbonate exchange system regulates pH by secretion of excess H^+ and reabsorption of HCO_3^- by the renal tubules. Bicarbonate is freely filtered in the glomerulus (approximately 4300 mEq/day) and reabsorbed or reclaimed in the tubules.[2] Each HCO_3^- that is reclaimed requires the secretion of H^+, a process that is tightly coupled with sodium reabsorption (Fig. 8-17). Bicarbonate reabsorption also requires the presence of carbonic anhydrase to catalyze the combination of CO_2 and H_2O to form H_2CO_3. Carbonic anhydrase is present both intracellularly as well as on the tubular surface, allowing secreted H^+ to combine with HCO_3^- in the tubular fluid to form H_2CO_3. The H_2CO_3

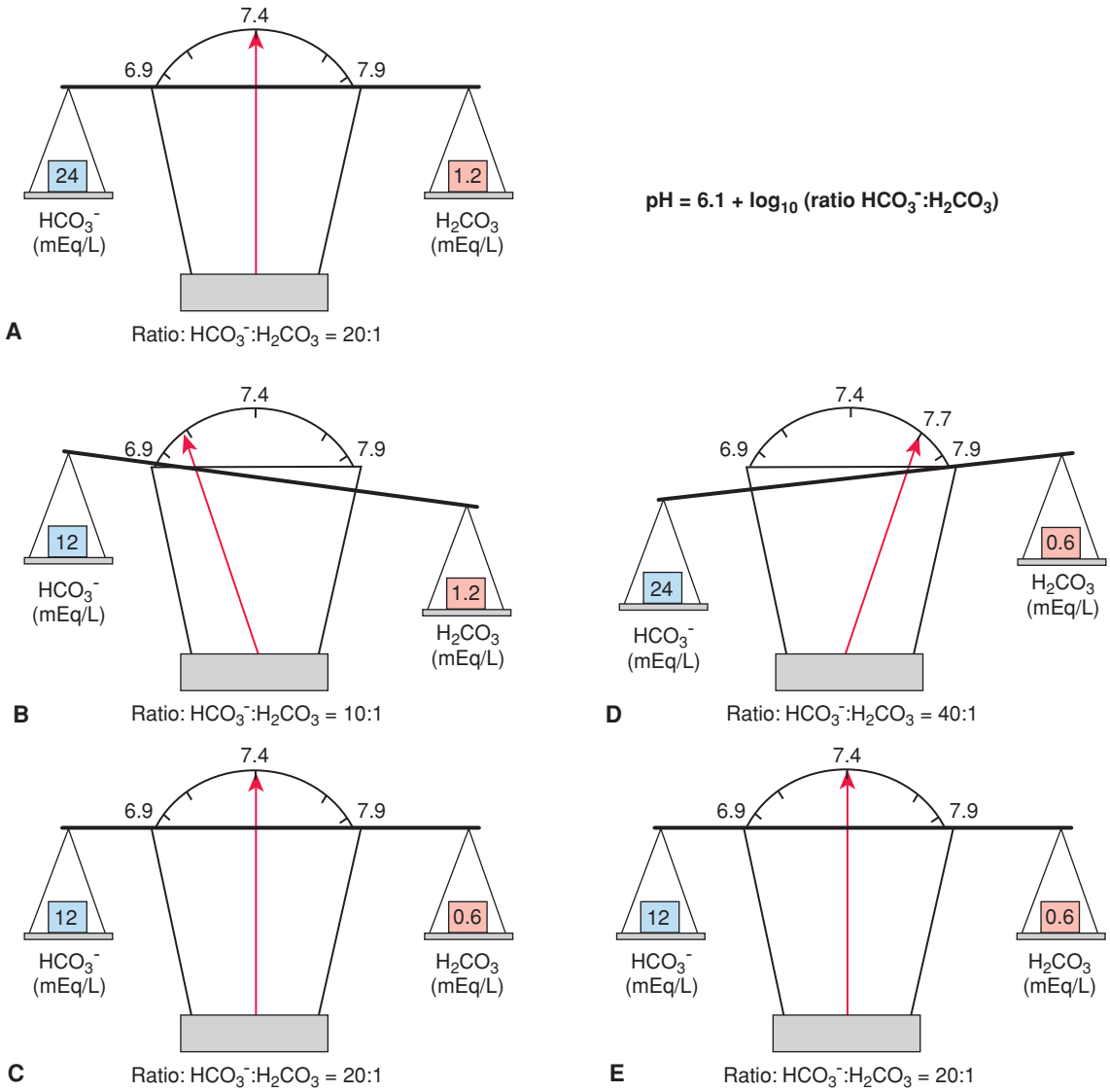


FIGURE 8-16. Normal and compensated states of pH and acid-base balance represented as a balance scale. **(A)** When the ratio of bicarbonate (HCO_3^-) to carbonic acid (H_2CO_3, arterial $CO_2 \times 0.03$) = 20:1, the pH = 7.4. **(B)** Metabolic acidosis with a HCO_3^-:H_3CO_3 ratio of 10:1 and a pH of 7.1. **(C)** Respiratory compensation lowers the H_3CO_3 to 0.6 mEq/L and returns the HCO_3^-:H_3CO_3 ratio to 20:1 and the pH to 7.4. **(D)** Respiratory alkalosis with a HCO_3^-:H_3CO_3 ratio of 40:1 and a pH of 7.7. **(E)** Renal compensation eliminates HCO_3^-, reducing serum levels to 12 mEq/L and returning the HCO_3^-:H_3CO_3 ratio to 20:1 and the pH to 7.4. Normally, these compensatory mechanisms are capable of buffering large changes in pH but do not return the pH completely to normal as illustrated here.

rapidly dissociates to form CO_2 and H_2O that can readily cross the tubular cell membrane. Inside the tubular cell, carbonic anhydrase again catalyzes the formation of H_2CO_3, which subsequently dissociates into HCO_3^- and H^+. The HCO_3^- then leaves the tubular cell and enters the ECF, and the H^+ is secreted into the tubular fluid to begin another cycle of HCO_3^- reclamation.

Reabsorption of Bicarbonate via Chloride/Bicarbonate Exchange. Another mechanism that the kidney uses in regulating HCO_3^- is the chloride/bicarbonate anion exchange that occurs in association with Na^+ reabsorption. Chloride is absorbed along with Na^+ throughout the tubules. In situations of volume depletion due to vomiting and chloride depletion, the kidney is forced to substitute HCO_3^- for the Cl^- anion, thereby increasing its absorption of HCO_3^-. *Hypochloremic alkalosis* refers to an increase in pH induced by excess HCO_3^- reabsorption due to a decrease in Cl^- levels, and *hyperchloremic acidosis* to a decrease in pH because of decreased HCO_3^- reabsorption due to an increase in Cl^- levels.

Potassium/Hydrogen Exchange. The potassium/hydrogen exchange system substitutes the reabsorption of K^+ for secretion of H^+ in the kidney. Hypokalemia is a potent stimulus for H^+ secretion and HCO_3^- reabsorption. When

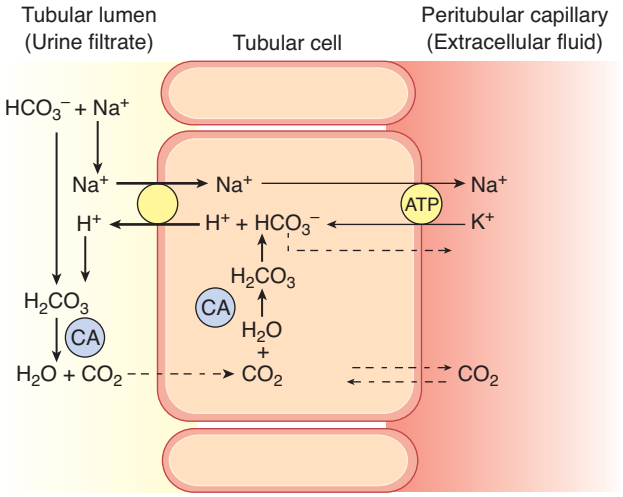


FIGURE 8-17. Hydrogen ion (H^+) secretion and bicarbonate ion (HCO_3^-) reabsorption in a renal tubular cell. Carbon dioxide (CO_2) diffuses from the blood or urine filtrate into the tubular cell, where it combines with water in a carbonic anhydrase (CA)-catalyzed reaction that yields carbonic acid (H_2CO_3). The H_2CO_3 dissociates to form H^+ and HCO_3^-. The H^+ is secreted into the tubular fluid in exchange for the sodium ion (Na^+). The Na^+ and HCO_3^- enter the extracellular fluid.

serum K^+ levels fall, there is movement of K^+ from the ICF into the ECF compartment and a reciprocal movement of H^+ from the ECF into the ICF compartment. A similar process occurs in the distal tubules of the kidney, where the Na^+/K^+-ATPase exchange pump actively reabsorbs K^+ as well as secreting H^+. Acidosis tends to increase H^+ elimination and decrease K^+ elimination, with a resultant increase in serum potassium levels, whereas alkalosis tends to decrease H^+ elimination and increase K^+ elimination, with a resultant decrease in serum potassium levels.[60–63]

Aldosterone also influences H^+ elimination by the kidney. It acts in the collecting duct to indirectly stimulate the secretion of H^+ into the urine filtrate while promoting extensive Na^+ reabsorption (see Chapter 32). This increased secretion of H^+ leads to increased excretion by the kidney and, therefore, metabolic acidosis.

Phosphate and Ammonia Buffers. Because an extremely acidic urine filtrate would be damaging to structures in the urinary tract, the elimination of H^+ requires a buffering system. There are two important intratubular buffer systems: the phosphate buffer system and the ammonia buffer system. The *phosphate buffer system* uses HPO_4^{2-} and $H_2PO_4^-$ that are present in the tubular filtrate to buffer H^+. The combination of H^+ with HPO_4^{2-} to form $H_2PO_4^-$ allows the kidneys to increase their secretion of H^+ ions. Because HPO_4^{2-} and $H_2PO_4^-$ are poorly absorbed, they become more concentrated as they move through the tubules.

Another important but more complex buffer system that facilitates the excretion of H^+ and generation of new HCO_3^- is the *ammonia buffer system*. Renal tubular cells are able to use the amino acid glutamine to synthesize ammonia (NH_3) and secrete it into the tubular fluid. Hydrogen ions then combine with the NH_3 to form ammonium ions (NH_4^+). The NH_4^+ ions, in turn, combine with Cl^- ions that are present in the tubular fluid to form ammonium chloride (NH_4Cl), which is then excreted in the urine. One of the most important features of the ammonia buffer system is that it is subject to physiologic control. Under normal conditions, the amount of H^+ ion eliminated by the ammonia buffer system is about 50% of the acid excreted and new HCO_3^- regenerated. However, with chronic acidosis, it can become the dominant mechanism for H^+ excretion and new HCO_3^- generation.

Laboratory Tests

Laboratory tests that are used in assessing acid-base balance include arterial blood gases and pH, CO_2 content and HCO_3^- levels, base excess or deficit, and blood and urine anion gaps. Although useful in determining whether acidosis or alkalosis is present, the pH measurements of the blood provide little information about the cause of an acid-base disorder.

Arterial blood gases provide a means of assessing the respiratory component of acid-base balance. H_2CO_3 levels are determined from arterial PCO_2 levels and the solubility coefficient for CO_2 (normal arterial PCO_2 is 38 to 42 mm Hg). Arterial blood gases are used because *venous blood gases* are highly variable, depending on metabolic demands of the various tissues that empty into the vein from where the sample is being drawn. Laboratory measurements of electrolytes include CO_2 content and measurement of bicarbonate. These measurements are determined by adding a strong acid to a blood sample and measuring the amount of CO_2 that is produced. More than 70% of the CO_2 in the blood is in the form of bicarbonate. The serum bicarbonate is then determined from the total CO_2 content of the blood.

Base excess or *deficit* is a measure of the HCO_3^- excess or deficit. It describes the amount of a fixed acid or base that must be added to a blood sample to achieve a pH of 7.4 (normal ± 2.0 mEq/L).[64] A base excess indicates metabolic alkalosis, and a base deficit indicates metabolic acidosis.

The *anion gap* describes the difference between the serum concentration of the major measured cation (Na^+) and the sum of the measured anions (Cl^- and HCO_3^-). This difference represents the concentration of unmeasured anions, such as phosphates, sulfates, organic acids, and proteins (Fig. 8-18). Normally, the anion gap ranges between 8 and 12 mEq/L (a value of 16 mEq/L is normal if both Na^+ and K^+ concentrations are used in the calculation). The anion gap is increased in conditions such as lactic acidosis and ketoacidosis that result in a decrease in HCO_3^-, and it is normal in hyperchloremic acidosis, where Cl^- replaces the normal HCO_3^- anion.[1]

Disorders of Acid-Base Balance

The terms *acidosis* and *alkalosis* describe the clinical conditions that arise as a result of changes in dissolved

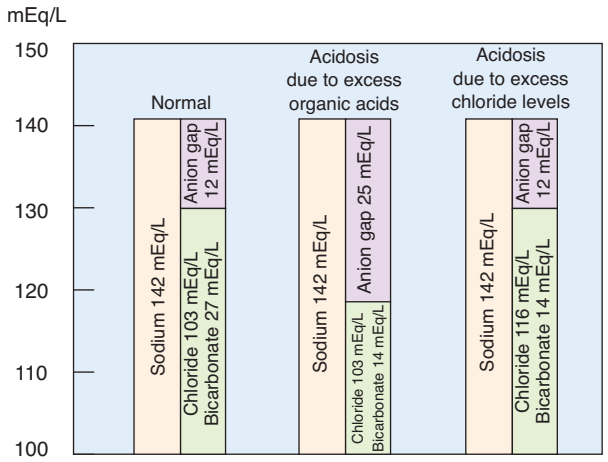


FIGURE 8-18. The anion gap in acidosis due to excess metabolic acids and excess serum chloride levels. Unmeasured anions such as phosphates, sulfates, and organic acids increase the anion gap because they replace bicarbonate. This assumes there is no change in sodium content.

CO_2 and HCO_3^- concentrations. An alkali represents a combination of one or more alkali metals such as sodium or potassium with a highly basic ion such as a hydroxyl ion (OH^-). Sodium bicarbonate ($NaHCO_3$) is the main alkali in the extracellular fluid. Although the definitions differ somewhat, the terms *alkali* and *base* are often used interchangeably. Hence, the term *alkalosis* has come to mean the opposite of *acidosis*.

Metabolic Versus Respiratory Acid-Base Disorders

There are two types of acid-base disorders: metabolic and respiratory (Table 8-8). *Metabolic disorders* produce an alteration in the serum HCO_3^- concentration and results from the addition or loss of nonvolatile acid or alkali to or from the extracellular fluids. A reduction in pH due to a decrease in HCO_3^- is called *metabolic acidosis*, and an elevation in pH due to increased HCO_3^- levels is called *metabolic alkalosis*. *Respiratory disorders* involve an alteration in the PCO_2, reflecting an increase or decrease in alveolar ventilation. *Respiratory acidosis* is characterized by a decrease in pH, reflecting a decrease in ventilation and an increase in PCO_2. *Respiratory alkalosis* involves an increase in pH, resulting from an increase in alveolar ventilation and a decrease in PCO_2.

Primary Versus Compensatory Changes in pH

Acidosis and alkalosis typically involve a *primary* or *initiating event* and a *compensatory* or *adaptive state* that results from homeostatic mechanisms that attempt to correct or prevent large changes in pH. For example, a person may have a primary metabolic acidosis as a result of overproduction of ketoacids and respiratory alkalosis because of a compensatory increase in ventilation (see Table 8-8).

Compensatory mechanisms provide a means to control pH when correction is impossible or cannot be immediately achieved. Often, compensatory mechanisms are interim measures that permit survival while the body

TABLE 8-8 Summary of Single Acid-Base Disturbances and Their Compensatory Responses

Acid-Base Imbalance	Primary Disturbance	Respiratory Compensation and Predicted Response*	Renal Compensation and Predicted Response*†
Metabolic acidosis	↓plasma pH and HCO_3^-	↑ventilation and ↓PCO_2 *1 mEq/L ↓HCO_3^- → 1 to 1.5 mm Hg ↓PCO_2*	↑H^+ excretion and ↑HCO_3^- reabsorption if no renal disease
Metabolic alkalosis	↑plasma pH and HCO_3^-	↓ventilation and ↑PCO_2 *1 mEq/L ↑HCO_3^- → 0.25 to 1.0 ↑PCO_2*	↓H^+ excretion and ↓HCO_3^- reabsorption if no renal disease
Respiratory acidosis	↓plasma pH and ↑PCO_2	None	↑H^+ excretion and ↑HCO_3^- reabsorption *Acute: 1 mm Hg ↑PCO_2 → 0.1 mEq/L ↑HCO_3^-* *Chronic: 1 mm Hg ↑PCO_2 → 0.4 mEq/L ↑HCO_3^-*
Respiratory alkalosis	↑plasma pH and ↓PCO_2	None	↑H^+ excretion and ↓HCO_3^- reabsorption *Acute: 1 mm Hg ↓PCO_2 → 0.2 mEq/L ↓HCO_3^-* *Chronic: 1 mm Hg ↓PCO_2 → 0.4 mEq/L ↓HCO_3^-*

Note: Predicted compensatory responses are in *italics.*

*If blood values are the same as predicted compensatory values, a single acid-base disorder is present; if values are different, a mixed acid-base disorder is present.[12]

†Acute renal compensation ≤48 hours, chronic renal compensation >48 hours.[12]

attempts to correct the primary disorder. Compensation requires the use of mechanisms that are different from those that caused the primary disorder. For example, the lungs cannot compensate for respiratory acidosis that is caused by lung disease, nor can the kidneys compensate for metabolic acidosis that occurs because of chronic kidney disease. The body can, however, use renal mechanisms to compensate for respiratory-induced changes in pH, and it can use respiratory mechanisms to compensate for metabolically induced changes in acid-base balance. Because compensatory mechanisms become more effective with time, there are often differences between the level of pH change that is present in acute and chronic acid-base disorders.

Single Versus Mixed Acid-Base Disorders. Thus far we have discussed acid-base disorders as if they existed as a single primary disorder such as metabolic acidosis, accompanied by a predicted compensatory response (i.e., hyperventilation and respiratory alkalosis). It is not uncommon, however, for persons to present with more than one primary disorder or a mixed disorder. For example, a person may present with a low serum HCO_3^- concentration due to metabolic acidosis and a high PCO_2 due to chronic lung disease. Values for the predicted renal or respiratory compensatory responses can be used in the diagnosis of these mixed acid-base disorders (Table 8-8).[1,61,63] If the values for the compensatory response fall outside the predicted values, it can then be concluded that more than one disorder (i.e., a mixed disorder) is present. Since the respiratory response to changes in HCO_3^- occurs almost immediately, there is only one predicted compensatory response for primary metabolic acid-base disorders. This is in contrast to the primary respiratory disorders, which have two ranges of predicted values, one for the acute and one for the chronic response. Renal compensation takes several days to become fully effective. The acute compensatory response represents the HCO_3^- levels before renal compensation has occurred and the chronic response after it has occurred. Thus, the values for the serum pH tend to be more normal in the chronic phase.

Metabolic Acidosis

Metabolic acidosis involves a decreased serum HCO_3^- concentration along with a decrease in pH. In metabolic acidosis, the body compensates for the decrease in pH by increasing the respiratory rate in an effort to decrease PCO_2 and H_2CO_3 levels. The PCO_2 can be expected to fall by 1 to 1.5 mm Hg for each 1 mEq/L fall in HCO_3^-.[1–3,5,61]

Metabolic acidosis can be caused by one or more of the following four mechanisms: (1) increased production of fixed metabolic acids or ingestion of fixed acids such as salicylic acid, (2) inability of the kidneys to excrete the fixed acids produced by normal metabolic processes, (3) excessive loss of bicarbonate via the kidneys or gastrointestinal tract, or (4) an increased serum Cl^- concentration.[61–63] The anion gap is often useful in determining the cause of the metabolic acidosis (Chart 8-2). The presence of excess metabolic acids produces an increase in the anion gap as sodium bicarbonate is replaced by the

Metabolic Acid-Base Disorders

- Metabolic acid-base disorders represent a primary change in the plasma HCO_3^- ion concentration.
- Metabolic acidosis can be defined as a decrease in plasma HCO_3^- and pH that is caused by an excess of production or accumulation of fixed acids or loss of HCO_3^- ion. Compensatory responses include an increase in ventilation and elimination of CO_2 and the reabsorption and generation of bicarbonate by the kidney.
- Metabolic alkalosis can be defined as an increase in plasma HCO_3^- and pH that is initiated by excess H^+ ion loss or HCO_3^- ion gain and maintained by conditions that impair the ability of the kidney to excrete the excess HCO_3^- ion. Compensatory responses include a decreased respiratory rate with retention of PCO_2 and increased elimination of HCO_3^- by the kidney.

CHART 8-2 The Anion Gap in Differential Diagnosis of Metabolic Acidosis

Decreased Anion Gap (<8 mEq/L)

Hypoalbuminemia (decrease in unmeasured anions)
Multiple myeloma (increase in unmeasured cationic IgG paraproteins)
Increased unmeasured cations (hyperkalemia, hypercalcemia, hypermagnesemia, lithium intoxication)

Increased Anion Gap (>12 mEq/L)

Presence of unmeasured metabolic anion
- Diabetic ketoacidosis
- Alcoholic ketoacidosis
- Lactic acidosis
- Starvation
- Renal insufficiency

Presence of drug or chemical anion
- Salicylate poisoning
- Methanol poisoning
- Ethylene glycol poisoning

Normal Anion Gap (8–12 mEq/L)

Loss of bicarbonate
- Diarrhea
- Pancreatic fluid loss
- Ileostomy (unadapted)

Chloride retention
- Renal tubular acidosis
- Ileal loop bladder
- Parenteral nutrition (arginine and lysine)

sodium salt of the offending acid (e.g., sodium lactate). When the acidosis results from an increase in serum Cl^- levels (e.g., hyperchloremic acidosis), the anion gap remains within normal levels.

Increased Production of Metabolic Acids. Among the causes of metabolic acidosis are an accumulation of lactic acid and excess production of ketoacids. *Acute lactic acidosis*, which is one of the most common types of metabolic acidosis, develops when there is excess production or diminished removal of lactic acid from the blood.[61,65,66] Lactic acid is produced by the anaerobic metabolism of glucose. Most cases of lactic acidosis are caused by inadequate oxygen delivery, as in shock or cardiac arrest.[67] Such conditions not only increase lactic acid production, but also tend to impair lactic acid clearance because of poor liver and kidney perfusion. Lactic acidosis can also occur during periods of intense exercise in which the metabolic needs of the exercising muscles outpace their aerobic capacity for production of ATP, causing them to revert to anaerobic metabolism and the production of lactic acid.[67] Lactic acidosis is also associated with disorders in which tissue hypoxia does not appear to be present. It has been reported in patients with leukemia, lymphomas, and other cancers; those with poorly controlled diabetes; and persons with severe liver failure.[68] Mechanisms causing lactic acidosis in these conditions are poorly understood. Some conditions such as neoplasms may produce local increases in tissue metabolism and lactate production or they may interfere with blood flow to noncancerous cells.

Ketoacids (i.e., acetoacetic and β-hydroxybutyric acid), produced in the liver from fatty acids, are the source of fuel for many body tissues. An overproduction of ketoacids occurs when carbohydrate stores are inadequate or when the body cannot use available carbohydrates as a fuel. Under these conditions, fatty acids are mobilized from adipose tissue and delivered to the liver, where they are converted to ketones. Ketoacidosis develops when ketone production by the liver exceeds tissue use. The most common cause of ketoacidosis is uncontrolled diabetes mellitus, in which an insulin deficiency leads to the release of fatty acids from adipose cells with subsequent production of excess ketoacids[69] (see Chapter 33). Ketoacidosis may also develop as the result of fasting or food deprivation, during which the lack of carbohydrates produces a self-limited state of ketoacidosis.[70,71]

Decreased Renal Function. Chronic kidney disease is the most common cause of chronic metabolic acidosis. The kidneys normally conserve HCO_3^- and secrete H^+ ions into the urine as a means of regulating acid-base balance. In chronic kidney disease, there is loss of both glomerular and tubular function, with retention of nitrogenous wastes and metabolic acids. In a condition called *renal tubular acidosis*, glomerular function is normal, but the tubular secretion of H^+ or reabsorption of HCO_3^- is abnormal (see Chapter 25).[72]

Increased Bicarbonate Losses. Increased HCO_3^- losses occur with the loss of bicarbonate-rich body fluids or with impaired conservation of HCO_3^- by the kidney. Intestinal secretions have a high HCO_3^- concentration. Consequently, excessive loss of HCO_3^- occurs with severe diarrhea; small-bowel, pancreatic, or biliary fistula drainage; ileostomy drainage; and intestinal suction. In diarrhea of microbial origin, HCO_3^- is also secreted into the bowel as a means of neutralizing the metabolic acids produced by the microorganisms causing the diarrhea.

Hyperchloremic Acidosis. Hyperchloremic acidosis occurs when Cl^- levels are increased.[73] Because Cl^- and HCO_3^- are exchangeable anions, the serum HCO_3^- decreases when there is an increase in Cl^-. Hyperchloremic acidosis can occur as the result of abnormal absorption of Cl^- by the kidneys or as a result of treatment with chloride-containing medications (i.e., sodium chloride, amino acid–chloride hyperalimentation solutions, and ammonium chloride). The administration of intravenous sodium chloride or parenteral hyperalimentation solutions that contain an amino acid–chloride combination can cause acidosis in a similar manner.[73] With hyperchloremic acidosis, the anion gap remains within the normal range, while serum Cl^- levels are increased and HCO_3^- levels are decreased.

Manifestations. Metabolic acidosis is characterized by a decrease in serum pH (<7.35) and HCO_3^- levels (<24 mEq/L) due to H^+ gain or HCO_3^- loss. Acidosis typically produces a compensatory increase in respiratory rate with a decrease in PCO_2. The manifestations of metabolic acidosis fall into three categories: signs and symptoms of the disorder causing the acidosis, changes in body function related to recruitment of compensatory mechanisms, and alterations in cardiovascular, neurologic, and musculoskeletal function resulting from the decreased pH (Table 8-9). The signs and symptoms of metabolic acidosis usually begin to appear when the serum HCO_3^- concentration falls to 20 mEq/L or less. A fall in pH to less than 7.0 to 7.10 can reduce cardiac contractility and predispose to potentially fatal cardiac dyrhythmias.[1]

Metabolic acidosis is seldom a primary disorder; it usually develops during the course of another disease. The manifestations of metabolic acidosis frequently are superimposed on the symptoms of the contributing health problem. With diabetic ketoacidosis, which is a common cause of metabolic acidosis, there is an increase in blood and urine glucose and a characteristic smell of ketones to the breath. In metabolic acidosis that accompanies chronic kidney disease, blood urea nitrogen levels are elevated and other tests of renal function yield abnormal results.

Manifestations related to respiratory and renal compensatory mechanisms usually occur early in the course of metabolic acidosis. In situations of acute metabolic acidosis, the respiratory system compensates for a decrease in pH by increasing ventilation to reduce PCO_2; this is accomplished through deep and rapid respirations. In diabetic ketoacidosis, this breathing pattern is referred to as *Kussmaul breathing*. For descriptive purposes, it can be said that Kussmaul breathing resembles the hyperpnea of exercise—the person breathes as though he or she had been running. There may be complaints of

TABLE 8-9 Manifestations of Metabolic Acidosis and Alkalosis

Metabolic Acidosis	Metabolic Alkalosis
Laboratory Tests	***Laboratory Tests***
pH decreased	pH increased
Bicarbonate (primary) decreased	Bicarbonate (primary) increased
PCO_2 (compensatory) decreased	PCO_2 (compensatory) increased
Signs of Compensation	***Signs of Compensation***
Increased respirations (rate and depth)	Decreased respirations (rate and depth) with various degrees of hypoxia and respiratory acidosis
Hyperkalemia	
Acid urine	
Increased ammonia in urine	
Gastrointestinal Effects	
Anorexia	
Nausea and vomiting	
Abdominal pain	
Nervous System Effects	***Nervous System Effects***
Weakness	Hyperactive reflexes
Lethargy	Tetany
Confusion	Confusion
Stupor	Seizures
Coma	
Depression of vital functions	
Cardiovascular Effects	***Cardiovascular Effects***
Peripheral vasodilation	Hypotension
Decreased heart rate	Cardiac arrhythmias
Cardiac arrhythmias	
Skin	
Warm and flushed	
Skeletal System Effects	
Bone disease (chronic acidosis)	

difficulty breathing or dyspnea with exertion; with severe acidosis, dyspnea may be present even at rest. Respiratory compensation for acute acidosis tends to be somewhat greater than for chronic acidosis. When kidney function is normal, H^+ excretion increases promptly in response to acidosis, and the urine becomes more acid.

Changes in pH have a direct effect on body function that can produce signs and symptoms common to most types of metabolic acidosis, regardless of cause. A person with metabolic acidosis often complains of weakness, fatigue, general malaise, and a dull headache. They also may have anorexia, nausea, vomiting, and abdominal pain. Tissue turgor is impaired, and the skin is dry when fluid deficit accompanies acidosis. In persons with undiagnosed diabetes mellitus, the nausea, vomiting, and abdominal symptoms may be misinterpreted as being caused by gastrointestinal flu or other abdominal disease, such as appendicitis. Acidosis depresses neuronal excitability and decreases binding of calcium to plasma proteins so that more free calcium is available to decrease neural activity. As acidosis progresses, the level of consciousness declines, and stupor and coma develop. The skin is often warm and flushed because blood vessels in the skin become less responsive to sympathetic nervous system stimulation and lose their tone.

When the pH falls to 7.0 to 7.1, cardiac contractility and cardiac output decrease, the heart becomes less responsive to catecholamines (i.e., epinephrine and norepinephrine), and arrhythmias, including fatal ventricular arrhythmias, can develop. A decrease in ventricular function may be particularly important in perpetuating shock-induced lactic acidosis, and partial correction of the acidemia may be necessary before tissue perfusion can be restored.[1]

Chronic acidemia, as in chronic kidney disease, can lead to a variety of musculoskeletal problems, some of which result from the release of calcium and phosphate during bone buffering of excess H^+ ions.[74] Of particular importance is impaired growth in children. In infants and children, acidemia may be associated with a variety of nonspecific symptoms such as anorexia, weight loss, muscle weakness, and listlessness.[1] Muscle weakness and listlessness may result from alterations in muscle metabolism.

Treatment. The treatment of metabolic acidosis focuses on correcting the condition that caused the disorder and restoring the fluids and electrolytes that have been lost from the body. The treatment of diabetic ketoacidosis is discussed in Chapter 33.

The use of supplemental sodium bicarbonate ($NaHCO_3$) may be indicated in the treatment of some forms of normal anion gap acidosis. However, its use in treatment of metabolic acidosis with an increased anion gap is controversial, particularly in cases of impaired tissue

perfusion.[75] In most patients with circulatory shock, cardiac arrest, or sepsis, impaired oxygen delivery is the primary cause of lactic acidosis. In these situations, the administration of large amounts of $NaHCO_3$ does not improve oxygen delivery and may produce hypernatremia, hyperosmolality, and decreased oxygen release by hemoglobin because of a shift in the oxygen dissociation curve.[75]

Metabolic Alkalosis

Metabolic alkalosis is a systemic disorder caused by an increase in serum pH due to a primary excess in HCO_3^-.[76,77] It is reported to be the second most common acid-base disorder in hospitalized adults, accounting for about 32% of all acid-base disorders.[77]

Most of the body's serum HCO_3^- is obtained from CO_2 that is produced during metabolic processes or from reabsorption of filtered HCO_3^- and generation of new HCO_3^- by the kidney. Usually, HCO_3^- production and renal reabsorption are balanced in a manner that prevents alkalosis from occurring. The proximal tubule reabsorbs 99.9% of the filtered HCO_3^-. When the serum levels of HCO_3^- rise above the threshold for tubular reabsorption, the excess is excreted in the urine. Many of the conditions that increase serum HCO_3^- also raise the level for HCO_3^- reabsorption, and thus an increase in HCO_3^- contributes not only to the generation of metabolic alkalosis, but also to its maintenance.

Metabolic alkalosis can be caused by factors that generate a loss of fixed acids or a gain of bicarbonate and those that maintain the alkalosis by interfering with excretion of the excess bicarbonate (see Table 8-9). They include (1) a gain of base via the oral or intravenous route, (2) loss of fixed acids, and (3) maintenance of the increased bicarbonate levels by contraction of the ECF volume, hypokalemia, and hypochloremia.

Excess Base Loading. Because the normal kidney is extremely efficient at excreting bicarbonate, excess base intake is rarely a cause of significant chronic metabolic alkalosis. Transient acute alkalosis, on the other hand, is a rather common occurrence during or immediately following excess oral ingestion of bicarbonate-containing antacids (e.g., Alka-Seltzer) or intravenous infusion of $NaHCO_3$ or base equivalent (e.g., acetate in hyperalimentation solutions, lactate in Ringer lactate, and citrate in blood transfusions). A condition called the *milk-alkali syndrome* is a condition in which the chronic ingestion of milk and/or calcium carbonate antacids leads to hypercalcemia and metabolic alkalosis. In this case, the antacids raise the serum HCO_3^- concentration, while the hypercalcemia prevents the urinary excretion of HCO_3^-. The most common cause at present is the administration of calcium carbonate as a phosphate binder to persons with chronic kidney disease.[3]

Loss of Fixed Acid. The loss of fixed acids occurs mainly through the loss of acid from the stomach and through the loss of chloride in the urine. Vomiting and removal of gastric secretions through the use of nasogastric suction are common causes of metabolic alkalosis in acutely ill or hospitalized patients. Bulimia nervosa with self-induced vomiting also is associated with metabolic alkalosis.[77] Gastric secretions contain high concentrations of HCl and lesser concentrations of potassium chloride. As Cl^- is taken from the blood and secreted into the stomach, it is replaced by HCO_3^-. Under normal conditions, each 1 mEq of H^+ that is secreted into the stomach generates 1 mEq of serum HCO_3^-.[78] Thus, the loss of gastric secretions through vomiting or gastric suction is a common cause of metabolic alkalosis. The accompanying ECF volume depletion, hypochloremia, and hypokalemia serve to maintain the metabolic alkalosis by increasing HCO_3^- reabsorption by the kidneys (Fig. 8-19).

The loop and thiazide diuretics are commonly associated with metabolic alkalosis, the severity of which varies directly with the degree of diuresis. The volume contraction and loss of H^+ in the urine contribute to the problem. The latter is primarily due to the enhanced H^+ secretion in the distal tubule that results from an interplay between the diuretic-induced increase in Na^+ delivery to the distal tubule and collecting duct where an accelerated excretion of H^+ and K^+ takes place and an increase in aldosterone secretion resulting from the volume contraction. Although aldosterone blunts the loss of Na^+, it also accelerates the secretion of K^+ and H^+. The resulting loss of K^+ also accelerates HCO_3^- reabsorption.

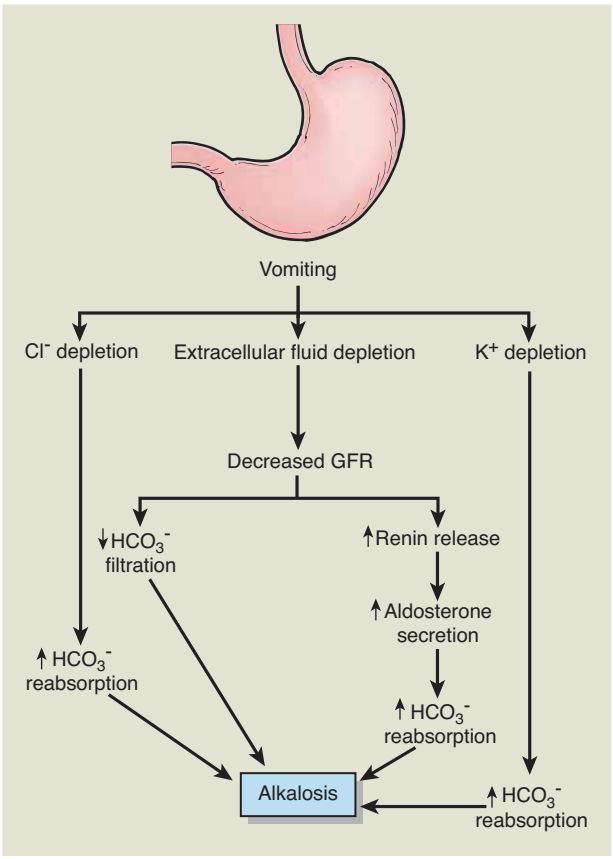


FIGURE 8-19. Renal mechanisms for bicarbonate (HCO_3^-) reabsorption and maintenance of metabolic alkalosis following depletion of extracellular fluid volume, chloride (Cl^-), and potassium (K^+) due to vomiting. GFR, glomerular filtration rate.

Metabolic alkalosis can also occur with abrupt correction of respiratory acidosis in persons with chronic respiratory acidosis. Chronic respiratory acidosis is associated with a compensatory loss of H^+ and Cl^- in the urine along with HCO_3^- retention. When respiratory acidosis is corrected abruptly, as with mechanical ventilation, metabolic alkalosis may develop due to a rapid drop in PCO_2, while serum HCO_3^-, which must be eliminated through the kidney, remains elevated.

Maintenance of Metabolic Alkalosis. Maintenance of metabolic alkalosis resides within the kidney and its inability to rid the body of the excess HCO_3^-. Many of the conditions that accompany the development of metabolic alkalosis, such as contraction of the ECF volume, hypochloremia, and hypokalemia, also increase reabsorption of HCO_3^- by the kidney, thereby contributing to its maintenance.

Depletion of the ECF causes a decline in the glomerular filtration rate with a subsequent increase in Na^+ and H_2O reabsorption. With depletion of Cl^- due to the loss of hydrochloric acid in conditions such as vomiting and nasogastric suction, the available anion for reabsorption with Na^+ is HCO_3^-. Hypokalemia, which generally accompanies metabolic alkalosis, also contributes to its maintenance. This is due partly to the direct effect of alkalosis on potassium excretion by the kidney and partly to a secondary hyperaldosteronism resulting from volume depletion. In hypokalemia, the distal tubular reabsorption of K^+ is accompanied by an increase in H^+ secretion. The secondary hyperaldosteronism, in turn, promotes extensive reabsorption of Na^+ from the distal and collecting tubules and at the same time stimulates the secretion of H^+ from cells in the collecting tubules. Hypokalemia induced in this manner further worsens the metabolic alkalosis by increasing HCO_3^- reabsorption in the proximal tubule and H^+ secretion in the distal tubule.

Manifestations. Metabolic alkalosis is characterized by a serum pH above 7.45, serum HCO_3^- above 29 mEq/L (29 mmol/L), and base excess above 3.0 mEq/L (3 mmol/L). Persons with metabolic alkalosis often are asymptomatic or have signs related to ECF volume depletion or hypokalemia. The manifestations of metabolic alkalosis are summarized in Table 8-9.

Neurologic signs and symptoms (e.g., hyperexcitability) occur less frequently with metabolic alkalosis than with other acid-base disorders because HCO_3^- enters the cerebrospinal fluid (CSF) more slowly than CO_2. When neurologic manifestations do occur, as in acute and severe metabolic alkalosis, they include mental confusion, hyperactive reflexes, tetany, and carpopedal spasm. Metabolic alkalosis also leads to a compensatory hypoventilation with development of various degrees of hypoxemia and respiratory acidosis. Significant morbidity occurs with severe metabolic alkalosis, including respiratory failure, arrhythmias, seizures, and coma.

Treatment. The treatment of metabolic alkalosis usually is directed toward correcting the cause of the condition. A chloride deficit requires correction. Potassium chloride usually is the treatment of choice when there is an accompanying potassium deficit. When potassium chloride is used as a therapy, the Cl^- anion replaces the HCO_3^- anion and the K^+ corrects the potassium deficit, allowing the kidneys to retain H^+ while eliminating K^+. Fluid replacement is used in the treatment of volume contraction alkalosis.

Respiratory Acidosis

Respiratory acidosis occurs in conditions that impair alveolar ventilation and cause an increase in serum PCO_2, also known as *hypercapnia*, along with a decrease in pH. Respiratory acidosis can occur as an acute or chronic disorder. Acute respiratory failure is associated with a rapid rise in arterial PCO_2 with a minimal increase in serum HCO_3^- and large decrease in pH. Chronic respiratory acidosis is characterized by a sustained increase in arterial PCO_2, resulting in renal adaptation with a more marked increase in serum HCO_3^- and a lesser decrease in pH.[78–80]

Respiratory acidosis occurs in acute or chronic conditions that impair effective alveolar ventilation and cause an accumulation of PCO_2. Impaired ventilation can occur as the result of decreased respiratory drive, lung disease, or disorders of the chest wall and respiratory muscle. Less commonly, it results from excess CO_2 production.

Acute Disorders of Ventilation. Acute respiratory acidosis can be caused by impaired function of the respiratory center in the medulla (as in narcotic overdose), lung disease, chest injury, weakness of the respiratory muscles, or airway obstruction. Almost all persons with acute respiratory acidosis are hypoxemic if they are breathing room air. In many cases, signs of hypoxemia develop prior to those of respiratory acidosis because CO_2 diffuses across the alveolar capillary membrane 20 times more rapidly than oxygen.[2,3]

Respiratory Acid-Base Disorders

- Respiratory acid-base imbalances are due to a primary disturbance in PCO_2, reflecting an increase or decrease in alveolar ventilation.
- Respiratory acidosis, or hypercapnia, represents an increase in PCO_2 and a decrease in plasma pH, resulting from a decrease in effective alveolar ventilation. Compensatory mechanisms include increased conservation and generation of HCO_3^- and elimination of H^+ by the kidney.
- Respiratory alkalosis, or hypocapnia, represents a decrease in PCO_2 and an increase in plasma pH, resulting from increased alveolar ventilation. Compensatory mechanisms include increased elimination of HCO_3^- and conservation of H^+ by the kidney.

Chronic Disorders of Ventilation. Chronic respiratory acidosis is a relatively common disturbance in persons with chronic obstructive lung disease. In these persons, the persistent elevation of PCO_2 stimulates renal H^+ secretion and HCO_3^- reabsorption. The effectiveness of these compensatory mechanisms can often return the pH to near-normal values as long as oxygen levels are maintained within a range that does not unduly suppress chemoreceptor control of respirations.

An acute episode of respiratory acidosis can develop in persons with chronic lung disease who receive oxygen therapy at a flow rate that is sufficient to raise their PO_2 to a level that produces a decrease in ventilation (see Chapter 23). In these persons, the medullary respiratory center has adapted to the elevated levels of CO_2 and no longer responds to increases in PCO_2. Instead, a decrease in the PO_2 becomes the major stimulus for respiration. If oxygen is administered at a flow rate that is sufficient to suppress this stimulus, the rate and depth of respiration decrease, and the PCO_2 increases. That being said, any person who is in need of additional oxygen should have it administered, albeit at a flow rate that does not depress the respiratory drive.

Increased Carbon Dioxide Production. Carbon dioxide is a product of the body's metabolic processes, generating a substantial amount of acid that must be excreted by the lungs or kidney to prevent acidosis. An increase in CO_2 production can result from numerous processes, including exercise, fever, sepsis, and burns. For example, CO_2 production increases by approximately 13% for each 1°C rise in temperature above normal.[80] Nutrition also affects the production of CO_2. A carbohydrate-rich diet produces larger amounts of CO_2 than one containing reasonable amounts of protein and fat. In healthy persons, the increase in CO_2 is usually matched by an increase in CO_2 elimination by the lungs, whereas persons with respiratory diseases may be unable to eliminate the excess CO_2.

Manifestations. Respiratory acidosis is associated with a serum pH below 7.35 and an arterial PCO_2 above 50 mm Hg. The signs and symptoms of respiratory acidosis (Table 8-10) depend on the rapidity of onset and whether the condition is acute or chronic. Because respiratory acidosis often is accompanied by hypoxemia, the manifestations of respiratory acidosis often are intermixed with those of oxygen deficit. Carbon dioxide readily crosses the blood-brain barrier, exerting its effects by changing the pH of brain fluids. Elevated levels of CO_2 produce vasodilation of cerebral blood vessels, causing headache, blurred vision, irritability, muscle twitching, and psychological disturbances. If the condition is severe and prolonged, it can cause an increase in CSF pressure and papilledema. Impaired consciousness, ranging from lethargy to coma, develops as the PCO_2 rises to extreme levels. Paralysis of extremities may occur, and there may be respiratory depression. Less severe forms of acidosis often are accompanied by warm and flushed skin, weakness, and tachycardia.

Treatment. The treatment of acute and chronic respiratory acidosis is directed toward improving ventilation. In severe cases, mechanical ventilation may be necessary. The treatment of respiratory acidosis due to respiratory failure is discussed in Chapter 23.

Respiratory Alkalosis

Respiratory alkalosis is a systemic acid-base disorder characterized by a primary decrease in blood PCO_2, also referred to as *hypocapnia*, which produces an elevation in pH and a subsequent decrease in HCO_3^-.[81,82] Because

TABLE 8-10 Manifestations of Respiratory Acidosis and Alkalosis

Respiratory Acidosis	Respiratory Alkalosis
Laboratory Tests	***Laboratory Tests***
pH decreased	pH increased
PCO_2 (primary) increased	PCO_2 (primary) decreased
Bicarbonate (compensatory) increased	Bicarbonate (compensatory) decreased
Signs of Compensation	***Signs of Compensation***
Acid urine	Alkaline urine
Nervous System Effects	**Nervous System Effects**
Dilation of cerebral vessels and decreased neuronal activity	Constriction of cerebral vessels and increased neuronal activity
Headache	Dizziness, panic, light-headedness
Behavioral changes	Tetany
Confusion	Numbness and tingling of fingers and toes
Depression	Seizures (severe)
Paranoia	
Hallucinations	
Weakness	
Tremors	
Paralysis	
Stupor and coma	
Skin	***Cardiovascular Effects***
Warm and flushed	Cardiac arrhythmias

respiratory alkalosis can occur suddenly, a compensatory decrease in bicarbonate level may not occur before respiratory correction has taken place.

Respiratory alkalosis is caused by hyperventilation or a respiratory rate in excess of that needed to maintain normal PCO_2 levels. It may occur as the result of central stimulation of the medullary respiratory center or stimulation of peripheral (e.g., carotid chemoreceptor) pathways to the medullary respiratory center.[82]

Mechanical ventilation may produce respiratory alkalosis if the rate and tidal volume are set so that CO_2 elimination exceeds CO_2 production. Carbon dioxide crosses the alveolar capillary membrane 20 times more rapidly than oxygen. Therefore, the increased minute ventilation may be necessary to maintain adequate oxygen levels while producing a concomitant decrease in CO_2 levels. In some cases, respiratory alkalosis may be induced through mechanical ventilation as a means of controlling disorders such as severe intracranial hypertension.[82]

Central stimulation of the medullary respiratory center occurs with anxiety, pain, pregnancy, febrile states, sepsis, encephalitis, and salicylate toxicity. Respiratory alkalosis has long been recognized as a common acid-base disorder in critically ill patients, and is a consistent finding in both septic shock and the systemic inflammatory response syndrome (see Chapter 20). Progesterone increases ventilation in women; during the progesterone phase of the menstrual cycle, normal women increase their PCO_2 values by 2 to 4 mm Hg and their pH by 0.01 to .02.[79] Women also develop substantial hypocapnia during pregnancy, most notably during the last trimester with PCO_2 values of 29 to 32 mm Hg.[79]

One of the most common causes of respiratory alkalosis is hyperventilation syndrome, which is characterized by recurring episodes of overbreathing often associated with anxiety. Persons experiencing panic attacks frequently present in the emergency room with manifestations of acute respiratory alkalosis.

Hypoxemia exerts its effect on pH through the peripheral chemoreceptors in the carotid bodies. Stimulation of peripheral chemoreceptors occurs in conditions that cause hypoxemia with relatively unimpaired CO_2 transport such as exposure to high altitudes.

Manifestations. Respiratory alkalosis manifests with a decrease in PCO_2 and a deficit in H_2CO_3. In respiratory alkalosis, the pH is above 7.45, arterial PCO_2 is below 35 mm Hg, and serum HCO_3^- levels usually are below 24 mEq/L (24 mmol/L).

The signs and symptoms of respiratory alkalosis are associated with hyperexcitability of the nervous system and a decrease in cerebral blood flow (Table 8-10). Alkalosis increases protein binding of extracellular calcium. This reduces ionized calcium levels, causing an increase in neuromuscular excitability. A decrease in the CO_2 content of the blood causes constriction of cerebral blood vessels. Because CO_2 crosses the blood-brain barrier rather quickly, the manifestations of acute respiratory alkalosis are usually of sudden onset. The person often experiences light-headedness, dizziness, tingling, and numbness of the fingers and toes. These manifestations may be accompanied by sweating, palpitations, panic, air hunger, and dyspnea. Chvostek and Trousseau signs may be positive, and tetany and convulsions may occur. Because CO_2 provides the stimulus for short-term regulation of respiration, short periods of apnea may occur in persons with acute episodes of hyperventilation.

Treatment. The treatment of respiratory alkalosis focuses on measures to correct the underlying cause. Hypoxia may be corrected by administration of supplemental oxygen. Changing ventilator settings may be used to prevent or treat respiratory alkalosis in persons who are being mechanically ventilated. Persons with hyperventilation syndrome may benefit from reassurance, rebreathing from a paper bag during symptomatic attacks, and attention to the psychological stress.

In summary, normal body function depends on the precise regulation of acid-base balance to maintain a pH within the narrow physiologic range of 7.35 to 7.45. Metabolic processes produce volatile and nonvolatile metabolic acids that must be buffered and eliminated from the body. The volatile acid H_2CO_3 is in equilibrium with dissolved PCO_2, which is eliminated through the lungs. The nonvolatile acids, which are derived mainly from protein metabolism and incomplete carbohydrate and fat metabolism, are excreted by the kidneys. It is the ratio of the HCO_3^- concentration to H_2CO_3 (PCO_2) that determines body pH. When this ratio is 20:1, the pH is 7.4. The ability of the body to maintain pH within the normal physiologic range depends on respiratory and renal mechanisms and on intracellular and extracellular buffers, the most important being the bicarbonate buffer system. The respiratory regulation of pH is rapid but does not return the pH completely to normal. The kidney aids in regulation of pH by eliminating H^+ ions or conserving HCO_3^- ions. In the process of eliminating H^+, it uses the phosphate and ammonia buffer systems. Body pH is also affected by the distribution of exchangeable cations (K^+ and H^+) and anions (Cl^- and HCO_3^-).

Metabolic acidosis is defined as a decrease in HCO_3^- and metabolic alkalosis as an increase in HCO_3^-. Metabolic acidosis is caused by an excessive production and accumulation of metabolic acids or excessive loss of HCO_3^-. Metabolic alkalosis is caused by an increase in HCO_3^- or a decrease in H^+ or Cl^-, with a resultant increase in renal reabsorption of HCO_3^-. Respiratory acidosis reflects a decrease in pH that is caused by conditions that produce hypoventilation, with a resultant increase in PCO_2 levels. Respiratory alkalosis reflects an increase in pH that is caused by conditions that produce hyperventilation, with a resultant decrease in PCO_2 levels.

The signs and symptoms of acidosis and alkalosis reflect alterations in body function associated with the disorder causing the acid-base disturbance, the effect of the change of pH on body function, and the body's attempt to correct and maintain the pH within a normal physiologic range. In general, neuromuscular excitability is decreased in acidosis and increased in alkalosis.

REVIEW EXERCISES

1. A 40-year-old man with advanced acquired immunodeficiency syndrome (AIDS) presents with an acute chest infection. Investigations confirm a diagnosis of *Pneumocystis carinii* pneumonia. Although he is being treated appropriately, his serum sodium level is 118 mEq/L. Tests of adrenal function are normal.

A. What is the likely cause of his electrolyte disturbance?
B. What are the five cardinal features of this condition?

2. A 70-year-old woman who is taking furosemide (a loop diuretic) for congestive heart failure complains of weakness, fatigue, and cramping of the muscles in her legs. Her serum potassium is 2.0 mEq/L, and her serum sodium is 140 mEq/L. She also complains that she notices a "strange heartbeat" at times.

A. What is the likely cause of this woman's symptoms?
B. An ECG shows a depressed ST segment and low T-wave changes. Explain the physiologic mechanism underlying these changes.
C. What would be the treatment for this woman?

3. A 50-year-old woman presents with symptomatic hypercalcemia. She has a recent history of breast cancer treatment.

A. How do you evaluate this person with increased serum calcium levels?
B. What is the significance of the recent history of malignancy?
C. What further tests may be indicated?

4. A 34-year-old woman with diabetes is admitted to the emergency room in a stuporous state. Her skin is flushed and warm, her breath has a sweet odor, her pulse is rapid and weak, and her respirations are rapid and deep. Her initial laboratory tests indicate a blood sugar of 320 mg/dL, serum HCO_3^- of 12 mEq/L (normal, 24 to 27 mEq/L), and a pH of 7.1 (normal, 7.35 to 7.45).

A. What is the most likely cause of her lowered pH and bicarbonate levels?
B. How would you account for her rapid and deep respirations?
C. How would you explain her warm, flushed skin and stuporous mental state?

5. A 16-year-old girl is seen by her primary care provider because her parents are concerned about her binge eating and their recent discovery that she engages in self-induced vomiting. Initial laboratory tests reveal a serum K^+ of 3.0 mEq/L and Cl^- of 93.

A. Explain her low K^+ and Cl^-.
B. What type of acid-base abnormality would you expect her to have?

6. A 65-year-old man with chronic obstructive lung disease has been using low-flow oxygen therapy because of difficulty in maintaining adequate oxygenation of his blood. He has recently developed a severe respiratory tract infection and has trouble breathing. He is admitted to the emergency room because his wife has had trouble arousing him. His respirations are 12 breaths/minute. She relates that he had "turned his oxygen way up" because of difficulty breathing.

A. What is the most likely cause of this man's problem?
B. How would you explain the lethargy and difficulty in arousal?
C. Arterial blood gases, drawn on admission to the emergency room, indicated a PO_2 of 85 mm Hg (normal, 90 to 95 mmHg) and a PCO_2 of 90 mm Hg (normal, 40 mm Hg). His serum HCO_3^- was 34 mEq/L (normal, 24 to 48 mEq/L). What is his pH?
D. What would be the main goal of treatment for this man in terms of acid-base balance?

REFERENCES

1. Berne R.M., Levy M.N., Koeppen B.M, et al. (Eds.). (2005). *Physiology* (5th ed., pp. 311–379, 659–684, 804–813). Philadelphia: Elsevier Saunders.
2. Guyton A., Hall J.E. (2006). *Text book of medical physiology* (11th ed., pp. 177–178, 183–190, 291–306, 358–363, 383–401, 887, 893–894, 983–992). Philadelphia: Elsevier Saunders.
3. Rose B.D., Post T.W. (2001). *Clinical physiology of acid-base and electrolyte disorders* (5th ed., pp. 187–190, 478–479, 547, 682–692, 823–842, 896–897). New York: McGraw-Hill.
4. Schrier R.W., Gurevich A.K., Abraham W.T. (2003). Renal sodium excretion, edematous disorders, and diuretic use. In Schrier R.W. (Ed.), *Renal and electrolyte disorders* (6th ed., pp. 64–114). Philadelphia: Lippincott Williams & Wilkins.
5. Costanzo L.S. (2002). *Physiology* (2nd ed., pp. 151–153, 275–299, 398–408). Philadelphia: Saunders.
6. Demling R.H. (2005). The burn edema process: Current concepts. *Journal of Burn Care and Rehabilitation* 26, 207–227.
7. O'Brien J.G., Chennubhotla R.V. (2005). Treatment of edema. *American Family Physician* 71(11), 2111–2117.
8. Stearns R.H., Spital A., Clark E.C. (1996). Disorders of water balance. In Kokko J., Tannen R.L. (Eds.), *Fluids and electrolytes* (3rd ed., pp. 65, 69, 95). Philadelphia: W.B. Saunders.
9. Metheney N.M. (2000). *Fluid and electrolyte balance* (4th ed., pp. 3, 18, 47, 56, 112). Philadelphia: Lippincott Williams & Wilkins.
10. Schrier R.W. (2006). Water and sodium retention in edematous disorders: Role of vasopressin and aldosterone. *American Journal of Medicine* 119, S47–S53.
11. Brewster U.C., Selaro J.F., Perazella M.A. (2003). The renin-angiotensin-aldosterone system: Cardiorenal effects and implications for renal and cardiovascular disease states. *American Journal of Medical Sciences* 326, 15–24.

12. McKinley M.J., Johnson A.K. (2004). The physiological regulation of thirst and fluid intake. *News in Physiological Sciences* 19, 1–6.
13. Kenney W.L., Chiu P. (2001). Influence of age on thirst and fluid intake. *Medicine & Science in Sports & Exercise* 33(9), 1524–1532.
14. Hodak S.P., Verbalis J.G. (2005). Abnormalities in water homeostasis in aging. *Endocrinology and Metabolism Clinics of North America* 34, 1031–1046.
15. Dundas B., Harris M., Narasimhan M. (2007). Psychogenic polydipsia. *Current Psychiatry Reports* 9(3), 236–241.
16. Seigel A.J. (2008). Hyponatremia in psychiatric patients: Update on evaluation and management. *Harvard Review of Psychiatry* 16(1), 13–24.
17. Treschan T.A., Peters J. (2006). The vasopressin system. *Anesthesiology* 105(3), 599–612.
18. Makaryus A.N., McFarlane S.I. (2006). Diabetes insipidus: Diagnosis and treatment of a complex disease. *Cleveland Clinic Journal of Medicine* 73(1), 65–71.
19. Sands J.M., Bichet D.G. (2006). Nephrogenic diabetes insipidus. *Annals of Internal Medicine* 144, 186–194.
20. Behan, L.A., Phillips, J., Thompson, L.T., et al. (2008). Neuroendocrine disorders after traumatic brain injury. *Journal of Neurology, Neurosurgery and Psychiatry* 79, 753–759.
21. Alexander M.P., Farag Y.M., Mattal B.V., et al. (2008). Lithium toxicity: A double-edged sword. *Kidney International* 73(2), 233–237.
22. Robertson G.L. (2006). Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *American Journal of Medicine* 119, S36–S42.
23. Adler S.M., Verbalis J.G. (2006). Disorders of water balance homeostasis in critical illness. *Endocrinology and Metabolism Clinics of North America* 35, 873–894.
24. Yeates K.E., Morton A.R. (2006). Vasopressin antagonist: Role in management of hyponatremia. *American Journal of Nephrology* 26, 348–355.
25. Lin M., Liu S.J., Lim I.T. (2005). Disorders of water imbalance. *Emergency Clinics of North America* 23, 749–770.
26. Adrogue H.J., Madias N.E. (2000). Hyponatremia. *New England Journal of Medicine* 343, 1581–1589.
27. Palmer B.F., Gates J.R., Lader M. (2003). Causes and management of hyponatremia. *Annals of Pharmacotherapy* 37, 1694–1702.
28. Gohl K.P. (2004). Management of hyponatremia. *American Family Physician* 69, 2387–2394.
29. Freda B.J., Davidson M.B., Hall P.M. (2004). Evaluation of hyponatremia: A little physiology goes a long way. *Cleveland Clinic Journal of Medicine* 71(8), 639–650.
30. Palm C., Pistrosch F., Herbrig K., et al (2006). Vasopressin antagonists as aquaretic agents for the treatment of hyponatremia. *American Journal of Medicine* 119, S87–S92.
31. Murase T., Sugimura Y., Takefuji S., et al. (2006). Mechanisms and therapy of osmotic demyelination. *American Journal of Medicine* 119(7A), S69–S73.
32. Hascal R. (2007). Current issues for nurse practitioners: Hyponatremia. *Journal of the American Academy of Nurse Practitioners* 19, 563–579.
33. Adrogue H.J., Madias N.E. (2000). Hypernatremia. *New England Journal of Medicine* 342, 1493–1499.
34. Rao M.C. (2004). Oral rehydration therapy. *Annual Review of Physiology* 66, 183–417.
35. Schaefer T.J., Wolford R.W. (2005). Disorders of potassium. *Medical Clinics of North America* 23, 723–747.
36. Peterson N.L., Levi M. (2003). Disorders of potassium metabolism. In Scheir R.W. (Ed.), *Renal and electrolyte disorders* (6th ed., pp. 171–215). Philadelphia: Lippincott Williams & Wilkins.
37. Schaefer T., Wolford R.W. (2005). Disorders of potassium. *Emergency Medicine Clinics of North America* 23, 723–747.
38. Woods S.L. (2005). *Cardiac nursing* (5th ed., pp. 179–183). Philadelphia: Lippincott Williams & Wilkins.
39. Gennari F.J. (1998). Hypokalemia. *New England Journal of Medicine* 339, 451–458.
40. Gennari J.F. (2002). Disorders of potassium homeostasis: Hypokalemia and hyperkalemia. *Critical Care Clinics* 18, 273–288.
41. Matfin G., Durand D., D'Agostino A., et al. (1998). Thyrotoxic hypokalemic periodic paralysis. *Hospital Practice* 1, 23–26.
42. Hollander-Rodriguez J.C., Calvert J.F. (2006). Hyperkalemia. *American Family Physician* 73(2), 283–290.
43. Moe S.M. (2008). Disorders involving calcium, phosphorous, and magnesium. *Primary Care* 35(2), 215–237.
44. Shoback D. (2008). Hypothyroidism. *New England Journal of Medicine* 359(4), 391–403.
45. Maitra A. (2008). The endocrine system. In Kumar V., Abbas A.K., Fausto N., et al. *Robbins basic pathology* (5th ed., pp. 771–775). Philadelphia: Saunders Elsevier.
46. Tangiera E.D. (2004). Hyperparathyroidism. *American Family Physician* 69, 333–340.
47. Ahmad R., Hammond J.M. (2004). Primary, secondary, and tertiary hyperthyroidism. *Otolaryngologic Clinics of North America* 17, 701–713.
48. Goodman W.G. (2003) Medical management of secondary hyperparathyroidism in chronic renal failure. *Nephrology, Dialysis and Transplantation* 18(Suppl 3), S2–S8.
49. Ariyan C.E., Sosa J.A. (2005). Assessment and management of patients with abnormal calcium. *Critical Care Medicine* 32(Suppl), S146–S154.
50. Reber R.M., Heath H. (1995). Hypocalcemic emergencies. *Medical Clinics of North America* 79, 93–165.
51. Carroll M.F., Schade D.S. (2003). A practical approach to hypercalcemia. *American Family Physician* 67, 1959–1966.
52. Stewart A.F. (2005). Hypercalcemia associated with cancer. *New England Journal of Medicine* 353(4), 373–379.
53. Swain R., Kaplan-Machlis B. (1999). Magnesium for the next millennium. *Southern Medical Journal* 92, 1040–1046.
54. Gums J.G. (2004). Magnesium in cardiovascular and other disorders. *American Journal of Health-System Pharmacies* 61, 1569–1576.
55. Konrad M., Schlingmann K.P., Gundermann T. (2003). Insights into the molecular nature of magnesium homeostasis. *American Journal of Physiology: Renal Physiology* 286, F599–F605.
56. Konrad M., Weber S. (2003). Recent advances in molecular genetics of hereditary magnesium-losing disorders. *Journal of the American Society of Nephrology* 14, 249–260.
57. Dube' L., Granry J. (2003). The therapeutic use of magnesium in anesthesiology, intensive care, and emergency medicine: A review. *Canadian Journal of Anesthesiology* 50(7), 732–746.
58. Topf J.M., Murray P.T. (2003) Hypomagnesemia and hypermagnesemia. *Reviews in Endocrine and Metabolic Disorders* 4, 195–206.
59. Adrogue H.E., Adrogue H.J. (2001). Acid-base physiology. *Respiratory Care* 46, 328–341.
60. Tanner G.A. (2002). Acid-base balance. In Rhoades R.A., Tanner G.A. (Eds). *Medical physiology* (2nd ed., pp. 426–447). Philadelphia: Lippincott Williams & Wilkins.
61. Whittier W.L., Rutecki G.W. (2004). Primer on clinical acid-base problem solving. *Disease of the Month* 50, 117–162.
62. Shapiro J.I., Kaehny W.D. (2003). Pathogenesis and management of metabolic acidosis and alkalosis. In Schrier R.W. (Ed.), *Renal and electrolyte disorders* (pp. 115–153). Philadelphia: Lippincott Williams & Wilkins.
63. Kraut J.A., Madias N.E. (2001). Approach to patients with acid-base disorders. *Respiratory Care* 46, 392–402.

64. Fischbach F. (2004). *A manual of laboratory and diagnostic tests* (7th ed., p. 946). Philadelphia: Lippincott Williams & Wilkins.
65. Adrogue H.J., Madias N.E. (1998). Management of life-threatening acid-base disorders: First of two parts. *New England Journal of Medicine* 338, 26–34.
66. Gauthier P.M., Szerlip H.M. (2002). Metabolic acidosis in the intensive care unit. *Critical Care Medicine* 18, 289–308.
67. Swenson E.R. (2001). Metabolic acidosis. *Respiratory Care* 46, 342–353.
68. Casaletto J.J. (2005). Differential diagnosis of metabolic acidosis. *Emergency Medical Clinics of North America* 23, 771–787.
69. Trachtenbarg D.E. (2005). Diabetic ketoacidosis. *American Family Physician* 71(9), 1705–1714.
70. Chen T-V., Smith W., Rosenstock J.L., et al. (2006). A life-threatening complication of Atkins diet. *Lancet* 367, 958.
71. Toth H.I., Greenbaum L.A. (2003). Severe acidosis caused by starvation and stress. *American Journal of Kidney Disease* 42, E16–E19.
72. Soriano J.R. (2002). Renal tubular acidosis. *Journal American Society of Nephrology* 13, 2160–2170.
73. Powers F. (1999). The role of chloride in acid-base balance. *Journal of Intravenous Nursing* 22, 286–291.
74. Alpern R.J., Sakhaee K. (1997). The clinical spectrum of chronic metabolic acidosis: Homeostatic mechanisms produce significant morbidity. *American Journal of Kidney Diseases* 29, 291–302.
75. Forsythe S.M., Schmidt G.A. (2000). Sodium bicarbonate for the treatment of lactic acidosis. *Chest* 117, 260–267.
76. Khanna A., Kurtzman N.A. (2001). Metabolic alkalosis. *Respiratory Care* 46, 354–365.
77. Galla J.H. (2000). Metabolic alkalosis. *Journal of the American Society of Nephrology*, 11, 369–375.
78. Adrogue H.J., Madias N.E. (1998). Management of life-threatening acid-base disorders. *New England Journal of Medicine* 338, 107–111.
79. Kaehny W.D. (2003). Pathogenesis and management of respiratory and mixed acid-base disorders. In Schrier R.W. (Ed.), *Renal and electrolyte disorders* (pp. 154–170). Philadelphia: Lippincott Williams & Wilkins.
80. Epstein S.K., Singh N. (2001). Respiratory acidosis. *Respiratory Care* 46, 366–383.
81. Laffey J.H., Kavenaugh B.P. (2002). Hypocapnia. *New England Journal of Medicine* 347, 43–53.
82. Foste G.T., Vaziri N.D., Sassoon C.S.H. (2001). Respiratory alkalosis. *Respiratory Care* 46, 384–391.

Stress and Adaptation
Homeostasis
Constancy of the Internal Environment
Control Systems
The Stress Response
Neuroendocrine Responses
Immune Responses
Adaptation to Stress
Factors Affecting the Ability to Adapt
Disorders of the Stress Response
Effects of Acute Stress
Acute Stress Associated with Trauma and Critical Illness
Effects of Chronic Stress
Posttraumatic Stress Disorder
Treatment of Stress Disorders
Relaxation Techniques
Guided Imagery
Music Therapy
Massage Therapy
Biofeedback

Chapter 9

Stress and Adaptation

Stress and adaptation and their relationship to health are a frequent topic of discussion. The human body and mind respond to stress by activating a complex repertoire of physiologic and behavioral adaptive responses, which, if inadequate or excessive, may affect emotional behavior and have adverse effects on physiologic functioning. Stress may contribute directly to the production or exacerbation of a disease, or it may contribute to the development of behaviors such as smoking, overeating, and drug abuse that increase the risk of disease.

The content in this chapter has been organized into two sections: the first focuses on stress and adaptation and the second on disorders of the stress response.

Stress and Adaptation

A variety of definitions have been ascribed to the phenomenon of stress. The concept of stress has been studied extensively by physiologists, psychologists, sociologists, and members of the health care professions. The nature of these disciplines and the individual work of their members have led to rather disparate bodies of knowledge about stress. Despite this disparity, the concept of stress is commonly viewed within the context of three major components: homeostasis, the stress response, and adaptation to stress.

Homeostasis

The concepts of stress and adaptation have their origin in the complexity of the human body and the interactions between the body's cells and its many organ systems. These interactions require that a level of homeostasis or constancy be maintained during the many changes that occur in the internal and external environments. In effecting a state of constancy, homeostasis requires feedback control systems that regulate cellular function and integrate the function of the different body systems.

Constancy of the Internal Environment

The environment in which body cells live is not the external environment that surrounds the organism, but rather

the local fluid environment that surrounds each cell. Claude Bernard, a 19th century physiologist, was the first to describe clearly the central importance of a stable internal environment, which he termed the *milieu intérieur.* Bernard recognized that body fluids surrounding the cells and the various organ systems provide the means for exchange between the external and the internal environments. It is from this internal environment that body cells receive their nourishment, and it is into this fluid that they secrete their wastes. Even the contents of the gastrointestinal tract and lungs do not become part of the internal environment until they have been absorbed into the extracellular fluid. A multicellular organism is able to survive only as long as the composition of the internal environment is compatible with the survival needs of the individual cells. For example, even a small change in the pH of the body fluids can disrupt the metabolic processes of the individual cells.

The concept of a stable internal environment was supported by Walter B. Cannon, who proposed that this kind of stability, which he called *homeostasis,* was achieved through a system of carefully coordinated physiologic processes that oppose change.[1] Cannon pointed out that these processes were largely automatic and emphasized that homeostasis involves resistance to both internal and external disturbances (Box 9-1).

In his book *Wisdom of the Body,* published in 1939, Cannon presented four tentative propositions to describe the general features of homeostasis.[1] With this set of propositions, Cannon emphasized that when a factor is known to shift homeostasis in one direction, it is reasonable to expect the existence of mechanisms that have the opposite effect. In the homeostatic regulation of blood sugar, for example, mechanisms that both raise and lower blood glucose would be expected to play a part. As long as the responding mechanism to the initiating disturbance can recover homeostasis, the integrity of the body and the status of normality are retained.

Box 9-1 Constancy of the Internal Environment

1. Constancy in an open system, such as our bodies represent, requires mechanisms that act to maintain this constancy. Cannon based this proposition on insights into the ways by which steady states such as glucose concentrations, body temperature, and acid-base balance were regulated.
2. Steady-state conditions require that any tendency toward change automatically meets with factors that resist change. An increase in blood sugar results in thirst as the body attempts to dilute the concentration of sugar in the extracellular fluid.
3. The regulating system that determines the homeostatic state consists of a number of cooperating mechanisms acting simultaneously or successively. Blood sugar is regulated by insulin, glucagon, and other hormones that control its release from the liver or its uptake by the tissues.
4. Homeostasis does not occur by chance, but is the result of organized self-government.

Cannon W.B. (1932). *The wisdom of the body* (pp. 299–300). New York: W.W. Norton.

Control Systems

The ability of the body to function and maintain homeostasis under conditions of change in the internal and external environment depends on the thousands of physiologic *control systems* that regulate body function. A homeostatic control system consists of a collection of interconnected components that function to keep a physical or chemical parameter of the body relatively constant. The body's control systems regulate cellular function, control life processes, and integrate functions of the different organ systems.

Of recent interest have been the neuroendocrine control systems that influence behavior. Biochemical messengers that exist in our brain control nerve activity, information flow, and, ultimately, behavior.[2,3] These control systems mediate the physical, emotional, and behavioral reactions to stressors that, taken together, are called the *stress response*.

Feedback Systems. Most control systems in the body operate by *negative feedback mechanisms,* which function in a manner similar to the thermostat on a heating system. When the monitored function or value decreases below the set point of the system, the feedback mechanism causes the function or value to increase, and when the function or value is increased above the set point, the feedback mechanism causes it to decrease (Fig. 9-1). For example, in the negative feedback mechanism that controls blood glucose levels, an increase in blood glucose stimulates an increase in insulin, which enhances the removal of glucose from the blood. When glucose has been taken up by cells and blood glucose levels fall, insulin secretion is inhibited and glucagon and other counterregulatory mechanisms stimulate the release of

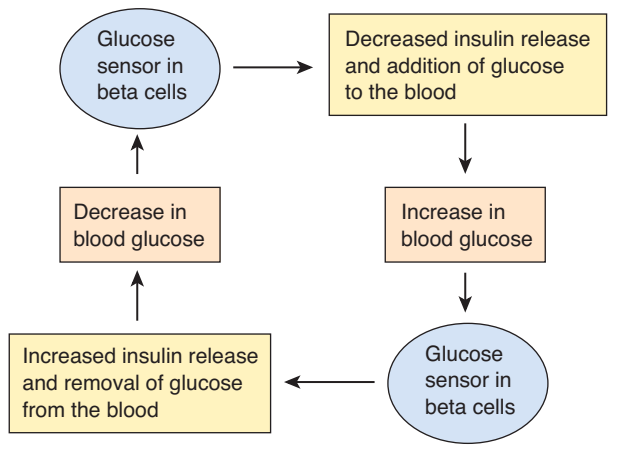


FIGURE 9-1. Illustration of negative feedback control mechanisms using blood glucose as an example.

glucose from the liver, which causes the blood glucose to return to normal.

The reason most physiologic control systems function under negative rather than *positive feedback mechanisms* is that a positive feedback mechanism interjects instability rather than stability into a system. It produces a cycle in which the initiating stimulus produces more of the same. For example, in a positive feedback system, exposure to an increase in environmental temperature would invoke compensatory mechanisms designed to increase rather than decrease body temperature.

The Stress Response

In the early 1930s, the world-renowned endocrinologist Hans Selye was the first to describe a group of specific anatomic changes that occurred in rats that were exposed to a variety of different experimental stimuli. He came to an understanding that these changes were manifestations of the body's attempt to adapt to stimuli. Selye described *stress* as "a state manifested by a specific syndrome of the body developed in response to any stimuli that made an intense systemic demand on it."[4] As a young medical student, Selye noticed that patients with diverse disease conditions had many signs and symptoms in common. He observed that "whether a man suffers from a loss of blood, an infectious disease, or advanced cancer, he loses his appetite, his muscular strength, and his ambition to accomplish anything; usually the patient also loses weight and even his facial expression betrays that he is ill."[5] Selye referred to this as the "syndrome of just being sick."

In his early career as an experimental scientist, Selye noted that a triad of adrenal enlargement, thymic atrophy, and gastric ulcers appeared in rats he was using for his studies. These same three changes developed in response to many different or nonspecific experimental challenges. He assumed that the hypothalamic-pituitary-adrenal (HPA) axis played a pivotal role in the development of this response. To Selye, the response to stressors was a process that enabled the rats to resist the experimental challenge by using the function of the system best able to respond to it. He labeled the response the *general adaptation syndrome* (GAS): *general* because the effect was a general systemic reaction, *adaptive* because the response was in reaction to a stressor, and *syndrome* because the physical manifestations were coordinated and dependent on each other.[4]

According to Selye, the GAS involves three stages: the alarm stage, the resistance stage, and the exhaustion stage. The *alarm stage* is characterized by a generalized stimulation of the sympathetic nervous system and the HPA axis, resulting in the release of catecholamines and cortisol. During the *resistance stage,* the body selects the most effective and economic channels of defense. During this stage, the increased cortisol levels that were present during the first stage drop because they are no longer needed. If the stressor is prolonged or overwhelms the ability of the body to defend itself, the *exhaustion stage* ensues, during which resources are depleted and signs of "wear and tear" or systemic damage appear.[6] Selye contended that many ailments, such as various emotional disturbances, mildly annoying headaches, insomnia, upset stomach, gastric and duodenal ulcers, certain types of rheumatic disorders, and cardiovascular and kidney diseases, appear to be initiated or encouraged by the "body itself because of its faulty adaptive reactions to potentially injurious agents."[5]

The events or environmental agents responsible for initiating the stress response were called *stressors*. According to Selye, stressors could be endogenous, arising from within the body, or exogenous, arising from outside the body.[5] In explaining the stress response, Selye proposed that two factors determine the nature of the stress response: the properties of the stressor and the conditioning of the person being stressed. Selye indicated that not all stress was detrimental; hence, he coined the terms *eustress* and *distress*.[6] He suggested that mild, brief, and controllable periods of stress could be perceived as positive stimuli to emotional and intellectual growth and development. It is the severe, protracted, and uncontrolled situations of psychological and physical distress that are disruptive of health.[5] For example, the joy of becoming a new parent and the sorrow of losing a parent are completely different experiences, yet their stressor effect—the nonspecific demand for adjustment to a new situation—can be similar.

It is becoming increasingly clear that the physiologic stress response is far more complicated than can be explained fully by a classic stimulus–response mechanism. Stressors tend to produce different responses in different persons or in the same person at different times, indicating the influence of the adaptive capacity of the person, or what Selye called *conditioning factors*. These conditioning factors may be internal (e.g., genetic predisposition, age, gender) or external (e.g., exposure to environmental agents, life experiences, dietary factors, level of social support).[5] The relative risk for development of a stress-related pathologic process seems, at least in part, to depend on these factors.

Richard Lazarus, a well-respected psychologist who devoted his career to the study of stress and emotions, considered "meanings and values to be at the center of human life and to represent the essence of stress, emotion and adaptation."[7] Others describe a "cognitive activation theory of stress" based on the belief that the stress response depends on what a person expects to happen in a given situation given previous learning experiences.[8] In other words, stimuli are filtered or evaluated before they reach a response system. Furthermore, there is evidence that the HPA axis, the adrenomedullary hormonal system, and the sympathetic nervous system are differentially activated depending on the type and intensity of the stressor.[9]

Neuroendocrine Responses

The manifestations of the stress response are strongly influenced by both the nervous and endocrine systems. The neuroendocrine systems integrate signals received along neurosensory pathways and from circulating mediators that are carried in the bloodstream. In addition, the

TABLE 9-1 Hormones Involved in the Neuroendocrine Responses to Stress

Hormones Associated with the Stress Response	Source of the Hormone	Physiologic Effects
Catecholamines (norepinephrine, epinephrine)	Locus ceruleus, adrenal medulla	Produces a decrease in insulin release and an increase in glucagon release resulting in increased glycogenolysis, gluconeogenesis, lipolysis, proteolysis, and decreased glucose uptake by the peripheral tissues; an increase in heart rate, cardiac contractility, and vascular smooth muscle contraction; and relaxation of bronchial smooth muscle
Corticotropin-releasing factor (CRF)	Hypothalamus	Stimulates ACTH release from anterior pituitary and increased activity of neurons in locus ceruleus
Adrenocorticotropic hormone (ACTH)	Anterior pituitary	Stimulates the synthesis and release of cortisol
Glucocorticoid hormones (e.g., cortisol)	Adrenal cortex	Potentiates the actions of epinephrine and glucagon; inhibits the release and/or actions of the reproductive hormones and thyroid-stimulating hormone; and produces a decrease in immune cells and inflammatory mediators
Mineralocorticoid hormones (e.g., aldosterone)	Adrenal cortex	Increases sodium absorption by the kidney
Antidiuretic hormone (ADH, vasopressin)	Hypothalamus, posterior pituitary	Increases water absorption by the kidney; produces vasoconstriction of blood vessels; and stimulates the release of ACTH

immune system both affects and is affected by the stress response. Table 9-1 summarizes the action of hormones involved in the neuroendocrine responses to stress. The results of the coordinated release of these neurohormones include the mobilization of energy, a sharpened focus and awareness, increased cerebral blood flow and glucose utilization, enhanced cardiovascular and respiratory functioning, redistribution of blood flow to the brain and muscles, modulation of the immune response, inhibition of reproductive function, and a decrease in appetite.[10,11]

The stress response is a normal, coordinated physiologic system meant to increase the probability of survival, but importantly is also designed to be an acute response—turned on when necessary to bring the body back to a stable state and turned off when the challenge to homeostasis abates. Therefore, under normal circumstances, the neural responses and the hormones that are released during the response do not persist long enough to cause damage to vital tissues. Since the early 1980s, the term *allostasis* has been used by some investigators to describe the interactive physiologic changes in the neuroendocrine, autonomic, and immune systems that occur in response to either real or perceived challenges to homeostasis. The persistence or accumulation of these allostatic changes (e.g., immunosuppression, activation of the sympathetic nervous and renin-angiotensin-aldosterone systems) has been called an *allostatic load*, and this concept has been used to measure the cumulative effects of stress on humans.[12–14]

The integration of the components of the stress response, which occurs at the level of the central nervous system (CNS), is complex and not completely understood. It relies on communication along neuronal pathways of the cerebral cortex, the limbic system, the thalamus, the hypothalamus, the pituitary gland, and the reticular activating system (RAS). The cerebral cortex is involved with vigilance, cognition, and focused attention, and the limbic system with the emotional components (e.g., fear, excitement, rage, anger) of the stress response (Fig. 9-2). The thalamus functions as the relay center and is important in receiving, sorting out, and distributing sensory input. The hypothalamus coordinates the responses of the endocrine and autonomic nervous systems (ANS). The RAS modulates mental alertness, ANS activity, and skeletal muscle tone, using input from other neural structures. The musculoskeletal tension that occurs during the stress response reflects increased activity of the RAS and its influence on the reflex circuits that control muscle tone. Adding to the complexity of this system is the fact that the individual brain circuits that participate in the mediation of the stress response interact and regulate the activity of each other. For example, reciprocal connections exist between neurons in the hypothalamus that initiate release of corticotropin-releasing factor (CRF) and neurons in the locus ceruleus associated with release of norepinephrine. Thus, norepinephrine stimulates the secretion of CRF, and CRF stimulates the release of norepinephrine.[10,11]

Locus Ceruleus. Central to the neural component of the neuroendocrine response to stress is an area of the brain stem called the *locus ceruleus* (LC).[10,11] The LC is densely populated with neurons that produce norepinephrine (NE) and is thought to be the central integrating site for the ANS response to stressful stimuli (Fig. 9-3). The LC-NE system has afferent pathways to the hypothalamus, the limbic system, the hippocampus, and the cerebral cortex.

The LC-NE system confers an adaptive advantage during a stressful situation. The sympathetic nervous system manifestation of the stress reaction has been called the

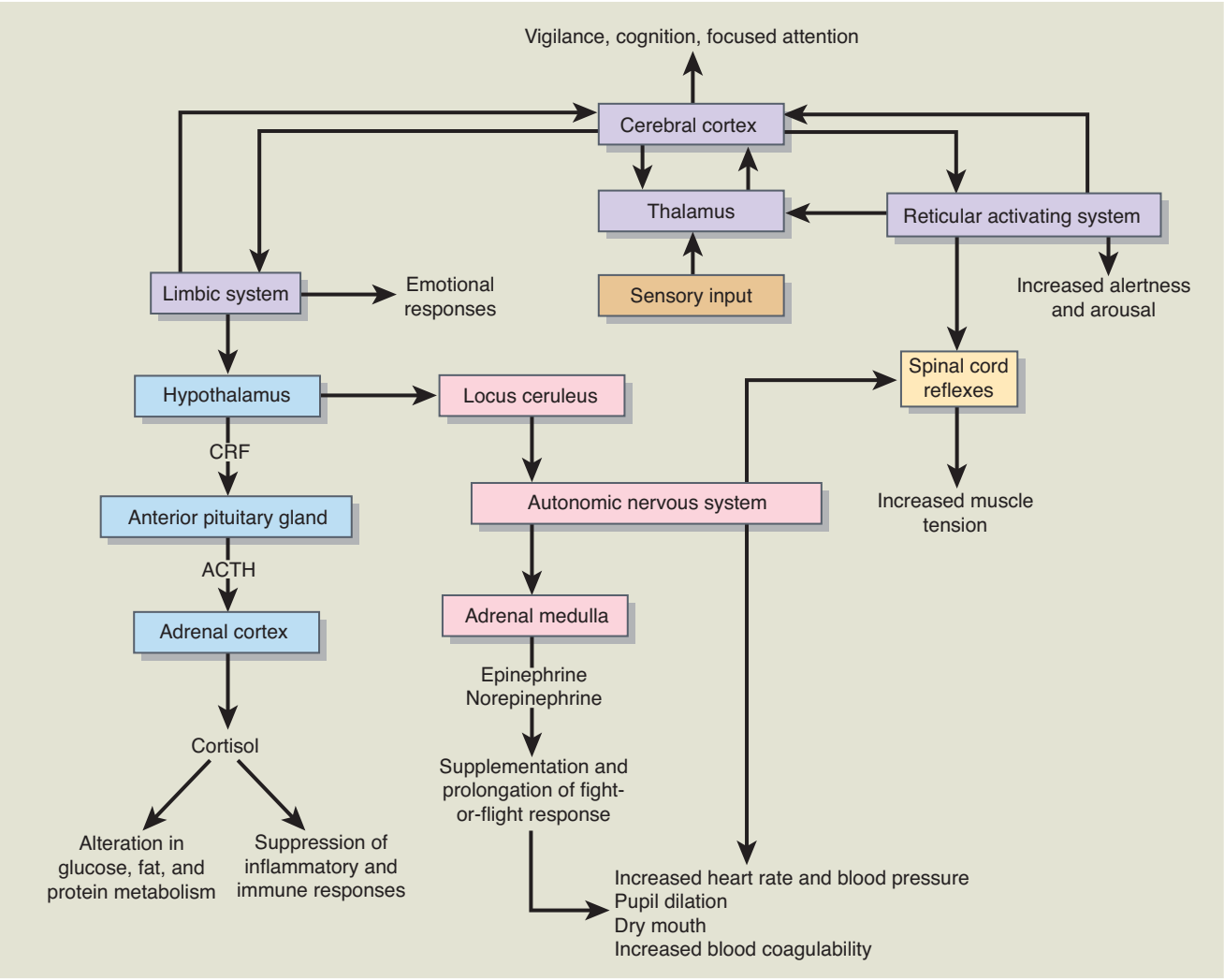


FIGURE 9-2. Neuroendocrine pathways and physiologic responses to stress. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor.

fight-or-flight response. This is the most rapid of the stress responses and represents the basic survival response of our primitive ancestors when confronted with the perils of the wilderness and its inhabitants. The increase in sympathetic activity in the brain increases attention and arousal and thus probably intensifies memory. The heart and respiratory rates increase, the hands and feet become moist, the pupils dilate, the mouth becomes dry, and the activity of the gastrointestinal tract decreases.

Corticotropin-Releasing Factor. CRF is central to the endocrine component of the neuroendocrine response to stress (see Fig. 9-3). CRF, also known as *corticotropin-releasing hormone*, is a small peptide hormone found in both the hypothalamus and extrahypothalamic structures, such as the limbic system and the brain stem. It is both an important endocrine regulator of pituitary and adrenal activity and a neurotransmitter involved in ANS activity, metabolism, and behavior.[3,10,11] Receptors for CRF are distributed throughout the brain as well as many peripheral sites. CRF from the hypothalamus induces secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH, in turn, stimulates the adrenal gland to synthesize and secrete the glucocorticoid hormones (e.g., cortisol).

The glucocorticoid hormones have a number of direct or indirect physiologic effects that mediate the stress response, enhance the action of other stress hormones, or suppress other components of the stress system. In this regard, cortisol acts not only as a mediator of the stress response but also as an inhibitor, such that overactivation of the stress response does not occur.[15,16] Cortisol maintains blood glucose levels and enhances the effect of catecholamines on the cardiovascular system. Blood glucose levels are elevated rapidly, in part by mobilization of glucose stores and by inhibition of further storage through the antagonizing effects of insulin.[15] It also suppresses osteoblast activity, hematopoiesis, protein and collagen synthesis, and immune responses. All of these functions are meant to protect the organism against the effects of a stressor and to focus energy on regaining balance in the face of an acute challenge to homeostasis.

Angiotensin II. Stimulation of the sympathetic nervous system also activates the peripheral renin-angiotensin-aldosterone system (RAAS), which mediates a peripheral increase in vascular tone and renal retention of sodium and water (see Chapter 18). These changes contribute to the physiologic changes that occur with the stress response and, if prolonged, may contribute to pathologic changes. Angiotensin II, peripherally delivered or locally produced, also has CNS effects; angiotensin II type 1 (AT_1) receptors are widely distributed in the hypothalamus and locus ceruleus. Through these receptors, angiotensin II enhances CRF formation and release, contributes to the release of ACTH from the pituitary, enhances stress-induced release of vasopressin from the posterior pituitary, and stimulates the release of norepinephrine from the locus ceruleus. Studies in animals of the effect of AT_1 receptor blockade suggest that receptor antagonists attenuate the activation of the stress response and may be an effective treatment for the effects of chronic stimulation of the stress response.[10,11]

Other Hormones. A wide variety of other hormones, including growth hormone, thyroid hormone, and the reproductive hormones, also are responsive to stressful situations. Systems responsible for reproduction, growth, and immunity are directly linked to the stress system, and the hormonal effects of the stress response profoundly influence these systems.

Although growth hormone is initially elevated at the onset of stress, the prolonged presence of cortisol leads to suppression of growth hormone, insulin-like growth factor 1 (IGF-1), and other growth factors, exerting a chronically inhibitory effect on growth. In addition, CRF directly increases somatostatin, which in turn inhibits growth hormone secretion. Although the connection is speculative, the effects of stress on growth hormone may provide one of the vital links to understanding failure to thrive in children.

Stress-induced cortisol secretion also is associated with decreased levels of thyroid-stimulating hormone and inhibition of conversion of thyroxine (T_4) to the more biologically active triiodothyronine (T_3) in peripheral tissues (see Chapter 32). Both changes may serve as a means to conserve energy at times of stress.

Antidiuretic hormone (ADH) released from the posterior pituitary is also involved in the stress response, particularly in hypotensive stress or stress due to fluid volume loss. ADH, also known as *vasopressin,* increases water retention by the kidneys and produces vasoconstriction of blood vessels. In addition, vasopressin synthesized in paraventricular neurons of the hypothalamus and transported to the anterior pituitary appears to synergize the capacity of CRF to stimulate the release of ACTH.

The neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) probably also plays a role in the stress response through neurons that innervate the hypothalamus, amygdala, and other limbic structures. Administration of 5-HT receptor agonists to laboratory animals was shown to increase the secretion of several stress hormones. In addition, it has been demonstrated that CRF inhibits the firing of serotonergic neurons.[10,11]

Other hormones that have a putative role in the stress response include vasoactive intestinal peptide, neuropeptide Y, cholecystokinin, and substance P. These hormones have well-characterized physiologic roles in the periphery, but they are also found in the CNS, and several studies suggest that they are involved in the stress response.[10,11]

The reproductive hormones are inhibited by CRF at the hypophyseal level and by cortisol at the pituitary, gonadal, and target tissue levels. Sepsis and severe trauma can induce anovulation and amenorrhea in

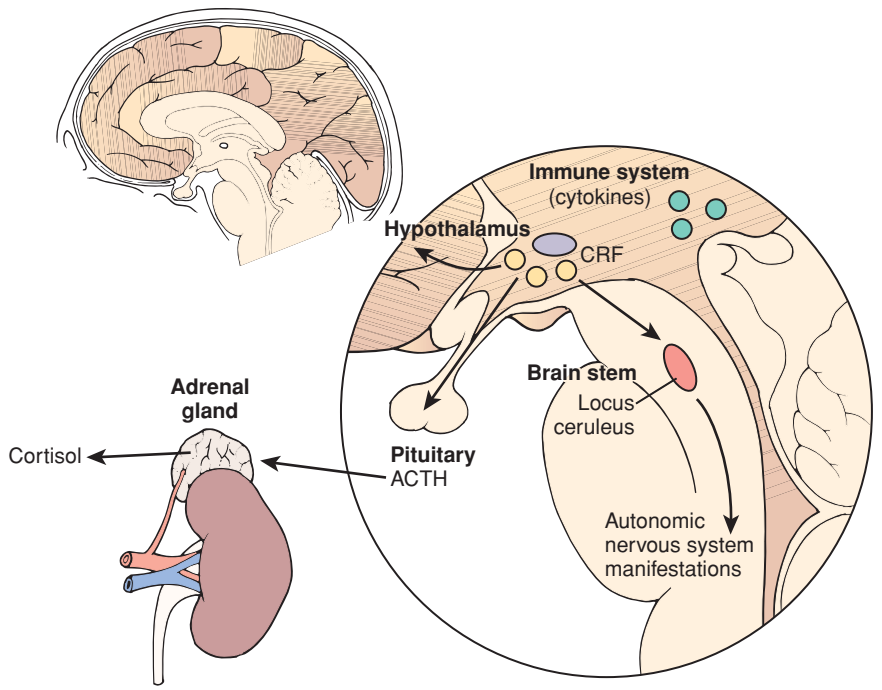


FIGURE 9-3. Neuroendocrine–immune system regulation of the stress response. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor.

women and decreased spermatogenesis and decreased levels of testosterone in men.

Immune Responses

The hallmark of the stress response, as first described by Selye, is the endocrine–immune interactions (i.e., increased corticosteroid production and atrophy of the thymus) that are known to suppress the immune response. In concert, these two components of the stress system, through endocrine and neurotransmitter pathways, produce the physical and behavioral changes designed to adapt to acute stress. Much of the literature regarding stress and the immune response focuses on the causal role of stress in immune-related diseases. It has also been suggested that the reverse may occur; emotional and psychological manifestations of the stress response may be a reflection of alterations in the CNS resulting from the immune response (see Fig. 9-3). Immune cells such as monocytes and lymphocytes can penetrate the blood-brain barrier and take up residence in the brain, where they secrete chemical messengers called *cytokines* that influence the stress response. In the case of cancer, this could mean that the subjective feelings of helplessness and hopelessness that have been repeatedly related to the onset and progression of cancers may arise secondary to the CNS effects of products released by immune cells during the early stage of the disease.[17,18]

The exact mechanism by which stress produces its effect on the immune response is unknown and probably varies from person to person, depending on genetic endowment and environmental factors. The most significant arguments for interaction between the neuroendocrine and immune systems derive from evidence that the immune and neuroendocrine systems share common signal pathways (i.e., messenger molecules and receptors), that hormones and neuropeptides can alter the function of immune cells, and that the immune system and its mediators can modulate neuroendocrine function. Receptors for a number of CNS-controlled hormones and neuromediators reportedly have been found on lymphocytes. Among these are receptors for glucocorticoids, insulin, testosterone, prolactin, catecholamines, estrogens, acetylcholine, and growth hormone, suggesting that these hormones and neuromediators influence lymphocyte function. For example, cortisol is known to suppress immune function, and pharmacologic doses of cortisol are used clinically to suppress the immune response. There is evidence that the immune system, in turn, influences neuroendocrine function.[19] For example, it has been observed that the HPA axis is activated by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor that are released from immune cells (see Chapter 15).

A second possible route for neuroendocrine regulation of immune function is through the sympathetic nervous system and the release of catecholamines. The lymph nodes, thymus, and spleen are supplied with ANS nerve fibers. Centrally acting CRF activates the ANS through multisynaptic descending pathways, and circulating epinephrine acts synergistically with CRF and cortisol to inhibit the function of the immune system.

Stress and Adaptation

- Stress is a state manifested by symptoms that arise from the coordinated activation of the neuroendocrine and immune systems, which Selye called the general adaptation syndrome.
- The hormones and neurotransmitters (catecholamines and cortisol) that are released during the stress response function to alert the individual to a threat or challenge to homeostasis, to enhance cardiovascular and metabolic activity in order to manage the stressor, and to focus the energy of the body by suppressing the activity of other systems that are not immediately needed.
- Adaptation is the ability to respond to challenges of physical or psychological homeostasis and to return to a balanced state.
- The ability to adapt is influenced by previous learning, physiologic reserve, time, genetic endowment, age, health status and nutrition, sleep–wake cycles, and psychosocial factors.

Not only is the quantity of immune expression changed because of stress, but also the quality of the response is changed. Stress hormones differentially stimulate the proliferation of subtypes of T-lymphocyte helper cells. Because these T-helper cell subtypes secrete different cytokines, they stimulate different aspects of the immune response. One subtype tends to stimulate T lymphocytes and the cellular-mediated immune response, whereas a second type tends to activate B lymphocytes and humoral-mediated immune responses.[2]

Adaptation to Stress

The ability to adapt to a wide range of environments and stressors is not peculiar to humans. According to René Dubos (a microbiologist noted for his study of human responses to the total environment), "adaptability is found throughout life and is perhaps the one attribute that distinguishes most clearly the world of life from the world of inanimate matter."[20] Living organisms, no matter how primitive, do not submit passively to the impact of environmental forces. They attempt to respond adaptively, each in its own unique and most suitable manner. The higher the organism is on the evolutionary scale, the larger its repertoire of adaptive mechanisms and its ability to select and limit aspects of the environment to which it responds. The most fully evolved mechanisms are the social responses through which individuals or groups modify their environments, their habits, or both to achieve a way of life that is best suited to their needs.

Human beings, because of their highly developed nervous system and intellect, usually have alternative mechanisms for adapting and have the ability to control many aspects of their environment. Air conditioning and central heating limit the need to adapt to extreme changes in environmental temperature. The availability of antiseptic agents, immunizations, and antibiotics eliminates the need to respond to common infectious agents. At the same time, modern technology creates new challenges for adaptation and provides new sources of stress, such as increased noise, air pollution, exposure to harmful chemicals, and changes in biologic rhythms imposed by shift work and transcontinental air travel.

Of particular interest are the differences in the body's response to events that threaten the integrity of the body's physiologic environment and those that threaten the integrity of the person's psychosocial environment. Many of the body's responses to physiologic disturbances are controlled on a moment-by-moment basis by feedback mechanisms that limit their application and duration of action. For example, the baroreflex-mediated rise in heart rate that occurs when a person moves from the recumbent to the standing position is almost instantaneous and subsides within seconds. Furthermore, the response to physiologic disturbances that threaten the integrity of the internal environment is specific to the threat; the body usually does not raise the body temperature when an increase in heart rate is needed. In contrast, the response to psychological disturbances is not regulated with the same degree of specificity and feedback control; instead, the effect may be inappropriate and sustained.

Factors Affecting the Ability to Adapt

Adaptation implies that an individual has successfully created a new balance between the stressor and the ability to deal with it. The means used to attain this balance are called *coping strategies* or *coping mechanisms*. Coping mechanisms are the emotional and behavioral responses used to manage threats to our physiologic and psychological homeostasis. According to Lazarus, how we cope with stressful events depends on how we perceive and interpret the event.[21] Is the event perceived as a threat of harm or loss? Is the event perceived as a challenge rather than a threat? Physiologic and anatomic reserve, time, genetic endowment and age, health status, nutrition, sleep–wake cycles, hardiness, and psychosocial factors influence a person's appraisal of a stressor and the coping mechanisms used to adapt to the new situation (Fig. 9-4).

Physiologic and Anatomic Reserve. Adaptation is greatly influenced by an individual's physiologic and anatomic reserve. The safety margin for adaptation of most body systems is considerably greater than that needed for normal activities. Red blood cells carry more oxygen than the tissues can use, the liver and fat cells store excess nutrients, and bone tissue stores calcium in excess of that needed for normal neuromuscular function. The ability of body systems to increase their function given the need to adapt is known as the *physiologic reserve*. Many body organs, such as the lungs, kidneys, and adrenals, are paired to provide anatomic reserve as well. Both organs are not needed to ensure the continued existence and maintenance of the internal environment. Many persons function normally with only one lung or one kidney.

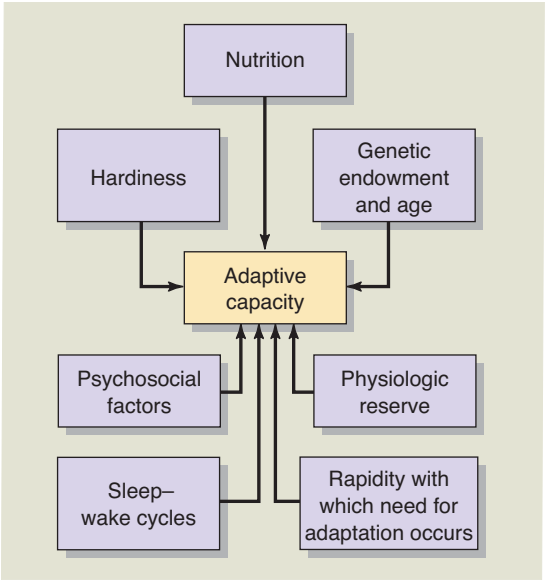


FIGURE 9-4. Factors affecting adaptation.

Time. Time is an essential element in adaptation. Adaptation is most efficient when changes occur gradually rather than suddenly. It is possible, for instance, to lose a liter or more of blood through chronic gastrointestinal bleeding over a week without manifesting signs of shock. However, a sudden hemorrhage that causes rapid loss of an equal amount of blood is likely to cause hypotension and shock.

Genetic Endowment and Age. Genetic endowment is increasingly being viewed as a contributing factor in the adaptation to stressful events, both physiologic and psychological. Recent advances in the field of genetic research suggest that different variants of certain genes determine how an individual responds to stressful life experiences. For example, an inherited variant of the serotonin transporter gene is associated with a number of conditions such as alcoholism, and individuals who have the variant are more vulnerable to respond to stressful experiences by developing depressive disorders.[14] There is also evidence linking variants in the glucocorticoid receptor gene that controls the body's response to cortisol during stressful situations to the development of depressive disorders. It seems likely that recent advances in genetic research methodology will allow investigators to identify additional patterns of response to stressful events and their link to psychological and physical health problems.

The capacity to adapt is also influenced by age. The ability to adapt is impaired by the immaturity of an infant, much as it is by the decline in functional reserve

that occurs with aging. For example, the infant has difficulty concentrating urine because of immature renal structures and therefore is less able than an adult to cope with decreased water intake or exaggerated water losses. A similar situation exists in the elderly owing to age-related changes in renal function.

Gender. Within the last decade, primarily because females have been included in basic science and clinical investigations, differences between the sexes in cardiovascular, respiratory, endocrine, renal, and neurophysiologic function have been found, and it has been hypothesized that sex hormones are the basis of these biologic differences. Technologic advances in cellular and molecular biology have made it clear, however, that there are fundamental differences in the locale and regulation of individual genes in the male and female genome that can account at a very basic level for the differences in physiologic function and disease manifestation.[22] These differences have general implications for the prevention, diagnosis, and treatment of disease and specific implications for our understanding of the sex-based differences in response to life's stressors.

Given the nature of sex-based differences, it is not surprising that there are differences in the physiologic stress response in both the HPA axis and the ANS. For example, the male hypothalamus produces more CRF and more ACTH than the premenopausal female hypothalamus in response to a psychological stressor (i.e., public speaking).[23] However, the secretion of arginine vasopressin (AVP), a hormone that has cardiovascular and renal effects and potentiates the release of ACTH, is greater in the female. Premenopausal women also tend to have a lower activation of the sympathetic nervous system than men in response to stressors. The phase of menstruation (luteal vs. follicular) as well as menopausal status can alter these responses and need to be taken into account when studying these responses.[23] These sex-based differences in activation of the stress response may partially explain differences in susceptibility to diseases in which the stress response may play a causal role. These research results are not definitive but are intriguing and can serve as a springboard for further research.

Health Status. Physical and mental health status determines physiologic and psychological reserves and is a strong determinant of the ability to adapt. For example, persons with heart disease are less able to adjust to stresses that require the recruitment of cardiovascular responses. Severe emotional stress often produces disruption of physiologic function and limits the ability to make appropriate choices related to long-term adaptive needs. Those who have worked with acutely ill persons know that the will to live often has a profound influence on survival during life-threatening illnesses.

Nutrition. There are 50 to 60 essential nutrients, including minerals, lipids, certain fatty acids, vitamins, and specific amino acids. Deficiencies or excesses of any of these nutrients can alter a person's health status and impair the ability to adapt. The importance of nutrition to enzyme function, immune response, and wound healing is well known. On a worldwide basis, malnutrition may be one of the most common causes of immunodeficiency.

Among the problems associated with dietary excess are obesity and alcohol abuse. Obesity is a common problem. It predisposes an individual to a number of health problems, including atherosclerosis and hypertension. Alcohol is commonly used in excess. It acutely affects brain function and, with long-term use, can seriously impair the function of the liver, brain, and other vital structures.

Sleep–Wake Cycles. Sleep is considered to be a restorative function in which energy is restored and tissues are regenerated.[24] Sleep occurs in a cyclic manner, alternating with periods of wakefulness and increased energy use. Biologic rhythms play an important role in adaptation to stress, development of illness, and response to medical treatment. Many rhythms such as rest and activity, work and leisure, and eating and drinking oscillate with a frequency similar to that of the 24-hour light–dark solar day. The term *circadian,* from the Latin *circa* ("about") and *dies* ("day"), is used to describe these 24-hour diurnal rhythms.

Sleep disorders and alterations in the sleep–wake cycle have been shown to alter immune function, the normal circadian pattern of hormone secretion, and physical and psychological functioning.[25] The two most common manifestations of an alteration in the sleep–wake cycle are insomnia and sleep deprivation or increased somnolence. In some persons, stress may produce sleep disorders, and in others, sleep disorders may lead to stress. Acute stress and environmental disturbances, loss of a loved one, recovery from surgery, and pain are common causes of transient and short-term insomnia. Air travel and jet lag constitute additional causes of altered sleep–wake cycles, as does shift work.

Hardiness. Studies by social psychologists have focused on individuals' emotional reactions to stressful situations and their coping mechanisms to determine those characteristics that help some people remain healthy despite being challenged by high levels of stressors. For example, the concept of *hardiness* describes a personality characteristic that includes a sense of having control over the environment, a sense of having a purpose in life, and an ability to conceptualize stressors as a challenge rather than a threat.[26] Many studies by nurses and social psychologists suggest that hardiness is correlated with positive health outcomes.[26]

Psychosocial Factors. Several studies have related social factors and life events to illness. Scientific interest in the social environment as a cause of stress has gradually broadened to include the social environment as a resource that modulates the relation between stress and health. Presumably, persons who can mobilize strong supportive resources from within their social relationships are better able to withstand the negative effects of stress on their health. Studies suggest that social support has direct and indirect positive effects on health status

and serves as a buffer or modifier of the physical and psychosocial effects of stress.

Social networks contribute in a number of ways to a person's psychosocial and physical integrity.[14] The configuration of significant others that constitutes this network functions to mobilize the resources of the person; these friends, colleagues, and family members share the person's tasks and provide monetary support, materials and tools, and guidance in improving problem-solving capabilities.

In summary, physiologic and psychological adaptation involves the ability to maintain the constancy of the internal environment (homeostasis) and behavior in the face of a wide range of changes in the internal and external environments. It involves negative feedback control systems that regulate cellular function, control life's processes, regulate behavior, and integrate the function of the different body systems.

The stress response involves the activation of several physiologic systems (sympathetic nervous system, the HPA axis, and the immune system) that work in a coordinated fashion to protect the body against damage from the intense demands made on it. Selye called this response the *general adaptation syndrome.* The stress response is divided into three stages: the *alarm stage,* with activation of the sympathetic nervous system and the HPA axis; the *resistance stage,* during which the body selects the most effective defenses; and the *exhaustion stage,* during which physiologic resources are depleted and signs of systemic damage appear. The activation and control of the stress response are mediated by the combined efforts of the nervous and endocrine systems. The neuroendocrine systems integrate signals received along neurosensory pathways and from circulating mediators that are carried in the bloodstream. In addition, the immune system both affects and is affected by the stress response.

Adaptation implies that an individual has successfully created a new balance between the stressor and his or her ability to deal with it. Adaptation is affected by a number of factors, including experience and previous learning, the rapidity with which the need to adapt occurs, genetic endowment and age, health status, nutrition, sleep–wake cycles, hardiness, and psychosocial factors.

Disorders of the Stress Response

Stressors can assume a number of patterns in relation to time. They may be classified as acute time limited, chronic intermittent, or chronic sustained. An acute time-limited stressor is one that occurs over a short time and does not recur; a chronic intermittent stressor is one to which a person is chronically exposed. The frequency or chronicity of circumstances to which the body is asked to respond often determines the availability and efficiency of the stress responses. The response of the immune system, for example, is more rapid and efficient on second exposure to a pathogen than it is on first exposure, but chronic exposure to a stressor can fatigue the system and impair its effectiveness.

Effects of Acute Stress

For the most part, the stress response is meant to be acute and time limited. The time-limited nature of the process renders the accompanying catabolic and immunosuppressive effects advantageous. The reactions to acute stress are those associated with the ANS, the fight-or-flight response. Centrally, there is facilitation of neural pathways mediating arousal, alertness, vigilance, cognition, and focused attention, as well as appropriate aggression. For persons with limited coping abilities, either because of physical or mental health, the acute stress response may be detrimental. This is true of persons with preexisting heart disease in whom the overwhelming sympathetic behaviors associated with the stress response can lead to arrhythmias. In healthy individuals, the acute stress response can redirect attention away from behaviors that promote health, such as attention to proper meals and getting adequate sleep. For those with health problems, it can interrupt compliance with medication regimens and exercise programs.

Acute Stress Associated with Trauma and Critical Illness

The acute physiologic stress associated with severe trauma, infection, and surgery can be extensive. Survival of such insults depends to a great part on the neuroendocrine component of the stress response, with activation of the HPA axis being one of the most important components of the response.[27–29] Cortisol, the primary glucocorticoid secreted by the adrenal cortex in response to activation of the HPA, has an important role in many of the physiologic functions during trauma and critical illness. The actions of cortisol include its anti-inflammatory effects, as well as its effects on blood glucose, vascular tone, endothelial integrity, and modulation of angiotensinogen synthesis.

Of recent concern has been the dramatic increase in blood glucose levels that occur during the acute stress response to critical injury and illness.[27,30,31] The causes of stress-induced hyperglycemia include (1) enhanced release of glucose from glycogen stores, (2) increased production of glucose from noncarbohydrate sources such as amino acids, and (3) an accompanying state of insulin resistance that impairs glucose uptake into skeletal muscle. Clinical data suggest that hyperglycemia results in worse outcomes and recovery from acute coronary syndromes (see Chapter 19), septic shock (see Chapter 20), and stroke (see Chapter 36).[27,30,31] These findings have led to a goal for strict control of blood glucose in most critically ill patients. This is often accomplished through the use of

low-dose insulin infusions. Insulin, itself, has been shown to produce anti-inflammatory, antioxidant, antithrombotic, and profibrinolytic effects separate from those involved in reducing blood glucose levels.[31] The optimal level for regulation of blood glucose in the critical care setting and how expeditiously insulin therapy should be started remain current areas of investigation.

Effects of Chronic Stress

The stress response is designed to be an acute self-limited response in which activation of the ANS and the HPA axis is controlled in a negative feedback manner. As with all negative feedback systems, pathophysiologic changes can occur in the stress response system. Function can be altered in several ways, including when a component of the system fails, when the neural and hormonal connections among the components of the system are dysfunctional, and when the original stimulus for the activation of the system is prolonged or of such magnitude that it overwhelms the ability of the system to respond appropriately. In these cases, the system may become overactive or underactive.

Chronicity and excessive activation of the stress response can result from chronic illnesses as well as contribute to the development of long-term health problems. It has been linked to a number of health disorders, including diseases of the cardiovascular, gastrointestinal, immune, and neurologic systems, as well as depression, chronic alcoholism and drug abuse, eating disorders, accidents, and suicide. Chronic activation of the stress response is also an important public health issue from both a health and a cost perspective. The National Institute for Occupational Safety and Health has declared stress a hazard in the workplace.[32]

Occurrence of the oral disease acute necrotizing gingivitis, in which the normal bacterial flora of the mouth become invasive, is known by dentists to be associated with acute stress, such as final examinations.[33] Similarly, herpes simplex virus type 1 infection (i.e., cold sores) often develops during periods of inadequate rest, fever, ultraviolet radiation, and emotional upset. The resident herpesvirus is kept in check by body defenses, probably T lymphocytes, until a stressful event occurs that causes suppression of the immune system. Psychological stress is associated in a dose–response manner with an increased risk for development of the common cold, and this risk is attributable to increased rates of infection rather than frequency of symptoms after infection.[34]

In a study in which participants were infected with the influenza virus, those persons who reported the greatest amount of premorbid stress also reported the most intense influenza symptoms and had a statistically greater production of interleukin-6, a cytokine that acts as a chemotactic agent for immune cells.[35] Elderly caregivers of a spouse with dementia had a significantly higher score for emotional distress and higher salivary cortisol than matched control subjects. The higher stress was correlated with a decreased immune response to the influenza vaccine.[36]

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is an example of chronic activation of the stress response as a result of experiencing a significant traumatic event.[37,38] A traumatic event has been defined as having the capacity to provoke fear, helplessness, or horror in response to the threat of injury or death.[39] It was formerly called *battle fatigue* or *shell shock* because it was first characterized in men and women returning from combat. Although war is still a significant cause of PTSD, other major catastrophic events, such as weather-related disasters (hurricanes and floods), airplane crashes, terrorist bombings, and rape or child abuse, also may result in development of the disorder. People who are exposed to such events are also at risk for development of major depression, panic disorder, generalized anxiety disorder, and substance abuse.[37] They also have bodily symptoms and physical illnesses, particularly hypertension, asthma, and chronic pain syndromes.

The term *posttraumatic stress disorder* was first used in the third edition (1980) of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III).[39] In the fourth edition, text revision (1994) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), the diagnosis of acute stress disorder (ASD) was added to distinguish individuals with milder or more transient difficulties from those with PTSD.[40]

Essential features of PTSD include exposure to a traumatic event that involves actual or threatened death or serious injury and a constellation of symptoms that are experienced as states of intrusion, avoidance, and hyperarousal.[37,38,42,43] Intrusion refers to the occurrence of "flashbacks" during waking hours or nightmares in which the past traumatic event is relived, often in vivid and frightening detail. *Avoidance* refers to the emotional numbing that accompanies this disorder and disrupts important personal relationships. Because a person with PTSD has not been able to resolve the painful feelings associated with the trauma, depression is commonly a part of the clinical picture. Survivor guilt also may be a product of traumatic situations in which the person survived the disaster but loved ones did not. *Hyperarousal* refers to the presence of increased irritability, difficulty concentrating, an exaggerated startle reflex, and increased vigilance and concern over safety. In addition, memory problems, sleep disturbances, and excessive anxiety are commonly experienced by persons with PTSD. The triad of symptoms of intrusion, avoidance, and hyperarousal that characterize PTSD must be present together for at least 1 month and the disorder must have caused clinically significant distress or impairment in social, occupational, and other areas of functioning.

Although the pathophysiology of PTSD is not completely understood, the revelation of physiologic changes related to the disorder has shed light on why some people recover from the disorder, whereas others do not. It has been hypothesized that the intrusive symptoms of PTSD may arise from exaggerated sympathetic nervous system activation in response to the traumatic event.

Persons with chronic PTSD have been shown to have increased levels of norepinephrine and increased activity of α_2-adrenergic receptors.[37] The increase in catecholamines, in tandem with increased thyroid hormone levels in persons with PTSD, is thought to explain some of the intrusive and somatic symptoms of the disorder.[37,43]

Recent neuroanatomic studies have identified alterations in two brain structures (the amygdala and hippocampus). Positron emission tomography and functional magnetic resonance imaging have shown increased reactivity of the amygdala and hippocampus and decreased reactivity of the anterior cingulate and orbitofrontal areas. These areas of the brain are involved in fear responses. The hippocampus also functions in memory processes. Differences in hippocampal function and memory processes suggest a neuroanatomic basis for the intrusive recollections and other cognitive problems that characterize PTSD.[37]

Importantly, the observed neuroanatomic changes in persons with PTSD do not uniformly resemble those seen with other types of stress.[42] For example, persons with PTSD demonstrate decreased cortisol levels, increased sensitivity of cortisol receptors, and an enhanced negative feedback inhibition of cortisol release with the dexamethasone suppression test. Dexamethasone is a synthetic glucocorticoid that mimics the effects of cortisol and directly inhibits the action of CRF and ACTH. This is in contrast to patients with major depression, who have a decreased sensitivity of glucocorticoid receptors, a high plasma level of cortisol, and decreased dexamethasone suppression.[43] The hypersuppression of cortisol observed with the dexamethasone test suggests that persons with PTSD do not exhibit a classic stress response as described by Selye. Because this hypersuppression has not been described in other psychiatric disorders, it may serve as a relatively specific marker for PTSD.

Little is known about the risk factors that predispose people to the development of PTSD. It is important to note that less than half of all people who are exposed to a traumatic event develop PTSD. It also has been found that children exposed to violent events but who have strong family relationships rarely develop PTSD.[44] Statistics indicate there is a need for studies to determine risk factors for PTSD as a means of targeting individuals who may need intensive therapeutic measures after a life-threatening event. Research also is needed to determine the mechanisms by which the disorder develops so that it can be prevented or, if that is not possible, so that treatment methods can be developed to decrease the devastating effects of this disorder on affected individuals and their families.[42]

The American Psychiatric Society has recently published guidelines for treatment of persons with PTSD.[45] The initial treatment of PTSD focuses on reducing or eliminating the symptoms and signs of PTSD and any trauma-related comorbid conditions. Next there is a need to improve adaptive functioning and return the person to a psychological state of safety and trust. Finally, general treatment measures focus on limiting any generalizations of the initial trauma and protecting the person with PTSD from subsequent relapse. Debriefing, or talking about the traumatic event at the time it happens, often is an effective therapeutic tool. Crisis teams are often among the first people to attend to the emotional needs of those caught in catastrophic events. Some people may need continued individual or group therapy. Often concurrent pharmacotherapy with antidepressant and antianxiety agents is useful and helps the individual participate more fully in therapy.

Treatment of Stress Disorders

The treatment of stress should be directed toward helping people avoid coping behaviors that impose a risk to their health and providing them with alternative stress-reducing strategies. Purposeful priority setting and problem solving can be used by persons who are overwhelmed by the number of life stressors to which they have been exposed. Nonpharmacologic methods used for stress reduction are relaxation techniques, guided imagery, music therapy, massage, and biofeedback.

Relaxation Techniques

Practices for evoking the relaxation response are numerous. They are found in virtually every culture and credited with producing a generalized decrease in sympathetic nervous system activity and musculoskeletal tension. According to Herbert Benson, a physician who worked in developing the technique, four elements are integral to the various relaxation techniques: a repetitive mental device, a passive attitude, decreased mental tonus, and a quiet environment.[46] Benson developed a noncultural method that is commonly used for achieving relaxation (Box 9-2). Progressive muscle relaxation, originally developed by Benson, is another method of relieving tension. His procedure, which has been modified by a number of therapists, consists of systematic contraction and

Box 9-2 The Relaxation Response

- Sit quietly in a comfortable position.
- Deeply relax all your muscles, beginning at your feet and progressing up to your face.
- Breathe through your nose. Become aware of your breathing. As you breathe out, say the word "one" silently to yourself. Continue for 20 minutes. When you have finished, sit quietly for several minutes, first with your eyes closed and then with them open.
- Do not worry about whether you are successful in achieving a deep level of relaxation. Maintain a positive attitude and permit the relaxation to occur at its own rate. Expect distracting thoughts, ignore them, and continue repeating "one" as you breathe out.

Modified from Benson H. (1977). Systemic hypertension and the relaxation response. *New England Journal of Medicine* 296, 1152.

relaxation of major muscle groups.[47] As the person learns to relax, the various muscle groups are combined. Eventually, the person learns to relax individual muscle groups without first contracting them.

The relaxation response has been shown to be an effective tool for treating stress-related disease processes, particularly certain immunologic, cardiovascular, and neurodegenerative disorders. It has been suggested that common underlying molecular mechanisms may exist that represent a connection between the stress response, pathophysiology of the stress-related diseases, and physiologic changes associated with the relaxation response.[48] Several molecular pathways have been suggested including those involving cortisol, norepinephrine/epinephrine, and nitric oxide signaling.

Guided Imagery

Guided imagery is another technique that can be used to achieve relaxation.[49] One method is scene visualization, in which the person is asked to sit back, close the eyes, and concentrate on a scene narrated by the therapist. Whenever possible, all five senses are involved: the person attempts to see, feel, hear, smell, and taste aspects of the visual experience. Other types of imagery involve imagining the appearance of each of the major muscle groups and how they feel during tension and relaxation.

Music Therapy

Music therapy is used for both its physiologic and psychological effects. It involves listening to selected pieces of music as a means of ameliorating anxiety or stress, reducing pain, decreasing feelings of loneliness and isolation, buffering noise, and facilitating expression of emotion. Music is defined as having three components: rhythm, melody, and harmony.[50,51] Rhythm is the order in the movement of the music. Rhythm is the most dynamic aspect of music, and particular pieces of music often are selected because they harmonize with body rhythms such as heart rhythm, respiratory rhythm, or gait. The melody is created by the musical pitch and the distance (or interval) between the musical tones. The melody contributes to the listener's emotional response to the music. The harmony results from the way pitches are blended together, with the combination of sounds described as consonant or dissonant by the listener. Music usually is selected based on a person's musical preference and past experiences with music. Depending on the setting, headphones may be used to screen out other distracting noises. Radio and television music is inappropriate for music therapy because of the inability to control the selection of pieces that are played, the interruptions that occur (e.g., commercials and announcements), and the quality of the reception.

Massage Therapy

Massage is the manipulation of the soft tissues of the body to promote relaxation and relief of muscle tension. The technique that is used may involve a gentle stroking along the length of a muscle (effleurage), application of pressure across the width of a muscle (pétrissage), deep massage movements applied by a circular motion of the thumbs or fingertips (friction), squeezing across the width of a muscle (kneading), or use of light slaps or chopping actions (hacking).[52] Massage may be administered by practitioners who have received special training in its use or by less prepared persons such as parents of small children[53] or caregivers of confused elders.[54] It often is used as a means of physiologic relaxation and stress relief in critically ill patients.[55]

Biofeedback

Biofeedback is a technique in which an individual learns to control physiologic functioning. It involves electronic monitoring of one or more physiologic responses to stress with immediate feedback of the specific response to the person undergoing treatment. Several types of responses are used: electromyographic (EMG), electrothermal, and electrodermal.[56] The EMG response involves the measurement of electrical potentials from muscles, usually the forearm extensor or frontalis. This is used to gain control over the contraction of skeletal muscles that occurs with anxiety and tension. The electrodermal sensors monitor skin temperature in the fingers or toes. The sympathetic nervous system exerts significant control over blood flow in the distal parts of the body such as the digits of the hands and feet. Consequently, anxiety often is manifested by a decrease in skin temperature in the fingers and toes. Electrodermal sensors measure conductivity of skin (usually the hands) in response to anxiety. Fearful and anxious people often have cold and clammy hands, which lead to a decrease in conductivity.

In summary, stress in itself is neither negative nor deleterious to health. The stress response is designed to be time limited and protective, but in situations of prolonged activation of the response because of overwhelming or chronic stressors, it could be damaging to health. The acute stress reaction and stress-induced hyperglycemia are of particular concern in persons with critical injuries or illness. PTSD is an example of chronic activation of the stress response as a result of experiencing a traumatic event that involved actual or threatened death or serious injury. Essential features of PTSD include a constellation of symptoms that are experienced as states of intrusion (flashbacks of the event), avoidance (emotional numbing), and hyperarousal (intense activation of the neuroendocrine system).

Treatment of stress should be aimed at helping people avoid coping behaviors that can adversely affect their health and providing them with other ways to reduce stress. Nonpharmacologic methods used in the treatment of stress include relaxation techniques, guided imagery, music therapy, massage therapy, and biofeedback.

REVIEW EXERCISES

1. A 21-year-old college student notices that she frequently develops "cold sores" during the stressful final exam week.

A. What is the association between stress and the immune system?
B. One of her classmates suggests that she listen to music or try relaxation exercises as a means of relieving stress. Explain how these interventions might work in relieving stress.

2. A 75-year-old woman with congestive heart failure complains that her condition gets worse when she worries and is under a lot of stress.

A. Relate the effects stress has on the neuroendocrine control of cardiovascular function and its possible relationship to a worsening of the woman's congestive heart failure.
B. She tells you that she dealt with much worse stresses when she was younger and never had any problems. How would you explain this?

3. A 30-year-old woman who was rescued from a collapsed building has been having nightmares recalling the event, excessive anxiety, and loss of appetite, and is afraid to leave her home for fear something will happen.

A. Given her history and symptoms, what is the likely diagnosis?
B. How might she be treated?

REFERENCES

1. Cannon W.B. (1939). *The wisdom of the body* (pp. 299–300). New York: W.W. Norton.
2. Wilcox R.E., Gonzales R.A. (1995). Introduction to neurotransmitters, receptors, signal transduction, and second messengers. In Schatzberg A.F., Nemeroff C.B. (Eds.), *Textbook of psychopharmacology* (pp. 3–29). Washington, DC: American Psychiatric Press.
3. Chrousos G.P. (1998). Stressors, stress, and neuroendocrine integration of the adaptive response. *Annals of the New York Academy of Sciences* 851, 311–335.
4. Selye H. (1976). *The stress of life* (rev. ed.). New York: McGraw-Hill.
5. Selye H. (1973). The evolution of the stress concept. *American Scientist* 61, 692–699.
6. Selye H. (1974). *Stress without distress* (p. 6). New York: New American Library.
7. Lazarus R. (1999). *Stress and emotion: A new synthesis* (p. 6). New York: Springer.
8. Ursin H., Eriksen H.R. (2004). The cognitive-activation theory of stress. *Psychoneuroendocrinology* 29, 567–592.
9. Goldstein D.S. (2003). Catecholamines and stress. *Endocrine Regulations* 37, 69–80.
10. Carrasco G.A., Van de Kar L.D. (2003). Neuroendocrine pharmacology of stress. *European Journal of Pharmacology* 463, 235–272.
11. Charmandari E., Tsigos C., Chrous G. (2005). Endocrinology of the stress response. *Annual Review of Physiology* 67, 259–284.
12. Motzer S.A., Hertig V. (2004). Stress, stress response, and health. *Nursing Clinics of North America* 39, 1–17.
13. Stewart J.A. (2006). The detrimental effects of allostasis: Allostatic load as a measure of cumulative stress. *Journal of Physiologic Anthropology* 25(1), 133–145.
14. McEwen B.S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Review* 87, 873–904.
15. Sapolsky R.M., Romero L.M., Munck A.U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews* 21, 55–89.
16. de Kloet E.R. (2003). Hormones, brain and stress. *Endocrine Regulations* 37, 51–68.
17. Sternberg E.M. (2006). Neural regulation of innate immunity: A coordinated nonspecific host response to pathogens. *Nature Reviews: Immunology* 6, 318–328.
18. Padgett D.A., Glaser R. (2003). How stress influences the immune response. *Trends in Immunity* 24(8), 444–448.
19. Woiciechowsky C., Schoning F., Lanksch W.R., et al. (1999). Mechanisms of brain mediated systemic anti-inflammatory syndrome causing immunodepression. *Journal of Molecular Medicine* 77, 769–780.
20. Dubos R. (1965). *Man adapting* (pp. 256, 258, 261, 264). New Haven, CT: Yale University Press.
21. Lazarus R. (2000). Evolution of a model of stress, coping, and discrete emotions. In Rice V.H. (Ed.), *Handbook of stress, coping, and health* (pp. 195–222). Thousand Oaks, CA: Sage.
22. Wizemann T.M., Pardue M.L. (Eds.). (2001). *Exploring the biological contributions to human health: Does sex matter?* Committee on Understanding the Biology of Sex and Gender Differences. Board on Health Sciences Policy, Institute of Medicine. Washington, DC: National Academy Press.
23. Kajantie E., Phillips D.I. (2006). The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology* 31, 151–178.
24. Adams K., Oswold I. (1983). Protein synthesis, bodily renewal and sleep-wake cycle. *Clinical Science* 65, 561–567.
25. Gillin J.C., Byerley W.F. (1990). The diagnosis and management of insomnia. *New England Journal of Medicine* 322, 239–248.
26. Ford-Gilboe M., Cohen J.A. (2000). Hardiness: A model of commitment, challenge, and control. In Rice V.H. (Ed.), *Handbook of stress, coping, and health* (pp. 425–436). Thousand Oaks, CA: Sage.
27. Baranov D., Neligan P. (2007). Trauma and aggressive homeostasis management. *Anesthesiology Clinics* 25, 49–63.
28. Gibson S.C., Hartman D.A., Schenck J.M. (2005). The endocrine responses to critical illness: Update and implications for emergency medicine. *Emergency Clinics of North America* 23, 909–929.
29. Arafah B.M. (2006). Review: Hypothalamic pituitary adrenal function during critical illness: Limitations of current assessment methods. *Journal of Clinical Endocrinology and Metabolism* 91, 3725–3745.
30. Marik P.E., Raghavan M. (2004). Stress-hyperglycemia, insulin and immunomodulation in sepsis. *Intensive Care Medicine* 30, 748–756.
31. Dandona P., Chaudhuri A., Ghanim H., et al. (2007). The effect of hyperglycemia and insulin in acute coronary syndromes. *American Journal of Cardiology* 99(suppl), 12H–18H.
32. National Institute for Occupational Safety and Health. (1999). *Stress at work* (pp. 1–26). Publication no. 99-101, HE 20.7102: ST 8/4. Bethesda, MD: U.S. Department of Health and Human Services.
33. Dworkin S.F. (1969). Psychosomatic concepts and dentistry: Some perspectives. *Journal of Periodontology* 40, 647.

34. Cohen S., Tyrrell D.A.J., Smith A.P. (1991). Psychological stress and susceptibility to the common cold. *New England Journal of Medicine* 325, 606–612.
35. Cohen S., Doyle W.J., Skoner D.P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine* 61, 175–180.
36. Vedhara K., Wilcock G.K., Lightman S.L., et al. (1999). Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 353, 627–631.
37. Yehuda R. (2002). Post-traumatic stress disorder. *New England Journal of Medicine* 346, 108–114.
38. Galea S., Nandi A., Viahov D. (2005). The epidemiology of post-traumatic stress disorder after disasters. *Epidemiologic Reviews* 27, 78–91.
39. American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed., DSM-III). Washington, DC: American Psychiatric Society.
40. American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental* (4th ed., DSM-IV). Washington, DC: American Psychiatric Society.
41. Vieweg W.V.R., Julius D.A., Fernandez A., et al. (2006). Post-traumatic stress disorder: Clinical features, pathophysiology, and treatment. *American Journal of Medicine* 119, 383–390.
42. Yehuda R. (2000). Biology of posttraumatic stress disorder. *Journal of Clinical Psychiatry* 61(Suppl 7), 14–21.
43. Yehuda R. (1998). Psychoneuroendocrinology of posttraumatic stress disorder. *Psychiatric Clinics of North America* 21, 359–379.
44. McCloskey L.A. (2000). Posttraumatic stress in children exposed to family violence and single event trauma. *Journal of the American Academy of Child and Adolescent Psychiatry* 39, 108–115.
45. American Psychiatric Association. (2004). Practice guidelines for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *American Journal of Psychiatry* 161(Suppl), 1–31.
46. Benson H. (1977). Systemic hypertension and the relaxation response. *New England Journal of Medicine* 296, 1152–1154.
47. Jacobson E. (1958). *Progressive relaxation.* Chicago: University of Chicago Press.
48. Esch T., Fricchione G.L., Stefano G.B. (2003). The therapeutic use of relaxation response in stress-related diseases. *Medical Science Monitor* 9(2), RA23–RA34.
49. Reed T. (2007). Imagery in the clinical setting: A tool for healing. *Nursing Clinics of North America* 42, 261–277.
50. Chlan L., Tracy M.F. (1999). Music therapy in critical care: Indications and guidelines for intervention. *Critical Care Nurse* 19(3), 35–41.
51. White J.M. (1999). Effects of relaxing music on cardiac autonomic balance and anxiety after acute myocardial infarction. *American Journal of Critical Care* 8, 220–230.
52. Vickers A., Zollman C. (1999). ABC of complementary therapies: Massage therapies. *British Medical Journal* 319, 1254–1257.
53. Rusy L.M., Weisman S.J. (2000). Complementary therapies for acute pediatric pain management. *Pediatric Clinics of North America* 47, 589–599.
54. Rowe M., Alfred D. (1999). The effectiveness of slow-stroke massage in diffusing agitated behaviors in individuals with Alzheimer's disease. *Journal of Gerontological Nursing* 25(6), 22–34.
55. Richards K.C. (1998). Effect of back massage and relaxation intervention on sleep in critically ill patients. *American Journal of Critical Care* 7, 288–299.
56. McKee M.G. (2008). Biofeedback: An overview in the context of heart-brain medicine. *Cleveland Clinic Journal of Medicine* 75(2), S31–S34.

Energy Metabolism and Nutritional Status
Energy Metabolism and Storage
Energy Storage
Nutritional Status
Recommended Dietary Allowances and Dietary Reference Intakes
Calories
Proteins, Fats, and Carbohydrates
Vitamins and Minerals
Fiber
Regulation of Food Intake and Energy Storage
Hunger, Appetite, and Food Intake
Assessment of Energy Stores and Nutritional Status
Anthropometric Measurements
Laboratory Studies
Overweight and Obesity
Causes of Overweight and Obesity
Adipose Tissue and Types of Obesity
Adipose Tissue as an Endocrine Organ
Adipose Tissue and the Inflammatory Process
Types of Obesity
Prevention and Treatment of Obesity
Childhood Obesity
Diagnosis and Treatment
Undernutrition and Eating Disorders
Malnutrition and Starvation
Protein-Energy Malnutrition
Malnutrition in Trauma and Illness
Diagnosis
Treatment
Eating Disorders
Anorexia Nervosa
Bulimia Nervosa
Binge Eating and Eating Disorder Not Otherwise Specified

Chapter 10

Disorders of Nutritional Status

Nutritional status describes the condition of the body related to the availability and use of nutrients. Nutrients that are taken into the body can be used to provide the energy needed to perform various body functions or they can be stored for future use. The stability and composition of body weight over time requires that a person's energy intake is balanced with energy expenditure. Also, because different foods contain different amounts of proteins, fats, carbohydrates, vitamins, and minerals, appropriate amounts of these dietary elements must be maintained to ensure that all parts of the body's metabolic systems can be supplied with requisite materials. This chapter discusses energy metabolism and nutritional status, overnutrition and obesity, and undernutrition and eating disorders.

Energy Metabolism and Nutritional Status

The nutrients from the foods we eat are used by cells to provide the body with the energy needed to perform almost all cellular functions. Energy is measured in heat units called *calories*. A calorie, spelled with a small "c" and also called a *gram calorie,* is the amount of heat or energy required to raise the temperature of 1 g of water by 1°C. A *kilocalorie* (kcal), or *large calorie* (spelled with a capital C), is the amount of energy needed to raise the temperature of 1 kg of water by 1°C. Because a calorie is so small, kilocalories often are used in nutritional and physiologic studies.

Energy Metabolism and Storage

Metabolism is the organized process through which nutrients such as carbohydrates, fats, and proteins are broken down, transformed, or otherwise converted into cellular energy. The oxidation of proteins provides 4 kcal/g; fats, 9 kcal/g; and carbohydrates, 4 kcal/g.[1]

The process of metabolism is unique in that it enables the continual release of energy, and it couples this energy with physiologic functioning. For example, the energy

Energy Metabolism

- All body activities require energy, whether they involve a single cell, a single organ, or the entire body.
- Energy, which is measured in **kilocalories (kcal or C),** is obtained from foods.
- Fats, which are a concentrated water-free energy source, contain 9 kcal/g. They are stored in fat cells as triglycerides, which are the main storage sites for energy.
- Carbohydrates are hydrated fuels, which supply 4 kcal/g. They are stored in limited quantities as glycogen and can be converted to fatty acids and stored in fat cells as triglycerides.
- Proteins are broken down into amino acids that generate 4 kcal/g. Amino acids are used in building body proteins. Amino acids in excess of those needed for protein synthesis are converted to fatty acids, ketones, or glucose and are stored or used as metabolic fuel.

used for muscle contraction is derived largely from energy sources that are stored in muscle cells and then released as the muscle contracts. Because most of our energy sources come from the nutrients in the food that is eaten, the ability to store energy and control its release is important. Normally, energy utilization is balanced with energy expenditure. When a person is overfed and the intake of food consistently exceeds energy expenditure, the excess energy is stored as fat, and the person becomes overweight. Conversely, when food intake is less than energy expenditure, fat stores and other body tissues are broken down, and the person loses weight.

Energy Storage

More than 90% of body energy is stored as triglycerides in the fat cells of the body. The body has a limited ability to store dietary carbohydrates and proteins as energy sources. Dietary carbohydrates are largely converted to glucose, which is stored as glycogen in liver and skeletal muscle cells. Liver glycogen stores reach a maximum of approximately 200 to 300 g after a high-carbohydrate meal, after which the liver begins to convert some of the excess glucose to triglycerides for storage in fat cells. The amino acids from protein in the diet are stored mainly in the form of structural proteins, enzymes, nucleoproteins, and other types of cellular proteins. After all the cells have reached their limits, the excess amino acids are converted to glucose and used for energy or stored in the liver as glycogen or in adipose tissue as triglycerides.

Triglycerides, which contain no water, have the highest caloric content of all nutrients and are an efficient form of energy storage. When calorie intake is restricted for any reason, the triglycerides in fat cells are broken down, and their fatty acids and glycerol released as energy sources. Fat cells synthesize triglycerides from glucose and fatty acids. Insulin is required for fat storage. It promotes glucose transport through the cell membrane of fat cells. Some of the glucose is used to synthesize fatty acids, but more importantly it forms large amounts of α-glycerol phosphate. This substance supplies the glycerol that combines with fatty acids to form triglycerides. Therefore, in the absence of insulin, the storage of triglycerides in adipose tissue is almost blocked.

Adipose Tissue. Fat cells, or *adipocytes*, are modified fibroblasts that store almost pure triglycerides in quantities as great as 80% to 95% of their total cell volume.[1] Adipocytes occur singly or in small groups in loose connective tissue. In many parts of the body, they cushion body organs such as the kidneys. In addition to isolated groups of fat cells, entire regions of fat tissue are committed to fat storage. Collectively, fat cells constitute a large body organ that is metabolically active in the uptake, synthesis, storage, and mobilization of lipids, which are the main source of fuel storage for the body. Some tissues, such as liver cells, are able to store small amounts of lipids, but when these lipids accumulate (so-called "ectopic" deposition, as occurs in fatty liver), they begin to interfere with normal cell function. Adipose tissue not only serves as a storage site for body fuels, but also provides insulation for the body, fills body crevices, and protects body organs.[2]

Early studies suggested that fully differentiated adipocytes do not divide and that the number of fat cells were fixed in early childhood and that subsequent gains in adipose tissue represented increases in fat cell size. This is no longer considered to be true, since adipose tissue in adults is now known to contain *preadipocytes*, capable of forming new fat cells, and fat deposition can result from proliferation of these immature adipocytes.[3] Some medications can also have an important effect on fat cell numbers. For example, the thiazolidinedione (TZD) class of antidiabetic drugs can stimulate the formation of new fat cells from the preadipocytes, allowing increased uptake of glucose into these cells (and storage as fat), resulting in the desired reduction in serum glucose levels but with unwanted weight gain.[4] In contrast, some drugs can cause loss of fat cells, resulting in lipodystrophy. This occurs in human immunodeficiency virus (HIV)-associated lipodystrophy in persons treated with highly active antiretroviral therapy (see Chapter 16). The mechanism of fat loss is not known; however, it may be due to increased programmed cell death of the adipocytes (i.e., increased apoptosis).

There are two types of adipose tissue: white (unilocular) and brown (multilocular).[2] *White fat*, which despite its name is cream colored or yellow, is the predominant form of adipose tissue in adults. The adipocytes of white fat are large spherical cells that become polyhedral or oval when crowded in adipose tissue. The functions of white fat include energy storage, insulation, and cushioning of vital organs. Unilocular adipose tissue forms a layer in the connective tissue under the skin. This subcutaneous

layer has significant insulating functions. Concentrations of adipose tissue are found in the connective tissue under the skin of the abdomen, buttocks, axilla, and thigh. Sex differences in the thickness of this fatty layer in different parts of the body account, in part, for the differences in body composition between males and females. Internally, white adipose tissue is preferentially located in the greater omentum, mesentery, and retroperitoneal space and is usually abundant around the kidney. It is also found in the orbits around the eyeballs, in the bone marrow, and between other tissues, where it fills spaces. It retains this structural function even during reduced caloric intake, when the lipid content of adipose tissue elsewhere has been depleted.[2]

Brown fat differs from white fat in terms of its thermogenic capacity or ability to produce heat. Brown fat is found primarily in early neonatal life in humans and in animals that hibernate. In humans, brown fat decreases with age but is still detectable in the sixth decade. This small amount of brown fat has a minimal effect on energy expenditure.

Nutritional Status

The body obtains the energy needed to perform its various functions and maintain the integrity and health of its cells from the various foods that are ingested in the diet. Because different foods contain different proportions of proteins, carbohydrates, fats, minerals, and vitamins, appropriate balances must be maintained among these constituents so that all segments of the body's metabolic systems can be supplied with the prerequisite materials.

Recommended Dietary Allowances and Dietary Reference Intakes

The *Dietary Reference Intake* (DRI) is a set of at least four nutrient-based reference values—the recommended dietary allowance, adequate intake, estimated average requirement, and tolerable upper intake level, each of which has specific uses.[5] The *Recommended Dietary Allowance* (RDA) defines the nutrient intakes that meet the needs of almost all healthy persons in a specific age and sex group.[5] The *Adequate Intake* (AI) is set when there is not enough scientific evidence to estimate an average requirement. The AI is derived from experimental or observational data that show a mean intake that appears to sustain a desired indicator of health. An *Estimated Average Requirement* (EAR) is the intake that meets the estimated nutrient need of half of the persons in a specific group. This figure is used as the basis for developing the RDA and is expected to be used by nutrition policy makers in the evaluation of the adequacy of a nutrient for a specific group and for planning how much of the nutrient the group should consume. The *Tolerable Upper Intake Level* (UL) is the maximum intake that is judged unlikely to pose a health risk in almost all healthy persons in a specified group. It refers to the total intakes from food, fortified food, and nutrient supplements. This value is not intended to be a recommended level of intake, and there is no established benefit for persons who consume nutrients at the RDA or AI levels.

The DRIs, which are periodically reviewed and updated by the Institute of Medicine's Food and Nutrition Board, are published by the National Academy of Sciences and available online through the United States Department of Agriculture Food and Nutrition Information Center.[6] The DRIs are used in advising persons about the level of nutrient intake they need to maintain an optimal state of health and decrease the risk for disease. The Food and Nutrition Board has also established *Acceptable Macronutrient Distribution Ranges* (AMDRs) as a percent of energy intake for fat, carbohydrate, linoleic and α-linolenic acids, and protein.

Food and supplement labels use *Daily Values* (DVs), which are set by the Food and Drug Administration (FDA). However, the DVs are based on data that is older than the data used to determine the DRIs. The *percent daily value* tells the consumer what percent of the DV one serving of a food or supplement supplies. Proteins, fats, carbohydrates, vitamins, and minerals each have their own function in providing the body with what it needs to maintain life and health. Recommended allowances have not been established for every nutrient; some are given as a safe and adequate intake, but others, such as carbohydrates and fats, are expressed as a percentage of the calorie intake.

Calories

Energy requirements are greater during growth periods. Infants require approximately 115 kcal/kg at birth, 105 kcal/kg at 1 year of age, and 80 kcal/kg of body weight between 1 to 10 years of age. During adolescence, boys require 45 kcal/kg of body weight and girls require 38 kcal/kg of body weight. During pregnancy, a woman needs an extra 300 kcal/day above her usual requirement, and during the first 3 months of breast-feeding, she requires an additional 500 kcal.[5] Table 10-1 can be used to predict the caloric requirements of healthy adults.[7]

Proteins, Fats, and Carbohydrates

Proteins are required for growth and maintenance of body tissues, enzymes and antibody formation, fluid and electrolyte balance, and nutrient transport. Proteins are composed of amino acids, nine of which are essential to the body. These are leucine, isoleucine, methionine, phenylalanine, threonine, tryptophan, valine, lysine, and histidine. The foods that provide these essential amino acids in adequate amounts are milk, eggs, meat, fish, and poultry. Dried peas and beans, nuts, seeds, and grains contain all the essential amino acids but in less than adequate proportions. These proteins need to be combined with each other or with complete proteins to meet the amino acid requirements for protein synthesis.

Unlike carbohydrates and fats, which are composed of hydrogen, carbon, and oxygen, proteins contain nitrogen; therefore, nitrogen excretion is an indicator of protein intake. The average protein contains about 16% nitrogen. About 90% of this is excreted in the urine as urea, uric acid, creatinine, and other less important nitrogen breakdown products, with the rest being excreted in

TABLE 10-1 Estimated Energy Requirements (EER) at Different Activity Levels for Men and Women 30 Years of Age With a Normal (<25), Overweight (25 to 29.9), and Obese (≥30) BMI

BMI	Height m (in)	Weight kg (lb)	Activity Level*	EER (kcal/d) Male	EER (kcal/d) Female
22.1	1.75	68	Rarely	2404	2055
Normal	(69)	(150)	Low activity	2627	2285
			Active	2911	2571
			Very active	3378	2915
26.5	1.75	77	Rarely	2620	2140
Overweight	(69)	(170)	Low activity	2867	2380
			Active	3182	2679
			Very active	3698	3038
31	1.75	95	Rarely	2837	2310
Obese	(69)	(210)	Low activity	3108	2570
			Active	3452	2894
			Very active	4018	3284

*Activity level definitions:
Sedentary = rarely exercise
Low active = less 1 hour/day
Active = about 1 hour/day
Very active = more than 1 hour/day

Developed using "Adult Energy Needs and BMI Calculator" from USDA/ARS Children's Nutrition Center at Baylor College of Medicine. [Online] Available: http://www.bcm.edu/cnrc/caloriesneed.htm. Accessed May 20, 2010.

the feces.[1] Therefore, the rate of protein breakdown can be estimated by measuring the amount of nitrogen in the urine. If the amount of nitrogen taken in by way of protein is equivalent to the nitrogen excreted, the person is said to be in nitrogen balance. A person is in positive nitrogen balance when the nitrogen consumed by way of protein is greater than the amount excreted. This occurs during growth, pregnancy, or healing after surgery or injury. A negative nitrogen balance often occurs with fever, illness, infection, trauma, or burns, when more nitrogen is excreted than is consumed.[1] It represents a state of tissue breakdown.

Dietary fats are composed primarily of triglycerides (i.e., a mixture of fatty acids and glycerol). The fatty acids are saturated (i.e., no double bonds), monounsaturated (i.e., one double bond), or polyunsaturated (i.e., two or more double bonds). The saturated fatty acids elevate blood cholesterol, whereas the monounsaturated and polyunsaturated fats lower blood cholesterol. Saturated fats are usually derived from animal sources and remain solid at room temperature. With the exception of coconut and palm oils (which are saturated), unsaturated fats are found in plant oils and usually are liquid at room temperature. *Trans fatty* acids are produced when unsaturated oils are partially hydrogenated and are called *artificial trans fats*. They are found primarily in vegetable shortenings and some margarines and foods containing either of these. There are also *natural trans fatty acids* that are found in dairy products, some meats, and other animal-based foods. Although trans fatty acids tend to increase low-density lipoprotein (LDL) cholesterol and decrease high-density lipoprotein (HDL) cholesterol, the naturally occurring trans fats may have a beneficial effect.

Dietary fats provide energy, function as carriers for the fat-soluble vitamins, serve as precursors of prostaglandins, and are a source of fatty acids. The polyunsaturated fatty acid linoleic acid is the only fatty acid that is required. A deficiency of linoleic acid results in dermatitis. An AI has been set for both linoleic and α-linolenic acids.[7] Because vegetable oils are rich sources of linoleic acid, this level can be met by including two teaspoons per day of vegetable oil in the diet. Other than linoleic acid, there are no specific requirements for specific fatty acids. The Food and Nutrition Board has set an ADMR for fat of no less than 20% to prevent the fall of HDL cholesterol associated with very–low-fat diets.[7] Guidelines from the National Cholesterol Education Program recommend that 25% to 35% of the calories in the diet should come from fats.[8] The daily dietary recommendation for cholesterol is less than 300 mg. The American Heart Association recommends limiting saturated fat to less than 7% and trans fatty acids to less than 1% of calories daily.[9]

Dietary carbohydrates are composed of simple sugars, complex carbohydrates, and undigested carbohydrates (i.e., fiber). Because of their vitamin, mineral, and fiber content, it is recommended that the bulk of the carbohydrate content in the diet be in the complex form rather than as simple sugars that contain few nutrients. Sucrose (i.e., table sugar) is implicated in the development of dental caries.

There is no specific dietary requirement for carbohydrates since all of the energy requirements of the body can be met by dietary fats and proteins. Although some tissues, such as the nervous system, require glucose as an energy source, this need can be met through the

conversion of amino acids and the glycerol part of the triglyceride molecule to glucose. The fatty acids from triglycerides are converted to ketones and used for energy by other body tissues. Therefore, a carbohydrate-deficient diet usually results in the loss of tissue proteins and the development of ketosis. Because protein and fat metabolism increases the production of osmotically active metabolic wastes that must be eliminated through the kidneys, there is also danger of dehydration and electrolyte imbalances. The amount of carbohydrate needed to prevent tissue wasting and ketosis is 50 to 100 g/day. In practice, most of the daily energy requirement should be from dietary carbohydrate sources. This is because protein is an expensive source of calories and because it is recommended that dietary fat not exceed 35% of the calorie intake. The AMDR indicates that carbohydrate intake should be limited to no less than 45% of the calories in the diet to prevent high intakes of fat.[7]

Vitamins and Minerals

Vitamins are a group of organic compounds that act as catalysts in various chemical reactions. A compound cannot be classified as a vitamin unless it is shown that a deficiency causes disease. Contrary to popular belief, vitamins do not provide energy directly. As catalysts, they are part of the enzyme systems required for the release of energy from protein, fat, and carbohydrates. Vitamins also are necessary for the formation of red blood cells, hormones, genetic materials, and the nervous system. They are essential for normal growth and development.

There are two types of vitamins: fat soluble and water soluble. The four fat-soluble vitamins are vitamins A, D, E, and K. The nine required water-soluble vitamins are thiamine, riboflavin, niacin, pyridoxine (vitamin B_6), pantothenic acid, vitamin B_{12}, folic acid, biotin, and vitamin C. Because the water-soluble vitamins are excreted in the urine, it is less likely that they may become toxic to the body, but the fat-soluble vitamins are stored in the body, and they may reach toxic levels.

Minerals serve many functions. They are involved in acid-base balance and in the maintenance of osmotic pressure in body compartments. Minerals are components of vitamins, hormones, and enzymes. They maintain normal hemoglobin levels, play a role in nervous system function, and are involved in muscle contraction and skeletal development and maintenance. Minerals that are present in relatively large amounts in the body are called *macrominerals*. These include calcium, phosphorus, sodium, chloride, potassium, magnesium, and sulfur. The remainder are classified as *trace minerals*; they include iron, manganese, copper, iodine, zinc, cobalt, fluorine, and selenium.

Fiber

Fiber, the portion of food that cannot be digested by the human intestinal tract, increases stool bulk and facilitates bowel movements. Soluble fiber, the type that produces a gel in the intestinal tract, binds with cholesterol and prevents it from being absorbed by the body. Soluble fiber also lowers blood glucose. More studies are needed to establish whether fiber prevents colon cancer and promotes weight loss. In 2002, the Food and Nutrition Board gave its first recommended intake for fiber. Men and women who are 50 years and younger should have 38 and 25 grams, respectively, of fiber daily, while those over 50 years should have 30 and 21 grams, respectively, each day. The recommendation for children ranges from 19 to 31 grams and for teenagers it is similar to adults.[7]

Regulation of Food Intake and Energy Storage

Stability of body weight and composition over time requires that energy intake matches energy utilization. Environmental, cultural, genetic, and psychological factors all influence food intake and energy expenditure. In addition, body weight is tightly controlled by various physiologic feedback control systems that contribute to the regulation of hunger and food intake.

Hunger, Appetite, and Food Intake

Hunger and appetite are closely associated with food intake. The sensation of *hunger* is associated with several sensory perceptions, such as the rhythmic contractions of the stomach and that "empty feeling" in the stomach that stimulates a person to seek food. A person's *appetite* is the desire for a particular type of food. It is useful in helping the person determine the type of food that is eaten. *Satiety* is the feeling of fullness or decreased desire for food.

The hypothalamus contains the feeding center for hunger and satiety[1] (Fig. 10-1). It receives neural input from the gastrointestinal tract that provides information about stomach filling, chemical signals from nutrients (glucose, amino acids, and fatty acids) in the blood, and input from the cerebral cortex regarding the smell, sight, and taste of the food. Centers in the hypothalamus also control the secretion of several hormones (e.g., thyroid and adrenocortical hormones) that regulate energy balance and metabolism.

The control of food intake can be divided into short-term regulation, which is concerned with the amount of food that is consumed at a meal or snack, and intermediate and long-term regulation, which is concerned with the maintenance of constant stores of nutrients in the tissues, preventing them from becoming too low or too high.[1]

Short-Term Regulation. The short-term regulation of food intake provides a person with the feeling of satiety and turns off the desire for eating when adequate food has been consumed. It requires rapid feedback mechanisms that signal the adequacy of food intake before digestion has taken place and nutrients have been absorbed into the blood. These mechanisms include stretch receptors that monitor filling of the gastrointestinal tract, oral receptors that monitor food intake, and gastrointestinal tract hormones that suppress or increase food intake. Stretch receptors in the gastrointestinal tract

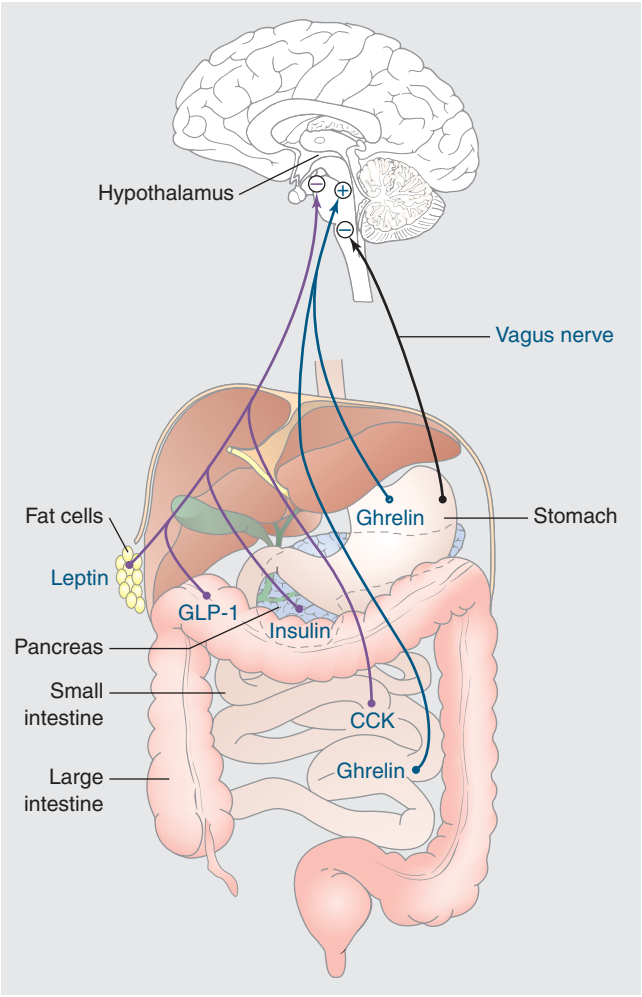


FIGURE 10-1. Feedback mechanisms for control of food intake. *Black lines* leading to – indicate feedback signals that decreased appetite and feeding, and *blue lines* with + indicate feedback signals that increase appetite and feeding. Stretch receptors in the stomach activate sensory afferent vagal pathways that inhibit food intake. Glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and insulin are gastrointestinal hormones that are released by the ingestion of food and suppress further feeding. Ghrelin, which is released by the stomach and small intestine, especially during fasting, stimulates appetite. Leptin is a hormone produced by increasing amounts of fat cells as they increase in size; it inhibits food intake. (Modified from Guyton A.C., Hall J.E. [2006]. *Textbook of medical physiology* [11th ed., p. 868]. Philadelphia: Elsevier Saunders.)

monitor gastrointestinal filling and send inhibitory impulses by way of the vagus nerve to the feeding center to suppress the desire for food. Oral receptors monitor the amount of food that passes through the mouth and sends impulses to the feeding center to suppress food intake. This effect occurs despite the fact that the gastrointestinal tract has not become the least bit filled and is thought to result from various oral factors such as tasting, chewing, and swallowing that meter food intake.[1] However, the inhibition caused by this mechanism is considerably less intense and of shorter duration than that caused by gastrointestinal filling.

The gastrointestinal tract hormones that contribute to the short-term regulation of food intake include cholecytokinin (CCK), glucagon-like peptide 1 (GLP-1), and ghrelin.[10,11] CCK, which is released in response to fat in the duodenum, and GLP-1, which is released from the lower small bowel in response to nutrients, especially carbohydrates, have a strong suppressant effect on the hypothalamic feeding center. Ghrelin is a hormone released mainly from the stomach and to a lesser extent by the intestine. Its levels peak just before eating and then fall after a meal, suggesting that it may also stimulate appetite and eating.[10] The presence of food in the stomach increases the release of insulin and glucagon, both of which suppress the neurogenic feeding signals from the brain.[1]

Intermediate and Long-Term Regulation. The intermediate and long-term regulation of food intake is determined by the amount of nutrients that are in the blood and in storage sites. It has long been known that a decrease in blood glucose causes hunger. In contrast, an increase in breakdown products of lipids such as ketoacids produces a decrease in appetite. The ketogenic weight loss diet (e.g., the Atkins diet) relies partly on the appetite suppressant effects of ketones in the blood.

Recent evidence suggests that the hypothalamus also senses the amount of energy through a hormone that is produced by fat cells called *leptin*.[1] The stimulation of leptin receptors in the hypothalamus has been shown to produce a decrease in appetite and food intake as well as an increase in metabolic rate and energy consumption. It also produces a decrease in insulin release from the beta cells of the pancreas, which decreases energy storage in fat cells.

Assessment of Energy Stores and Nutritional Status

The nutritional status of an individual can be assessed in a number of ways including a history of weight gain or loss, dietary intake, gastrointestinal symptoms that affect food intake, functional capacity, and physical signs of fat loss and muscle wasting. This information is usually combined with other objective measures of fat stores and skeletal muscle mass.

Anthropometric Measurements

Anthropometric measurements provide a means for assessing body composition, particularly fat stores and skeletal muscle mass.[12] This is done by measuring height, weight, body circumferences, and thickness of various skinfold areas. These measurements commonly are used to determine growth patterns in children and appropriateness of current weight in adults.

Body weight is the most frequently used method of assessing nutritional status; it should be used in combination with measurements of body height to establish whether a person is underweight or overweight. For weight measurement, subjects should ideally be in light clothing and bare feet, fasting, and with an empty bladder.

TABLE 10-2 Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk*

			Disease Risk* Relative to Normal Weight and Waist Circumference	
	BMI (kg/m²)	Obesity Class	*Men ≤102 cm (≤40 in) Women ≤88 cm (≤35 in)*	*Men >102 cm (>40 in) Women >88 cm (>35 in)*
Underweight	<18.5		—	—
Normal†	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

BMI, body mass index.

*Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

†Increased waist circumference also can be a marker for increased risk, even in persons of normal weight.

Expert Panel. (1998). *Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults*. National Institutes of Health. [Online] Available: http://www.nhlbi.nih.gov/guidelines/ob_gdlns.htm.

Repeat measurements are best made at the same time of the day.

The body mass index (BMI) uses height and weight to determine healthy weight (Table 10-2). It is calculated by dividing the weight in kilograms by the height in meters squared (BMI = weight [kg]/height [m²]).[13] A BMI less than 18.5 is classified as being underweight and one between 25 and 29.9 is considered overweight.[13] A BMI greater than 30.0 is diagnosed as obesity and is furthered classified into classes I (BMI 30.0 to 34.9), II (BMI 35.0 to 39.9), and III or extreme obesity (BMI >40). Body weight reflects both lean body mass and adipose tissue and cannot be used as a method for describing body composition or the percentage of fat tissue present. Statistically, the best percentage of body fat for men is between 12% and 20%, and for women, it is between 20% and 30%.[14] During physical training, body fat usually decreases, and lean body mass increases.

Among the methods used to estimate body fat are body circumferences, skinfold thickness, bioelectrical impedance, computed tomography (CT), and magnetic resonance imaging (MRI).[12] The measurement of *body circumferences*, has received attention because excess visceral (or intra-abdominal) fat is closely associated with the metabolic syndrome (i.e., a syndrome described by a collection of cardiovascular risk factors).[15,16] Measurements of *skinfold thickness* can provide a reasonable assessment of body fat, particularly if taken at multiple sites. They can provide information about the location of the fat and can be used together with equations and tables to estimate the percentage of lean body mass and fat tissue. However, these measurements often are difficult to perform, are subject to considerable variation between observers, and do not provide information about abdominal and intramuscular fat.

Bioelectrical impedance involves the use of electrodes attached to the wrist and ankles to send a harmless current through the body. The flow of the current is affected by the amount of water in the body. Because fat-free tissue contains virtually all the water and current-conducting electrolytes, measurements of the resistance (i.e., impedance) can be used to estimate the percentage of body fat present.

Computed tomography and MRI can be used to provide quantitative pictures from which the thickness of fat can be determined. CT scans also can be used to provide quantitative estimates of regional fat and give a ratio of intra-abdominal to extra-abdominal fat. Because these methods are costly, they usually are reserved for research studies.

Laboratory Studies

Various laboratory tests can aid in evaluating nutritional status. Some of the most commonly performed tests are serum albumin and prealbumin to assess the protein status, total lymphocyte count and delayed hypersensitivity reaction to assess cellular immunity, and creatinine–height index to assess skeletal muscle protein. Vitamin and mineral deficiencies can be determined by measurements of their levels in blood, saliva, and other body tissues or by measuring nutrient-specific chemical reactions.

In summary, nutritional status describes the condition of the body related to the availability and use of nutrients. Nutrients provide the energy and materials necessary for performing the activities of daily living and for the growth and repair of body tissues. Metabolism is the organized process whereby nutrients such as carbohydrates, fats, and proteins are broken down, transformed, or otherwise converted to cellular energy. These fuel sources are ingested during meals and stored for future use. Glucose is stored as glycogen or converted to triglycerides in fat cells for storage. Fats are stored in adipose tissue as triglycerides. Amino acids are the

building blocks of proteins, and most of the stored amino acids are contained in body proteins and as fuel sources for cellular metabolism.

Nutritional status is dependent on the amount of proteins, carbohydrates, fats, minerals, and vitamins that are ingested in the diet. The *Dietary Reference Intake* includes a set of at least four nutrient-based reference values—the recommended dietary allowance, the adequate intake, the estimated average requirement, and the tolerable upper intake level—that can be used to determine the appropriate level of nutrient intake. The acceptable macronutrient distribution range is a guide for the percent of energy intake from fat, carbohydrate, linoleic and α-linolenic acids, and protein in the diet. Stability of body weight and composition over time requires that energy intake matches energy utilization. In addition to the environmental, genetic, cultural, and psychological factors that influence food intake and energy expenditure, body weight is tightly controlled by various physiologic systems that contribute to the regulation of hunger, appetite, and food intake.

The nutritional status of a person can be assessed by evaluation of dietary intake, anthropometric measurements, and laboratory tests. Anthropometric measurements, which are used for assessing body composition, include measurements of height and weight, body circumferences, and skinfold thickness; bioelectrical impedance; and CT scans. Serum albumin and prealbumin can be used to assess the protein status, total lymphocyte count to assess cellular immunity, and creatinine–height index to assess skeletal muscle protein.

Overweight and Obesity

- Obesity results from an imbalance between energy intake and energy consumption. Because fat is the main storage form of energy, obesity represents an excess of body fat.
- Overweight and obesity are determined by measurements of BMI and waist circumference. A BMI of 25 to 29.9 is considered overweight, a BMI of 30 or greater as obese, and a BMI greater than 40 as very or morbidly obese.
- Waist circumference is used to determine the distribution of body fat. Central, or abdominal, obesity is an independent predictor of morbidity and mortality associated with obesity.

Overweight and Obesity

Overweight and obesity have become global health problems, increasing the risk of hypertension, hyperlipidemia, type 2 diabetes, coronary heart disease, and other health problems. According to recent worldwide estimates, 1.7 billion people are classified as overweight, more than 1 billion have hypertension, and more than 500 million have either diabetes or impaired glucose tolerance.[17]

Obesity is defined as having excess body fat, enlarged fat cells, and even an increased number of fat cells.[18] Clinically, obesity and overweight have been defined in terms of the BMI. Historically, various world bodies have used different BMI cutoff points to define obesity. In 1997, the World Health Organization (WHO) defined the various classifications of overweight (BMI ≥25) and obesity (BMI ≥30). This classification was subsequently adopted by the National Institutes of Health (NIH).[13] The use of a BMI cutoff of 25 as a measure of overweight raised some concern in that the BMI of some men might be increased due to muscle rather than fat weight. However, it has been shown that a BMI cutoff of 25 can sensitively detect most overweight people and does not erroneously detect overlean people.

Obesity is associated with increased risk for developing many medical, psychosocial, and behavioral problems. In terms of health problems, a great many disorders occur more frequently in obese people (Fig. 10-2). The most important and common of these are hyperlipidemia, hypertension, coronary artery disease, stroke, and type 2 diabetes mellitus. The increased weight associated with obesity stresses the bones and joints, increasing the likelihood of osteoarthritis. Certain cancers (endometrial, prostate, colon, uterine, ovarian), thromboembolic disorders, and gastrointestinal tract disease (gastroesophageal reflux and gallbladder disease) are also more prevalent in the obese.[19] Other conditions associated with obesity include sleep apnea and pulmonary dysfunction, menstrual irregularities and complications of pregnancy, psychological distress, and nonalcoholic fatty liver disease (discussed in Chapter 30). Because some drugs are lipophilic and exhibit increased distribution in fat tissue, the administration of these drugs, including some anesthetic agents, can be more dangerous in obese persons. If surgery is required, obese persons heal slower and are at increased risk from anesthesia. Massive obesity, because of its close association with so many health problems, can be regarded as a disease in its own right. It is the second leading cause of preventable death.

Causes of Overweight and Obesity

Factors that are thought to lead to the development of overweight and obesity include the interaction of genotype and environmental factors, including diet and physical activity. Obesity is known to run in families, suggesting a hereditary component. The question that surrounds this observation is whether the disorder arises because of genetic endowment or environmental influences. Studies of twin and adopted children have provided evidence that heredity contributes to the disorder.[20] The most recent update of the human obesity gene map suggests that there are 20 to 30 obesity candidate genes that might contribute to the risk of obesity in humans.[21]

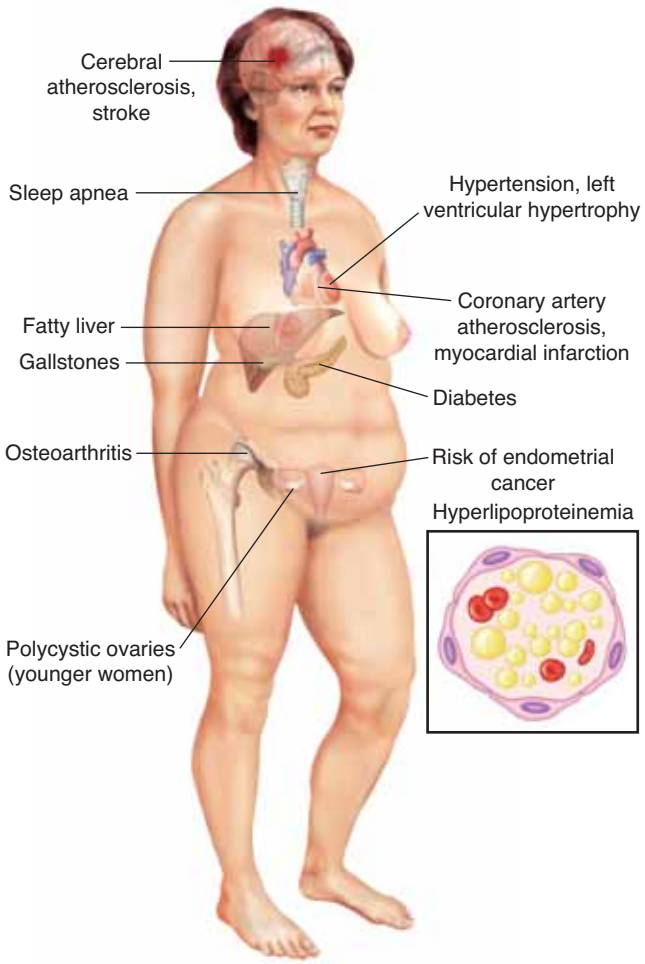


FIGURE 10-2. Clinical manifestations of obesity.

It is unknown what combinations of genes and mutations are involved in these risk factors and how environmental causes interact with them.

Although genetic factors may explain some of the individual variations in terms of excess weight, environmental influences are major contributors. These influences include family eating patterns, inactivity because of labor-saving devices and time spent on the computer and watching television, reliance on the automobile for transportation, easy access to food, energy density of food, increased consumption of sugar-sweetened beverages,[22] and increasing portion sizes.[23] The obese may be greatly influenced by the availability of food, the flavor of food, time of day, and other cues. The composition of the diet also may be a causal factor, and the percentage of dietary fat independent of total calorie intake may play a part in the development of obesity. Psychological factors include using food as a reward, comfort, or means of getting attention. Eating may be a way to cope with tension, anxiety, and mental fatigue.

Adipose Tissue and Types of Obesity

Adipose tissue is no longer simply viewed as a reservoir for energy storage. Adipose tissue is now known to express and secrete a variety of bioactive peptides, known as *adipokines* (e.g., leptin, tumor necrosis factor-α [TNF-α], interleukin-6) that have autocrine, paracrine, and endocrine effects on the brain, liver, skeletal muscle, and other tissues of the body.[24] In addition, adipose tissue expresses numerous receptors that allow it to respond to afferent signals from traditional hormone systems as well as the central nervous system. Through this interactive network adipose tissue is integrally involved in coordinating a variety of physiologic processes including energy metabolism, neuroendocrine function, and immune function. It is the dysfunctional aspects of these processes that are implicated in the pathogenesis and adverse effects of adipose tissue excess or obesity.

Adipose Tissue as an Endocrine Organ

Adipose tissue is now recognized as an endocrine organ that produces several hormones, including *leptin*, an important mediator of body weight, and *resistin*, which regulates sensitivity to insulin and may be involved in the pathogenesis of type 2 diabetes.[24,25] The discovery of leptin (from the Greek meaning "thin"), a peptide released from adipocytes, has led to renewed interest in the function of adipose tissue and its role in energy homeostasis. Leptin acts through binding to and activation of specific leptin receptors found in several peripheral tissues and in many areas of the brain including specific regions of the hypothalamus. Receptors in these hypothalamic regions are known to be involved in appetite, food intake, sympathetic nervous system activity, temperature regulation, and insulin release by the pancreatic beta cells. Leptin levels rise following food intake, signaling the sensation of satiety, and fall during fasting, stimulating the sensation of appetite. Congenital leptin deficiency has been associated with hyperphagia (excessive eating) and obesity, impaired thermogenesis, insulin resistance, and hyperlipidemia, all reversed by leptin treatment.[25] The biology of leptin in normal individuals and whether leptin is involved in obesity and obesity-related diseases remains uncertain.

Adipose Tissue and the Inflammatory Process

Recent evidence suggests that excess adipose tissue is also associated with a chronic inflammatory response, which is characterized by abnormal cytokine production; increased synthesis of acute-phase reactants, such as C-reactive protein; and activation of proinflammatory signaling pathways.[26] Systemic chronic inflammation has been proposed to have an important role in the pathogenesis of obesity-related insulin resistance and development of type 2 diabetes. It might also contribute to a state of endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease.[26,27] Although there is evidence that the proinflammatory pathways are activated in adipose tissue in obesity, the source of the inflammatory mediators remains unclear. Besides adipocytes, adipose tissue contains a connective tissue matrix and macrophages, which may contribute to the production of inflammatory mediators.

Types of Obesity

Two types of obesity based on distribution of fat have been described: upper body and lower body obesity. *Upper body obesity* is also referred to as *central*, *abdominal*, or *visceral* obesity. Lower body obesity is also known as *peripheral* or *gluteal-femoral* obesity. Persons with upper body obesity are often referred to as being shaped like an "apple," compared with those with lower body obesity, who are more "pear" shaped (Fig. 10-3). The obesity type is determined by dividing the waist by the hip circumference. A waist-to-hip ratio greater than 1.0 in men and 0.8 in women indicates upper body obesity. Research suggests that fat distribution may be a more important factor for morbidity and mortality than overweight or obesity.

The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and mortality. Both BMI and waist circumference are positively correlated with total body adipose tissue, but waist circumference is a better predictor of abdominal or visceral fat content than BMI.[28] A waist circumference of 88 cm (35 inches) or greater in women and 102 cm (40 inches) or greater in men has been associated with increased health risk[13] (see Table 10-2). In general, men have more intra-abdominal fat and women more subcutaneous fat. As men age, the proportion of intra-abdominal fat to subcutaneous fat increases. After menopause, women tend to acquire more intra-abdominal fat. Increasing weight gain, alcohol, and low levels of activity are associated with central obesity.

Central obesity can be further differentiated into intra-abdominal or visceral fat and subcutaneous fat by the use of CT or MRI scans. However, visceral fat is usually considered to be synonymous with central obesity. Visceral fat stores are believed to be more lipolytically active than subcutaneous fat and have a greater potential to impact liver metabolism, given the fact that the fatty acids in their venous drainage flow directly to the liver. In addition to their lipolytic effects, visceral adipocytes produce greater amounts of adipokines (e.g., TNF-α, adiponectin) that contribute to the development of systemic insulin resistance, hypertension, and hyperlipidemia. Higher levels of these adipokines and circulating free fatty acids in obese persons, particularly those with upper body obesity, are thought to be associated with greater cardiometabolic risk and many of the adverse effects of obesity.[15]

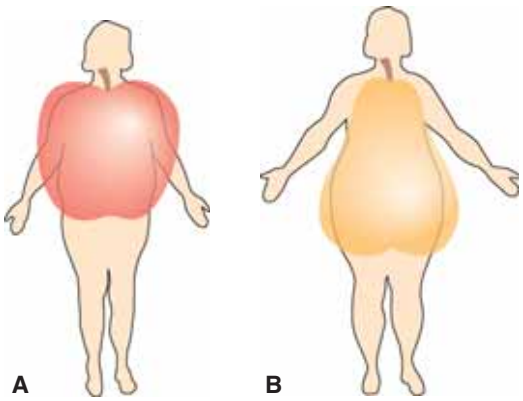


FIGURE 10-3. Distribution of adipose tissue in **(A)** upper body or central (visceral) obesity and **(B)** lower body or peripheral (subcutaneous) obesity. People with upper body obesity are often described as having an "apple-shaped" body and those with lower body obesity as having a "pear-shaped" body.

Cardiometabolic risk represents the overall risk of developing diabetes and/or atherosclerotic cardiovascular disease (e.g., myocardial infarction, stroke) due to a cluster of modifiable risk factors, such as dyslipidemia (elevated levels of triglycerides and decreased levels of high-density lipoproteins), hypertension, insulin resistance, and elevated blood glucose levels, and emerging risk factors, such as the presence of inflammatory cytokines, endothelial dysfunction, and a prothrombotic state. Both the traditional and emerging cardiovascular risk factors are key components of what is termed the *metabolic syndrome* (see Chapter 33).[15,16] Visceral obesity is also associated with many other conditions including cancer (e.g., breast and endometrial cancer), gallbladder disease, osteoarthritis, menstrual irregularities, and infertility (especially as part of the polycystic ovarian syndrome) (see Fig. 10-2).

Weight loss causes a preferential loss of visceral fat (due to higher turnover of visceral fat cells than subcutaneous) and can result in improvements in metabolic and hormonal abnormalities. Although peripheral obesity is associated with varicose veins in the legs and mechanical problems, it is not as strongly associated with cardiometabolic risk.

Prevention and Treatment of Obesity

Emphasis is being placed on the prevention of obesity. It has been theorized that obesity is preventable because the effect of hereditary factors is no more than moderate. A more active lifestyle together with a low-fat diet (<30% of calories) is seen as the strategy for prevention. The target audience should be young children, adolescents, and young adults.[29] Tools needed to achieve this goal include promotion of regular meals, increased intake of fruits and vegetables, substituting water for calorie-containing beverages, decreased television viewing time, a low-fat diet, and increased activity.[30] Other experts target the high-risk period from 25 to 35 years, menopause, and the year after successful weight loss.

The current recommendation is that treatment is indicated in all individuals who have a BMI of 30 or higher or who have a BMI of 25 to 29.9 or a high waist circumference plus two or more risk factors.[31] Treatment should focus on individualized lifestyle modification through a combination of a reduced-calorie diet, increased physical activity, and behavior therapy. Pharmacotherapy and surgery are available as an adjunct to lifestyle changes in individuals who meet specific criteria. Before treatment begins, an assessment should be made of the degree of overweight, the person's eating habits, the person's physical activity level, and the presence of obesity-associated risk factors and complications.[31] It also is advisable to determine the person's barriers and readiness to lose weight.

Dietary therapy should be individually prescribed based on the person's overweight status and risk profile.[30] The diet should be a personalized plan with realistic goals that are 500 to 1000 kcal/day less than the current intake. The aim should be for weight loss initially, followed by a strategy for weight maintenance. Many popular diets exist such as Atkins, Ornish, Weight Watchers, South Beach, etc. A recent study comparing several of these diets suggested that adherence to the diet, not the diet itself, is most closely associated with weight loss (i.e., the best diet is the one the person likes best).[32]

There is convincing evidence that increased physical activity decreases the risk of overweight and obesity. In addition, it reduces cardiovascular and diabetes risk beyond that achieved by weight loss alone. Although physical activity is an important part of weight loss therapy and helps with maintaining weight loss, it does not independently lead to a significant weight loss.[33] It may, however, help reduce abdominal fat, increase cardiorespiratory fitness, and prevent the decrease in muscle mass that often occurs with weight loss. Exercise should be started slowly with the duration and intensity increased independent of each other.

Techniques for changing behavior include self-monitoring of eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring, social support, and relapse prevention.[30] Pharmacotherapy and surgery are available as adjuncts to lifestyle changes in individuals who meet specific criteria. Pharmacotherapy is usually considered only after combined diet, exercise, and behavioral therapy have been in effect for a reasonable period of time. Weight loss surgery is usually limited to persons with a BMI greater than 40, those with a BMI greater than 35 who have comorbid conditions and in whom efforts at medical therapy have failed, and those who have complications of extreme obesity.

Childhood Obesity

Obesity is the most prevalent nutritional disorder affecting the pediatric population in industrialized countries in the world.[34–36] The definition for obesity in children is a BMI at or above the sex- and age-specific 95th percentile, while a BMI between the 85th and 95th percentile is defined as being overweight.[34] These criteria have been selected because they correspond to an adult BMI of 30 and 25, respectively.[37] The findings from the National Health and Nutrition Examination Survey (NHANES), conducted between 2003 and 2004, indicated that 18.8% of children ages 6 to 11 years and 17.4% of children ages 12 to 19 years were overweight.[35]

The major concern of childhood obesity is that obese children will grow up to become obese adults. Health care providers are now beginning to see hypertension, dyslipidemia, type 2 diabetes, and psychosocial stigma in obese children and adolescents. In North America, type 2 diabetes now accounts for half of all new diagnoses of diabetes (type 1 and type 2) in some populations of adolescents.[38] In addition, there is a growing concern that childhood and adolescent obesity may be associated with negative psychosocial consequences such as low self-esteem and discrimination by adults and peers.[34]

Childhood obesity is determined by a combination of hereditary and environmental factors. It is associated with obese parents, gestational diabetes and excessive weight gain during pregnancy, formula feeding, parenting style, parental eating habits, energy-dense food choices, erratic eating patterns, ethnicity, and sedentary lifestyle.[34–36,38,39] Children with overweight parents are at highest risk.[39] One of the factors leading to childhood obesity is the increase in inactivity. Increasing perceptions that neighborhoods are unsafe has resulted in less time spent outside playing and walking and more time spent indoors engaging in sedentary activities such as television viewing and computer usage. Television viewing is associated with consumption of calorie-dense snacks and decreased indoor activity. Studies have shown a 10% decrease in obesity risk for each hour per day of moderate to vigorous physical activity, while the risk increased by 12% for each hour per day of television viewing.[38] Obese children also may have a deficit in recognizing hunger sensations, stemming perhaps from parents who use food as gratification. The impact of fast food, increased portion size, calorie density, sugar-sweetened soft drinks, and high-glycemic-index foods all are likely contributing to the increased weights in children and adolescents.

Diagnosis and Treatment

Given the enormity of the problem of overweight and obesity in children, the American Medical Association (AMA), the Department of Health and Human Services' Health Resources and Services Administration (HRSA), and the Centers for Disease Control and Prevention (CDC) assembled an expert committee to develop recommendations for the assessment, prevention, and treatment of this public health problem.[37] Their recommendations include a yearly assessment of weight status in all children by measurement of height and weight to determine BMI for age and comparing it to standard growth charts. Children who are 2 to 18 years of age with a BMI greater than or equal to the 95th percentile for age and sex or a BMI greater than 30 (whichever is smaller) should be classified as obese. Those children with a BMI greater than or equal to the 85th percentile but less than the 95th percentile for age and sex should be placed in the overweight category.

Because adolescent obesity is predictive of adult obesity, treatment of childhood obesity is desirable.[36] The goals of therapy in uncomplicated obesity are directed toward healthy eating and activity, not achievement of ideal body weight. Families should be taught awareness of current eating habits, activity, and parenting behavior and how to modify them. In children with complications secondary to the obesity, the medical goal should be to improve that problem. The weight loss interventions should include all family members and caregivers; begin early at a point when the family is ready for change; and assist the family to learn to monitor eating and activity patterns and make small and acceptable changes in these patterns.

Overweight children should be treated using a staged method based on their age, BMI, and related comorbidities. Dietary goals should focus on well-balanced, healthy meals with a healthy approach to eating. Specific strategies can include reduction of specific high-calorie foods or an appropriate balance of foods that are low, medium, and high calorie. Commercial diets should be used with caution. Pharmacologic therapy and bariatric surgery should be reserved for children with complications and for severe obesity, respectively.

In summary, obesity is defined as excess body fat resulting from consumption of calories in excess of those expended for exercise and activities. Heredity; socioeconomic, cultural, and environmental factors; psychological influences; and activity levels have been implicated as causative factors in the development of obesity. The cardiometabolic risks associated with obesity include hyperlipidemia, insulin resistance, and hypertension, which together predispose to the development of type 2 diabetes mellitus and atherosclerotic cardiovascular disease (e.g., coronary artery disease, stroke). Obesity is also associated with gallbladder disease, infertility, osteoarthritis, sleep apnea, complications of pregnancy, menstrual irregularities, nonalcoholic fatty liver disease, thromboembolic disorders, and poor wound healing. There are two types of obesity—upper body or central (visceral) obesity and lower body or peripheral obesity. The adipocytes in visceral obesity release free fatty acids and adipokines that increase cardiometabolic risk and produce many of the adverse effects of obesity. The treatment of obesity focuses on nutritionally adequate weight loss diets, behavior modification, exercise, social support, and, in situations of marked obesity, pharmacotherapy and surgical methods.

Obesity is the most prevalent nutritional disorder affecting the pediatric population in industrialized countries in the world. Factors that predispose to childhood obesity include erratic eating patterns, dense calorie food choices, and lack of exercise and sedentary lifestyle. Health care providers are now beginning to see hypertension, dyslipidemia, type 2 diabetes mellitus, and psychosocial stigma in obese children and adolescents. Because of the enormity of the problem, it recommended that the weight status of all children be evaluated yearly and that measures to prevent and treat obesity be included in the health care plan for all children.

Undernutrition and Eating Disorders

Undernutrition continues to be a major health problem throughout the world.[40] Protein-energy malnutrition is most obvious in developing countries of the world, where it is indirectly responsible for half of all deaths of young children.[41] Even in developed nations, malnutrition remains a problem.

Malnutrition and Starvation

Malnutrition and starvation are conditions in which a person does not receive or is unable to use an adequate amount of nutrients for body function. An adequate diet should provide sufficient energy in the form of carbohydrates, fats, and proteins; essential amino acids and fatty acids for use as building blocks for synthesis of structural and functional proteins and lipids; and the necessary vitamins and minerals, to function as coenzymes or hormones in vital metabolic processes or, as in the case of calcium and phosphate, as an important structural component of bone.[42]

Among the many causes of malnutrition are poverty and lack of knowledge, acute and chronic illness, and self-imposed dietary restriction. Homeless people, the elderly, and children of the poor often demonstrate the effects of protein and energy malnutrition, as well as vitamin and mineral deficiencies. Even the affluent may fail to recognize that infants, adolescents, and pregnant women have increased nutritional needs. Some types of malnutrition are caused by acute and chronic illnesses, such as occurs in persons with Crohn disease who are unable to absorb their food. Anorexia nervosa and less overt eating disorders affect a large population of persons who are concerned about body image or athletic performance.

Protein-Energy Malnutrition

Protein and energy (calorie) malnutrition represents a depletion of the body's lean tissues caused by starvation or a combination of starvation and catabolic stress. The lean tissues are the fat-free, metabolically active tissues of the body, namely, the skeletal muscles, viscera, and cells of the blood and immune system. Because lean tissues are the largest body compartment, their rate of loss is the main determinant of total body weight in most cases of protein-energy malnutrition.

Much of the literature on malnutrition and starvation has dealt with infants and children in underdeveloped countries in which food deprivation results in an inadequate intake of protein and calories to meet the body's energy needs. Protein-energy malnutrition in this population commonly is divided into two distinct conditions: marasmus (protein and calorie deficiency) and kwashiorkor (protein deficiency). The pathologic changes for both types of malnutrition include humoral and cellular immunodeficiencies resulting from protein deficiency and lack of immune mediators. There is impaired synthesis of pigments of the hair and skin (e.g., hair color may change and the skin may become hyperpigmented) due to a lack of substrate (tyrosine) and coenzymes.

There are two functional compartments involved in the distribution of proteins within the body: the *somatic compartment*, represented by the skeletal muscles, and the *visceral compartment*, represented by protein stores in body organs, principally the liver.[42] These two compartments

are regulated differently, with the somatic compartment being affected more severely in marasmus, and the visceral compartment more severely in kwashiorkor.

Marasmus represents a progressive loss of muscle mass and fat stores due to inadequate food intake that is equally deficient in calories and protein.[42,43] It results in a reduction in body weight adjusted for age and size. The child with marasmus has a wasted appearance, with loss of muscle mass, stunted growth, and loss of subcutaneous fat; a protuberant abdomen (from muscular hypotonia); wrinkled skin; sparse, dry, and dull hair; and depressed heart rate, blood pressure, and body temperature. Diarrhea is common. Since immune function is impaired, concurrent infections occur and place additional stress on an already weakened body. An important characteristic of marasmus is growth failure; if sufficient food is not provided, these children will not reach their full potential stature.[43]

Kwashiorkor results from a deficiency in protein in diets that are relatively high in carbohydrates.[42,43] The term *kwashiorkor* comes from an African word meaning "the disease suffered by the displaced child," because the condition develops soon after a child is displaced from the breast after the arrival of a new infant and placed on a starchy gruel feeding. Kwashiorkor is a more severe form of malnutrition than marasmus. Unlike marasmus, severe protein deficiency is associated with severe loss of the visceral protein compartment with a resultant hypoalbuminemia that gives rise to generalized or dependent edema. The child with kwashiorkor usually presents with edema, desquamating skin, discolored hair, anorexia, and extreme apathy (Fig. 10-4). There are "flaky paint" lesions of the skin on the face, extremities, and perineum and the hair becomes a sandy or reddish color, with linear depigmentation (flag sign).[43] There is generalized growth failure and muscle wasting as in marasmus, but subcutaneous fat is normal, since calorie intake is adequate. Other manifestations include skin lesions, hepatomegaly and distended abdomen, cold extremities, and decreased cardiac output and tachycardia.

Marasmus-kwashiorkor is an advanced protein-calorie deficit together with increased protein requirement or loss. This results in a rapid decrease in anthropometric measurements with obvious edema and wasting and loss of organ mass. One essential aspect of severe protein-energy malnutrition is fatty degeneration of such diverse organs as the heart and liver. This degeneration causes subclinical and overt cardiac dysfunction, especially when malnutrition is accompanied by edema. A second injurious aspect is the loss of subcutaneous fat, which markedly reduces the body's capacity for temperature regulation and water storage. As a consequence, malnourished children become dehydrated and hypothermic more quickly and more severely than normally nourished children.[40] Most children with severe protein-energy malnutrition have asymptomatic infections because their immune system fails to respond appropriately.

Malnutrition in Trauma and Illness

In industrialized societies, protein-energy malnutrition most often occurs secondary to trauma or illness. Kwashiorkor-like secondary protein-energy malnutrition occurs most commonly in association with hypermetabolic acute illnesses, such as trauma, burns, and sepsis.[44] Marasmus-like secondary protein-energy malnutrition typically results from chronic illnesses such as chronic obstructive pulmonary disease (COPD), congestive heart failure, cancer, and HIV infection. Approximately half of all persons with cancer experience tissue wasting in which the tumor induces metabolic changes leading to a loss of adipose tissue and muscle mass.[45]

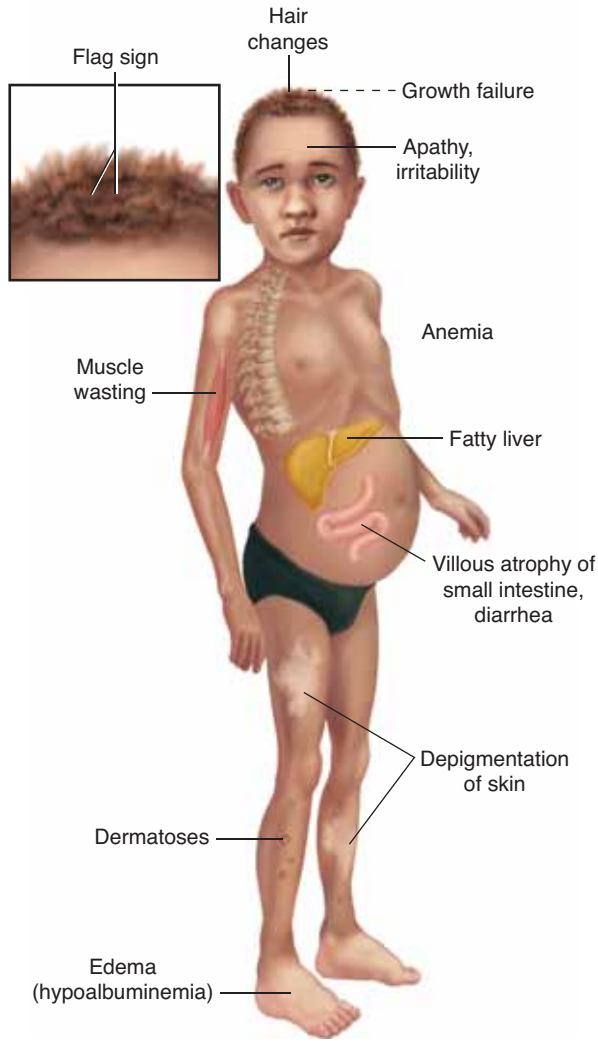


FIGURE 10-4. Clinical manifestations of kwashiorkor.

In healthy adults, body protein homeostasis is maintained by a cycle in which the net loss of protein in the postabsorptive state is matched by a net postprandial gain of protein.[46] In persons with severe injury or illness, net protein breakdown is accelerated and protein rebuilding disrupted. Protein mass is lost from the liver, gastrointestinal tract, kidneys, and heart. As protein is lost from the liver, hepatic synthesis of proteins declines and plasma protein levels are decreased. There also is a decrease in immune cells. Wound healing is poor, and the body is unable to fight off infection because of multiple immunologic malfunctions throughout the body. The gastrointestinal tract undergoes mucosal atrophy with

loss of villi in the small intestine, resulting in malabsorption. The loss of protein from cardiac muscle leads to a decrease in myocardial contractility and cardiac output. The muscles used for breathing become weakened, and respiratory function becomes compromised as muscle proteins are used as a fuel source. A reduction in respiratory function has many implications, especially for persons with burns, trauma, infection, or chronic respiratory disease and for persons who are being mechanically ventilated because of respiratory failure.

In hospitalized patients, malnutrition increases morbidity and mortality rates, incidence of complications, and length of stay. Malnutrition may present at the time of admission or develop during hospitalization. The hospitalized patient often finds eating a healthful diet difficult and commonly has restrictions on food and water intake in preparation for tests and surgery. Pain, medications, special diets, and stress can decrease appetite. Even when the patient is well enough to eat, being alone in a room where unpleasant treatments may be given is not conducive to eating. Although hospitalized patients may appear to need fewer calories because they are on bed rest, their actual need for caloric intake may be higher because of other energy expenditures. For example, more calories are expended during fever, when the metabolic rate is increased. There also may be an increased need for protein to support tissue repair after trauma or surgery.

Diagnosis

No single diagnostic measure is sufficiently accurate to serve as a reliable test for malnutrition. Techniques of nutritional assessment include evaluation of dietary intake, anthropometric measurements, clinical examination, and laboratory tests.[44] Evaluation of weight is particularly important. Body weight can be assessed in relation to height using the BMI. Evaluation of body composition can be performed by inspection or using anthropometric measurements such as skinfold thickness. Serum albumin and prealbumin are used in the diagnosis of protein-calorie malnutrition. Albumin, which has historically been used as a determinant of nutrition status, has a relatively large body pool and a half-life of 20 days and is less sensitive to changes in nutrition than prealbumin, which has a shorter half-life and a relatively small body pool.[44]

Treatment

The treatment of severe protein-calorie malnutrition involves the use of measures to correct fluid and electrolyte abnormalities and replenish proteins, calories, and micronutrients.[44] Treatment is started with modest quantities of proteins and calories based on the person's actual weight. Concurrent administration of vitamins and minerals is needed. Either the enteral or parenteral route can be used. The treatment should be undertaken slowly to avoid complications. The administration of water and sodium with carbohydrates can overload a heart that has been weakened by malnutrition and result in congestive failure. Enteral feedings can result in malabsorptive symptoms due to abnormalities in the gastrointestinal tract. Refeeding edema is a benign dependent edema that results from renal sodium reabsorption and poor skin and blood vessel integrity. It is treated by elevation of the dependent area and modest sodium restrictions. Diuretics are ineffective and may aggravate electrolyte deficiencies.

Eating Disorders

Eating disorders, which include anorexia nervosa, bulimia nervosa, and binge-eating disorder and their variants, incorporate serious disturbances in eating, such as restriction of intake and binging, with an excessive concern over body shape or body weight.[47–49] Eating disorders typically occur in adolescent girls and young women, although 10% of cases of anorexia nervosa and bulimia nervosa occur in boys and men.[50] Binge-eating disorder is more prevalent in men than anorexia nervosa and bulimia combined. Compared with women, men tend to experience less pressure to engage in behaviors such as self-induced vomiting or laxative use when overeating, less of a sense of loss of control when binge eating, and a greater tendency to use compulsive exercise rather than purging for weight control.[50]

Eating Disorders

- Eating disorders are serious disturbances in eating, such as willful restriction of intake and binge eating, as well as excessive concern over body weight and shape.
- Anorexia nervosa is characterized by a refusal to maintain a minimally normal body weight (e.g., at least 85% of minimal expected weight), an excessive concern over gaining weight and how the body is perceived in terms of size and shape, and amenorrhea (in girls and women after menarche).
- Bulimia nervosa is characterized by recurrent binge eating; inappropriate compensatory behaviors such as self-induced vomiting, fasting, or excessive exercise that follow the binge-eating episode; and extreme concern over body shape and weight.
- Binge eating consists of consuming unusually large quantities of food during a discrete period (e.g., within any 2-hour period) along with lack of control over the binge-eating episode.
- Binge-eating disorders are characterized by eating behaviors such as eating rapidly, eating until becoming uncomfortably full, eating large amounts when not hungry, eating alone because of embarrassment, and disgust, depression, or guilt because of eating episodes.

Eating disorders are more prevalent in industrialized societies and occur in all socioeconomic and major ethnic groups. A combination of genetic, neurochemical, developmental, and sociocultural factors is thought to contribute to the development of the disorders.[47,48] The American Psychiatric Society's *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, text revision (DSM-IV-TR) has established criteria for the diagnosis of anorexia nervosa and bulimia nervosa.[49] Although these criteria allow clinicians to make a diagnosis in persons with a specific eating disorder, the symptoms often occur along a continuum between those of anorexia nervosa and bulimia nervosa. Preoccupation with weight and excessive self-evaluation of weight and shape are common to both disorders, and persons with eating disorders may demonstrate a mixture of both disorders.[48,51] The female athlete triad, which includes disordered eating, amenorrhea, and osteoporosis, does not meet the strict DSM-IV-TR criteria for anorexia nervosa or bulimia nervosa, but shares many of the characteristics and therapeutic concerns[52] (see Chapter 44). Persons with eating disorders may require concomitant evaluation for psychiatric illness because eating disorders often are accompanied by mood, anxiety, and personality disorders.

Anorexia Nervosa

Anorexia nervosa is an eating disorder that usually begins in adolescence and is characterized by determined dieting, often accompanied by compulsive exercise and, in a subgroup of persons, purging behavior with or without binge eating, resulting in sustained low weight.[53] Other features include a disturbed body image, a pervasive fear of becoming obese, and obsession with severely restricted caloric intake.

The causes of anorexia appear to be multifactorial, with determinants that include genetic influence, personality traits of perfectionism and compulsiveness, anxiety disorders, family history of depression and obesity, and peer, familial, and cultural pressures with respect to appearance.[53] The DSM-IV-TR diagnostic criteria for anorexia nervosa are (1) a refusal to maintain a minimally normal body weight for age and height (e.g., at least 85% of minimal expected weight or BMI ≥17.5); (2) an intense fear of gaining weight or becoming fat; (3) a disturbance in the way one's body size, weight, or shape is perceived; and (4) amenorrhea (in girls and women after menarche).[54] Other psychiatric disorders often coexist with anorexia nervosa, including major depression or dysthymia and obsessive-compulsive disorder. Alcohol and substance abuse may also be present, more often among those with the binging-purging type of anorexia nervosa.[53]

Many organ systems are affected by the malnutrition that occurs in persons with anorexia nervosa. The severity of the abnormalities tends to be related to the degree of malnutrition and is reversed by refeeding. The most frequent complication of anorexia is amenorrhea and loss of secondary sex characteristics with decreased levels of estrogen, which can eventually lead to osteoporosis. Bone loss can occur in young women after as short a period of illness as 6 months.[48] Symptomatic compression fractures and kyphosis have been reported. Constipation, cold intolerance and failure to shiver in cold, bradycardia, hypotension, decreased heart size, electrocardiographic changes, blood and electrolyte abnormalities, and skin with lanugo (i.e., increased amounts of fine hair) are common. Abnormalities in cognitive function may also occur. The brain loses both white and gray matter during severe weight loss; weight restoration results in return of white matter, but some loss of gray matter may persist.[53] Unexpected sudden deaths have been reported; the risk appears to increase as weight drops to less than 35% to 40% of ideal weight. It is believed that these deaths are caused by myocardial degeneration and heart failure rather than arrhythmias.

The most exasperating aspect of the treatment of anorexia is the inability of the person with anorexia to recognize there is a problem. However, persons with the disorder are usually willing to talk about their preoccupation with weight loss, food refusal, rituals about food, excessive exercise routines, purging and laxative use, and withdrawal from activities and relationships.[55] Because anorexia is a form of starvation, it can lead to death if left untreated. A multidisciplinary approach appears to be the most effective method of treating persons with the disorder.[52] The goals of treatment are eating and weight gain, resolution of issues with the family, healing of pain from the past, and efforts to work on psychological, relationship, and emotional issues. Adults whose weight loss is more than 25% below the expected weight (or with less weight loss if there are coexisting medical or psychiatric conditions, or both) and children or adolescents who are losing weight rapidly generally require hospitalization to ensure an adequate food intake and to limit physical activity.[53]

Bulimia Nervosa

Bulimia nervosa is defined by recurrent binge eating and activities including vomiting, fasting, excessive exercise, and use of diuretics, laxatives, or enemas to compensate for that behavior. Bulimia nervosa usually begins during adolescence, with a peak period of onset around 18 years of age.[55]

The DSM-IV-TR criteria for bulimia nervosa are (1) recurrent binge eating (at least two times per week for 3 months); (2) inappropriate compensatory behaviors such as self-induced vomiting, abuse of laxatives or diuretics, fasting, or excessive exercise that follow the binge-eating episode; (3) self-evaluation that is unduly influenced by body shape and weight; and (4) a determination that the eating disorder does not occur exclusively during episodes of anorexia nervosa.[54] In contrast to anorexia nervosa, which is characterized by a weight that is less than 85% of the normal value, most persons with bulimia nervosa are of normal weight. The diagnostic criteria for bulimia nervosa now include subtypes to distinguish patients who compensate by purging (e.g., vomiting or abuse of laxatives or diuretics) and those who use nonpurging behaviors (e.g., fasting or excessive exercise).[54] The disorder may be associated with other psychiatric disorders such as anxiety disorder or depression.

There is also an association with substance abuse and risky and self-destructive behaviors.[56]

The complications of bulimia nervosa include those resulting from overeating, self-induced vomiting, and cathartic and diuretic abuse.[56,57] Among the complications of self-induced vomiting are dental disorders, parotitis, and fluid and electrolyte disorders. Dental abnormalities, such as sensitive teeth, increased dental caries, and periodontal disease, occur with frequent vomiting because the high acid content of the vomitus causes tooth enamel to dissolve. Esophagitis, dysphagia, and esophageal stricture are common. With frequent vomiting, there often is reflux of gastric contents into the lower esophagus because of relaxation of the lower esophageal sphincter. Vomiting may lead to aspiration pneumonia, especially in intoxicated or debilitated persons. Potassium, chloride, and hydrogen are lost in the vomitus, and frequent vomiting predisposes to metabolic acidosis with hypokalemia (see Chapter 8). An unexplained physical response to vomiting is the development of benign, painless parotid gland enlargement.

The weights of persons with bulimia nervosa may fluctuate, although not to the dangerously low levels seen in anorexia nervosa. Their thoughts and feelings range from fear of not being able to stop eating to a concern about gaining too much weight. They also experience feelings of sadness, anger, guilt, shame, and low self-esteem.

Treatment strategies include psychological and pharmacologic treatments. Cognitive behavioral therapy is the psychosocial therapy predominately used.[57] This therapy is designed to help individuals become aware of other ways to cope with the feelings that precipitate the desire to purge and to try and correct maladaptive beliefs regarding their self-image. Unlike persons with anorexia nervosa, persons with bulimia nervosa are upset by the behaviors practiced and the thoughts and feelings experienced, and they are more willing to accept help. Pharmacotherapeutic agents include the tricyclic antidepressants, the selective serotonin reuptake inhibitors, and other antidepressant medications.[56]

Binge Eating and Eating Disorder Not Otherwise Specified

Eating disorder not otherwise specified is a new diagnosis category for patients who have eating disorder symptoms but do not meet the full criteria for either anorexia nervosa or bulimia nervosa. This condition is diagnosed in 50% of primarily adolescent patients admitted to eating disorder programs. Within this group is the subgroup binge-eating disorder. These are usually obese patients who do not use behaviors to compensate for the binge eating. Many of these individuals are found in weight control programs.[58]

Binge eating is characterized by recurrent episodes of binge eating at least 2 days per week for 6 months and at least three of the following: (1) eating rapidly; (2) eating until becoming uncomfortably full; (3) eating large amounts when not hungry; (4) eating alone because of embarrassment; and (5) disgust, depression, or guilt because of eating episodes. The great majority of persons with binge-eating disorder are overweight, and in turn, obese persons have a higher prevalence of binge-eating disorder than the nonobese populations.[57,58]

The primary goal of therapy for binge-eating disorders is to establish a regular, healthful eating pattern. Persons with binge-eating disorders who have been successfully treated for their eating disorder have reported that making meal plans, eating a balanced diet at three regular meals a day, avoiding high-sugar foods and other binge foods, recording food intake and binge-eating episodes, exercising regularly, finding alternative activities, and avoiding alcohol and drugs are helpful in maintaining their more healthful eating behaviors after treatment.

In summary, undernutrition can range from a selective deficiency of a single nutrient to starvation, in which there is deprivation of all ingested nutrients. Malnutrition and starvation are among the most widespread causes of morbidity and mortality in the world. Protein-energy malnutrition in this population commonly is divided into two distinct conditions: marasmus (protein and calorie deficiency) and kwashiorkor (protein deficiency). There are two functional compartments involved in the distribution of proteins within the body: the somatic compartment, represented by the skeletal muscles, and the visceral compartment, represented by protein stores in body organs, principally the liver. In marasmus, there is a great loss of protein from the skeletal muscle compartment, and in kwashiorkor a greater loss of visceral proteins, particularly those of the liver. Malnutrition is common during illness, recovery from trauma, and hospitalization. The effects of malnutrition and starvation on body function are widespread. They include loss of muscle mass, impaired wound healing, impaired immunologic function, decreased appetite, loss of calcium and phosphate from bone, anovulation and amenorrhea in women, and decreased testicular function in men.

Anorexia nervosa, bulimia nervosa, and binge eating are eating disorders that result in malnutrition. In anorexia nervosa, distorted attitudes about eating lead to determined dieting, weight loss to below 85% of normal body weight, and malnutrition. Bulimia nervosa is characterized by secretive episodes or binges of eating large quantities of easily consumed, high-caloric foods, followed by compensatory behaviors such as fasting, self-induced vomiting, or abuse of laxatives or diuretics. Binge eating disorder is characterized by eating large quantities of food but is not accompanied by purging and other inappropriate compensatory behaviors seen in persons with bulimia nervosa. Eating disorder not otherwise specified is a new diagnosis category for patients who have eating disorder symptoms but do not meet the full criteria for either anorexia nervosa or bulimia nervosa.

REVIEW EXERCISES

1. A 25-year-old woman is 65 inches (165 cm) tall and weighs 300 pounds (136 kg). She works as a receptionist in an office, brings her lunch to work with her, spends her evenings watching television, and gets very little exercise. She reports that she has been fat ever since she was a little girl, she has tried "every diet under the sun," and when she diets she loses some weight but gains it all back again.

A. Calculate her BMI using the website referred to in Table 10-1.
B. How would you classify her obesity?
C. What are her risk factors for obesity?
D. What would be one of the first steps in helping her develop a plan to lose weight?

2. A 16-year-old high school student is brought into the physician's office by her mother, who is worried because her daughter insists on dieting because she thinks she is too fat. The daughter is 67 inches tall and weighs 96 pounds. Her history reveals that she is a straight A student, plays in the orchestra, and is on the track team. Although she had been having regular menstrual periods, she has not had a period in 4 months. She is given a tentative diagnosis of anorexia nervosa.

A. What are the diagnostic criteria for a diagnosis of anorexia nervosa?
B. What is the physiologic reason for her amenorrhea?
C. What are some of the physiologic manifestations associated with malnutrition and severe weight loss?

REFERENCES

1. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (10th ed., pp. 852–858, 865–880). Philadelphia: W.B. Saunders.
2. Ross M.H., Kaye G.I., Pawlina W. (2003). *Histology* (4th ed., pp. 156–162). Philadelphia: Lippincott Williams & Wilkins.
3. Casteilla L., Dani C. (2006). Adipose tissue-derived cells: From physiology to regenerative medicine. *Diabetes and Metabolism* 32(5 pt 1), 393–401.
4. Chou F.S., Wang P.S., Kulp S., et al. (2007). Effects of thiazolidinediones on differentiation, proliferation, and apoptosis. *Molecular Cancer Research* 5(6), 523–530.
5. Otten J.J., Hellwig J.P., Meyers L.D. (2006). *Dietary reference intakes: The essential guide to nutrient requirements.* Washington, DC: National Academy Press.
6. U.S. Department of Agriculture. Food and Nutrition Center. [Online] Available: http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=3&tax_subject=256&topic_id=1342&level3_id=5140. Accessed May 17, 2010.
7. Trumbo P., Schlicker S., Yates A.A., et al. (2002). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. *Journal of the American Dietetic Association* 102, 1621–1630.
8. National Institutes of Health Expert Panel. (2002). *Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).* NIH publication no. 02-5215. Bethesda, MD: National Institutes of Health.
9. Lichtenstein A.L., Apple L.J., Brandis M., et al. (2006). AHA scientific statement. Diet and lifestyle recommendations revision 2006: A scientific statement from AHA Nutrition Committee. *Circulation* 114, 82–96.
10. Murphy K.G., Bloom S.R. (2006). Gut hormones and the regulation of energy homeostasis. *Nature* 444, 854–859.
11. Chaudhri O.B., Salem V., Murphy K.G., et al. (2008). Gastrointestinal satiety signals. *Annual Review of Physiology* 70, 239–255.
12. Han T.S., Sattar N., Lean M. (2006). Assessment of obesity and its clinical implications. *British Medical Journal* 333, 695–698.
13. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. NIH publication no. 98-4083. (1998). *Obesity Research* 6(Suppl 2), 51S–209S.
14. Abernathy R.P., Black D.R. (1996). Healthy body weight: An alternative perspective. *American Journal of Clinical Nutrition* 63(Suppl), 448S–451S.
15. Eckel R., Grundy S., Zimmet P. (2005). Metabolic syndrome. *Lancet* 365, 1415–1428.
16. Scott M., Grundy J.I., Cleeman S.R., et al. (2005). Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112, 2735–2752.
17. Hossain P., Kawar B., El Nahas M. (2007) Obesity and diabetes in the developing world - A growing challenge. *New England Journal of Medicine* 356, 213–215.
18. Bray G.A. (2006). Obesity: The disease. *Journal of Medicinal Chemistry* 49, 4001–4007.
19. Hellerstein M.K., Parks E.J. (2007). Obesity and overweight. In Gardner D.G., Shoback D. (Eds.), *Greenspan's basic endocrinology* (8th ed., pp. 796–808). New York: McGraw-Hill.
20. Soreneson T.J., Holst C., Stunkard A.J., et al. (1992). Correlations of body mass index of adult adoptees and their biological and adoptive relatives. *International Journal of Obesity and Related Metabolic Disorders* 16, 227–236.
21. Rankinen T., Zuberi A., Chagnon Y.C., et al. (2006). The human obesity gene map: The 2005 update. *Obesity* 14, 529–644.
22. Malik V.S., Schulze M.B., Hu F.B. (2006). Intake of sugar-sweetened beverages and weight gain: A systematic review. *American Journal of Clinical Nutrition* 84, 274–288.
23. Young L.R., Nestle M. (2002). The contribution of expanding portion sizes to U.S. obesity epidemic. *American Journal of Public Health* 92, 246–249.
24. Kershaw E.E., Flier J.S. (2004). Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology and Metabolism* 89, 2548–2556.
25. Ahima R. (2006). Adipose tissue as an endocrine organ. *Obesity* 14, 242S–248S.
26. Tilg H., Moschen A.R. (2006). Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. *Nature* 5, 772–782.
27. Greenberg A.S., Obin M.S. (2006). Obesity and the role of adipose tissue in inflammation and metabolism. *American Journal of Clinical Nutrition* 83(Suppl), 461S–465S.
28. Klein S., Allison D.B., Heymsfield S.B., et al. (2007). Waist circumference and cardiometabolic risk: A consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *American Journal of Clinical Nutrition* 85, 1197–1202.
29. Task Force on Prevention and Treatment of Obesity. (1994). Towards prevention of obesity: Research directives. *Obesity Research* 2, 571.

30. Avenell A., Sattar N., Lean M. (2006). Management: Part 1-Behaviour change, diet, and activity. *British Medical Journal* 333, 740–743.
31. U.S. Department of Health and Human Services. (2000). *The practical guide: Identification, evaluation, and treatment of overweight and obesity in adults*. NIH publication no. 00-4084. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Health; National Heart, Lung, and Blood Institute; North American Association of the Study of Obesity.
32. Dalsinger M.L., Gleason J.A., Griffith J.L., et al. (2005). Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease reduction. *JAMA* 293, 43–53.
33. Jakicic J.M., Marcus B.H., Gallagher K.I., et al. (2003). Effect of exercise duration and intensity on weight loss in overweight, sedentary women: A randomized trial. *Journal of the American Medical Association* 290, 1323–1330.
34. Centers for Disease Control and Prevention. (2007). *Childhood overweight and obesity.* [Online] Available: http://www.cdc.gov/NCCDPHP/DNPA/obesity/childhood/index.htm. Accessed February 24, 2009.
35. Virani T., Lappan-Gracons, S., McConnell H., et al. (2007). *Primary prevention of childhood obesity.* Ontario, Canada: Registered Nurses' Association of Ontario.
36. Reilly J.J., Wilson D. (2006). Childhood obesity. *British Medical Journal* 333, 1207–1210.
37. Expert Committee Recommendations on the Assessment, Prevention, and Treatment of Child and Adolescent Overweight and Obesity. (2007). [Online] Available: http://www.ama-assn.org/ama1/pub/upload/mm/433/ped_obesity_recs.pdf. Accessed February 24, 2009.
38. Fagot-Campagna A., Pettitt D.J., Engelgau N.M., et al. (2000). Type 2 diabetes among North American children and adolescents: An epidemiologic review and a public health perspective. *Journal Pediatrics* 136, 664–672.
39. The Obesity Society. *Childhood overweight*. [Online] Available: http://www.obesity.org/information/childhood_overweight.asp. Accessed February 24, 2009.
40. Müller O., Krawinkel M. (2005). Malnutrition and health in developing countries. *Canadian Medical Association Journal* 173(3), 279–286.
41. Judge B.S., Eisenger B.H. (2005). Disorders of fuel metabolism: Medical complications associated with starvation, eating disorders, dietary fads, and supplements. *Emergency Clinics of North America* 23, 789–813.
42. Kumar V., Abbas A.K., Fausto N., Aster J.C. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 438–443). Philadelphia: Saunders Elsevier.
43. Rubin R., Strayer D.E. (2008). Environmental and nutritional pathology. In Rubin R., Strayer D.E. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 277–278). Philadelphia: Lippincott Williams & Wilkins.
44. Baron R.B. (2009). Nutrition. In McPhee S.J., Papadakis M.A. (Eds.), *Current diagnosis and treatment* (48th ed., pp. 1107–1125). New York: McGraw-Hill.
45. Tisdale M.J. (1999). Wasting in cancer. *Journal of Nutrition* 129(IS Suppl), 43S–46S.
46. Biolo G., Gabriele T., Cicchi B., et al. (1999). Metabolic response to injury and sepsis: Changes in protein metabolism. *Journal of Nutrition* 129(IS Suppl), 53S–57S.
47. Rome E.S., Ammerman S., Rosen D.S. (2003). Children and adolescents with eating disorders: The state of the art. *Pediatrics* 111, e98–e108.
48. Ricanati E.H.W., Rome E.S. (2005). Eating disorders: Recognizing early to prevent complications. *Cleveland Clinic Journal of Medicine* 72(10), 895–906.
49. Becker A., Grinspoon S.K., Klibanski A., et al. (1999). Eating disorders. *New England Journal of Medicine* 340, 1092–1098.
50. Weltzin T.E., Weisensel N., Francyk D., et al. (2005). Eating disorders in men. *Journal of Men's Health and Gender* 2(2), 186–193.
51. American Psychiatric Society. (2006). *Practice guideline for the treatment of patients with eating disorders* (3rd ed.). [Online] Available: http://www.psychiatryonline.com/pracGuide/pracGuideTopic_12.aspx. Accessed February 24, 2009.
52. Brunet M. (2005). Female athlete triad. *Clinics in Sports Medicine* 24, 623–636.
53. Yager J., Anderson A.E. (2005). Anorexia nervosa. *New England Journal of Medicine* 353(14), 1481–1488.
54. American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision, DSM-IV-TR). Washington, DC: American Psychiatric Association.
55. Zerbe K.J. (1999). *Women's mental health in primary care* (pp. 109–137). Philadelphia: W.B. Saunders.
56. Mehler P.S. (2003). Bulimia nervosa. *New England Journal of Medicine* 349(9), 875–881.
57. Kondo D.G., Sokol M.S. (2006). Eating disorders in primary care. *Postgraduate Medicine* 119, 59–65.
58. Schneider M. (2003). Bulimia nervosa and binge-eating disorders in adolescents. *Adolescent Medicine* 14, 119–131.

UNIT 3

Hematopoietic Function

Hematopoietic and Lymphoid Tissues
- *The Bone Marrow and Hematopoiesis*
  - Hematopoietic Growth Factors
- *Leukocytes (White Blood Cells)*
  - Granulocytes
  - Agranulocytes
  - Leukocyte Developmental Stages
- *Lymphoid Tissues*

Nonneoplastic Disorders of White Blood Cells
- *Neutropenia (Agranulocytosis)*
  - Pathogenesis
  - Clinical Course
- *Infectious Mononucleosis*
  - Pathogenesis
  - Clinical Course

Neoplastic Disorders of Hematopoietic and Lymphoid Origin
- *Leukemias*
  - Classification
  - Etiology and Molecular Biology
  - Acute Leukemias
  - Chronic Leukemias
- *Malignant Lymphomas*
  - Non-Hodgkin Lymphomas
  - Hodgkin Lymphoma
- *Plasma Cell Dyscrasias*
  - Multiple Myeloma

Chapter 11

Disorders of White Blood Cells and Lymphoid Tissues

The hematopoietic system and lymphoid tissues are responsible for the generation and regulation of the blood cells that function in the transport of oxygen, defense against microorganisms, and preservation of the integrity of the vascular system. The discussion in this chapter is divided into two parts: the first provides an introduction to the hematopoietic system, lymphoid tissues, and the white blood cells, and the second focuses on disorders of the white blood cells, including those of nonneoplastic (neutropenia and infectious mononucleosis) and neoplastic (lymphomas, leukemias, and multiple myeloma) origin. The megakaryocytes and platelets are discussed in Chapter 12, the red cells in Chapter 13, and the immune cells (lymphocytes and monocytes) in Chapter 15.

Hematopoietic and Lymphoid Tissues

Blood consists of blood cells (i.e., leukocytes or white blood cells, thrombocytes or platelets, and erythrocytes or red blood cells) and the plasma in which the cells are suspended. These cells all derive from a single pool of pluripotent stem cells in the bone marrow, which give rise

to two types of multipotential stem cells: the hematopoietic stem cells, which remain in the bone marrow, and the lymphopoietic stem cells, which migrate to the thymus, lymph nodes, spleen, and mucosa-associated lymphoid tissues.

The Bone Marrow and Hematopoiesis

The bone marrow consists of hematopoietic or blood-forming cells and stromal tissue that provides support for the blood-forming cells. The blood-forming population of bone marrow is made up of three types of cells: pluripotent stem cells, multipotent stem cells, and committed progenitor cells that develop into the various types of blood cells[1–4] (Fig. 11-1). The pluripotent stem cells give rise to two types of multipotential stem cells, the common lymphoid and the common myeloid stem cells. The common lymphoid stem cells, in turn, differentiate into lineage-specific precursor cells that develop into T lymphocytes (T cells), B lymphocytes (B cells), and natural killer (NK) cells. From the common myeloid stem cells arise precursor cells capable of differentiating along the erythrocyte/megakaryocytic and granulocyte-monocyte pathways.

Several levels of differentiation lead to the development of committed unipotential cells, which are the progenitors for each of the blood cell types. These cells are referred to as *colony-forming units* (CFUs).[3] These progenitor cells have only limited capacity for self-renewal but retain the potential to differentiate into lineage-specific precursor cells. These precursor cells have morphologic characteristics that permit them to be recognized as the first cell of a particular cell line. They have lost their ability for self-renewal but undergo cell division and differentiation, eventually giving rise to mature lymphocytes, monocytes, granulocytes, megakaryocytes, or erythrocytes.

Hematopoietic Growth Factors

Under normal conditions, the numbers and total mass for each type of circulating blood cell remain relatively constant. This regulation of blood cells is thought to be at least partially controlled by hormonelike growth factors called *cytokines*. The cytokines are a family of short-lived mediators that stimulate the proliferation,

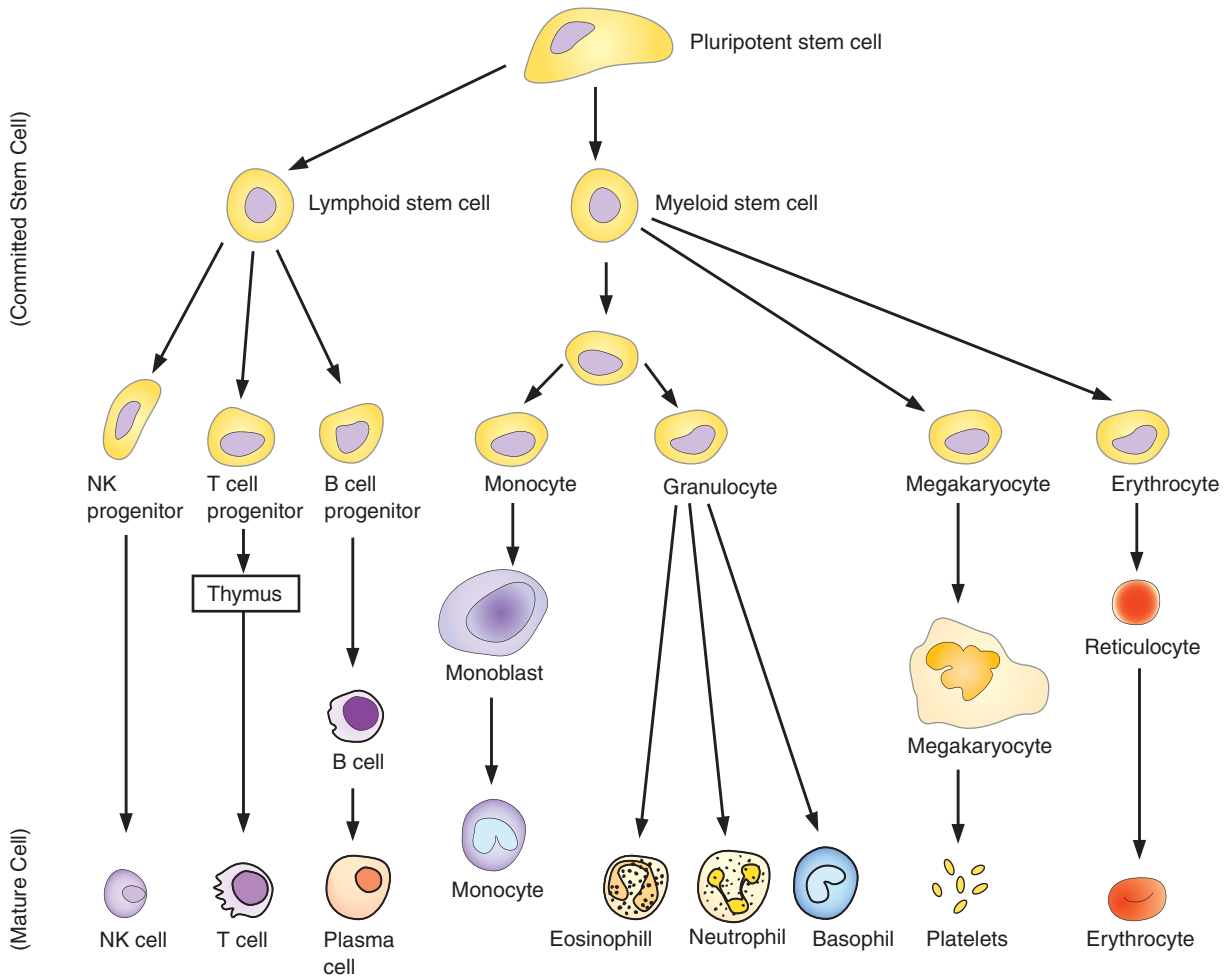


FIGURE 11-1. Major developmental stages of blood cells. NK, natural killer cell.

Hematopoiesis

- The white blood cells are formed from hematopoietic stem cells that differentiate into committed progenitor cells that in turn develop into the myelocytic and lymphocytic lineages needed for the formation of the different types of white blood cell.
- The growth and reproduction of the different stem cells is controlled by colony-stimulating factors, other growth factors, and chemical mediators.
- The life span of white blood cells is relatively short so that constant renewal is necessary to maintain normal blood levels. Any conditions that decrease the availability of stem cells or hematopoietic growth factors produce a decrease in white blood cells.

differentiation, and functional activation of the various blood cells.

Many cytokines derived from lymphocytes or bone marrow stromal cells stimulate the growth and production of new blood cells. Several members of this family are called *colony-stimulating factors* (CSFs) because of their ability to promote the growth of hematopoietic cell colonies in the laboratory. The CSFs that act on committed progenitor cells include erythropoietin (EPO); thrombopoietin (TPO); *granulocyte-monocyte colony-stimulating factor* (GM-CSF), which stimulates progenitors for granulocytes, monocytes, erythrocytes, and megakaryocytes; *granulocyte colony-stimulating factor* (G-CSF), which promotes the proliferation of neutrophils; and *macrophage colony-stimulating factor* (M-CSF), which induces macrophage colonies.[3–5] Other cytokines, such as the interleukins, interferons, and tumor necrosis factor, support the proliferation of stem cells and the development of lymphocytes and act synergistically to aid the multiple functions of the CSFs.

The genes for most hematopoietic growth factors have been cloned and their recombinant proteins have been generated for use in a wide range of clinical conditions. The clinically useful factors include EPO, G-CSF, and GM-CSF.[5] They are used to treat bone marrow failure caused by chemotherapy or aplastic anemia, the anemia of kidney failure and cancer, hematopoietic neoplasms, infectious diseases such as acquired immunodeficiency syndrome (AIDS), and congenital and myeloproliferative disorders. Growth factors are used to increase peripheral stem cells for transplantation and to accelerate cell proliferation after bone marrow engraftment.

Leukocytes (White Blood Cells)

The leukocytes or white blood cells, which are the focus of this chapter, originate in the bone marrow and circulate throughout the lymphoid tissues of the body. Leukocytes are commonly classified into two groups based on the presence or absence of specific prominent granules in their cytoplasm.[1,2] Those containing specific granules (neutrophils, eosinophils, basophils) are classified as *granulocytes,* and those that lack granules (lymphocytes and monocytes) as *agranulocytes* (Fig. 11-2). The granulocytes and the agranular monocytes/macrophages are derived from the myeloid stem cell in the bone marrow and circulate in the blood (Fig. 11-1). The lymphocytes originate from lymphoid stem cells in the bone marrow and migrate between the blood and the lymphatic system.

Granulocytes

Granulocytes are spherical and have distinctive multilobar nuclei. They are all phagocytic cells that are identifiable because of their cytoplasmic granules. They have two types of granules: *specific granules* that bind neutral, basic, or acidic dye components, and *azurophilic granules*. The azurophilic granules stain purple and are lysosomes. The granulocytes are divided into three types—neutrophils, eosinophils, and basophils—according to the staining properties of their specific granules.

Neutrophils. The neutrophils, which constitute 60% to 65% of the total white blood cells, have specific granules that are neutral and do not stain with an acidic or a basic dye.[1] Because these white cells have nuclei that are divided into three to five lobes, they are often called *polymorphonuclear leukocytes* (PMNs).

The neutrophils are primarily responsible for maintaining normal host defenses against invading bacteria and fungi, cell debris, and a variety of foreign substances. After release from the marrow, the neutrophils spend only approximately 4 to 8 hours in the circulation before moving into the tissues. They survive in the tissues for approximately 4 to 5 days.[1] They die in the tissues by discharging their phagocytic function or from senescence. The pool of circulating neutrophils (i.e., those that appear in the blood count) is in a closely maintained equilibrium with a similar-sized pool of cells marginating along the walls of small blood vessels. These are the neutrophils that respond to chemotactic factors and migrate into the tissues toward the offending agent during an inflammatory reaction.

Eosinophils. The specific cytoplasmic granules of the eosinophils stain red with the acidic dye eosin. These leukocytes constitute 1% to 3% of the total white blood cells and increase in number during allergic reactions and parasitic infections.[1] During allergic reactions, they are thought to release enzymes or chemical mediators that detoxify agents associated with the reaction. In parasitic infections, the eosinophils use surface markers to attach themselves to the parasite and then release hydrolytic enzymes that kill it.

Basophils. The basophils are the least numerous of the white blood cells, accounting for only 0.3% to 0.5% of the total leukocytes.[1] The specific granules of the basophils

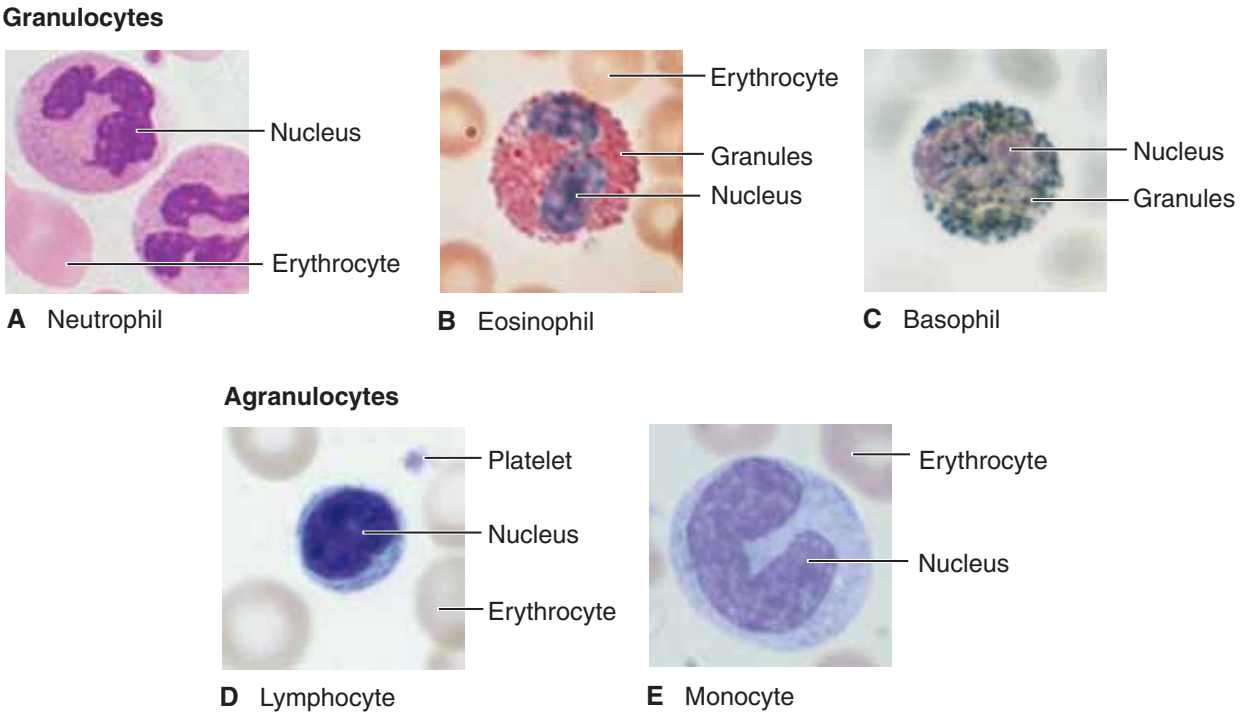


FIGURE 11-2. White blood cells. Granulocytes (A–C) and agranulocytes (D, E). **(A)** The neutrophil has a large, segmented nucleus. **(B)** The eosinophil has many bright red–staining granules. **(C)** The basophil has large dark blue–staining granules. **(D)** The lymphocyte has a large undivided nucleus. **(E)** The monocyte is the largest of the leukocytes. (From Cohen, B.J. [2009]. *Memmler's The Human Body in Health and Disease* (11th ed., p. 284). Baltimore: Wolters Kluwer Health/Lippincott Williams & Wilkins)

stain blue with a basic dye. These granules contain heparin, an anticoagulant; histamine, a vasodilator; and other mediators of inflammation. The basophil, which is a blood cell, is related to, but not identical with, the connective tissue mast cell that contains similar granules. Both the basophils and mast cells are thought to be involved in allergic and hypersensitivity reactions.

Agranulocytes

Agranulocytes are leukocytes that lack cytoplasmic granules. They include both the lymphocytes and monocytes/macrophages.

Lymphocytes. Lymphocytes are the most common of the agranulocytes, accounting for approximately 30% of the total blood leukocytes.[1] They originate in the bone marrow from lymphoid stem cells and migrate through the peripheral lymphoid organs where they recognize antigen and participate in immune responses.

There are three types of lymphocytes: B lymphocytes, T lymphocytes, and natural killer cells.[1,2] The *B lymphocytes* are so named because they were first recognized as a separate population in the bursa of Fabricius in birds and bursa-equivalent organs (e.g., bone marrow) in mammals. They differentiate to form antibody-producing plasma cells and are involved in humoral-mediated immunity. The *T lymphocytes* differentiate in the thymus. They activate other cells of the immune system (helper T cells) and are involved in cell-mediated immunity (cytotoxic T cells). *Natural killer cells* participate in innate or natural immunity and their function is to destroy foreign cells. The lymphocytes of the three different subsets have unique surface markers that can be identified and used to define their function and diagnose disease (discussed in Chapter 15).

Although all lymphocytes are morphologically similar, they comprise elements that vary in terms of lineage, cell membrane molecules and receptors, function, and response to antigen. These cells are often distinguished by surface proteins that can be identified using panels of monoclonal antibodies. These identified proteins are then correlated with cell functions. The standard nomenclature for these proteins is the "CD" (clusters of differentiation) numeric designation (CD4, CD8), which is used to delineate surface proteins that define a particular cell type or stage of cell differentiation and are recognized by a cluster or group of antibodies.[2] Although this nomenclature was originally developed for lymphocytes, it is now common practice to apply it to blood cells other than lymphocytes.

Monocytes/Macrophages. Monocytes are the largest of the white blood cells and constitute approximately 3% to 8% of the total leukocyte count. They are distinguished by a large amount of cytoplasm and a darkly stained kidney-shaped nucleus. Although these cells are considered agranular, they contain small, dense, azurophilic granules that contain lysosomal enzymes similar to those found in the azurophilic granules of neutrophils. Monocytes travel from the bone marrow to the body tissues, where they differentiate into various tissue

phagocytes including the *histiocytes* of loose connective tissue, *microglial cells* of the brain, *Kupffer cells* of the liver, and tissue macrophages. During inflammation, monocytes leave the blood vessel at the site of inflammation and transform into tissue macrophages that phagocytose bacteria and tissue debris. Macrophages also play an important role in immune responses by activating lymphocytes and by presenting antigen to T cells (see Chapter 15).

Leukocyte Developmental Stages

Leukocyte development begins with the myeloid and lymphoid stem cells in the bone marrow[2–4] (Fig. 11-3). The immature precursor cells for each of the cell lines are called *blast cells*. The names of the various leukocyte developmental stages are often used in describing blood cell changes that occur in hematopoietic disorders (e.g., acute lymphoblastic leukemia, chronic myelogenous leukemia).

The granulocytic precursor cells, which are called *myeloblasts,* have round to oval nuclei, with delicate chromatin and a blue to gray cytoplasm. During their next stage of development, the myeloblasts are transformed into *promyelocytes* with similar nuclei, but with a cytoplasm containing many primary granules. In the subsequent *metamyelocyte* stage, the nuclei distort and become arclike, producing the band developmental stage. Maturation from metamyelocyte to mature neutrophil involves progressive condensation of nuclear chromatin, increasing nuclear lobulation, and the appearance of secondary (specific) granules. Eosinophils and basophils undergo similar developmental stages but develop different secondary granules. Like granulocytes, monocytes develop from the granulocyte-monocyte progenitor cell and progress through a monoblast and promonocyte stage.

Lymphocytes derive from lymphoid stem cells and progress through the lymphoblast and prolymphocyte stages. The prolymphocytes leave the bone marrow and travel to the lymphoid tissues, where further differentiation into T and B lymphocytes occurs.

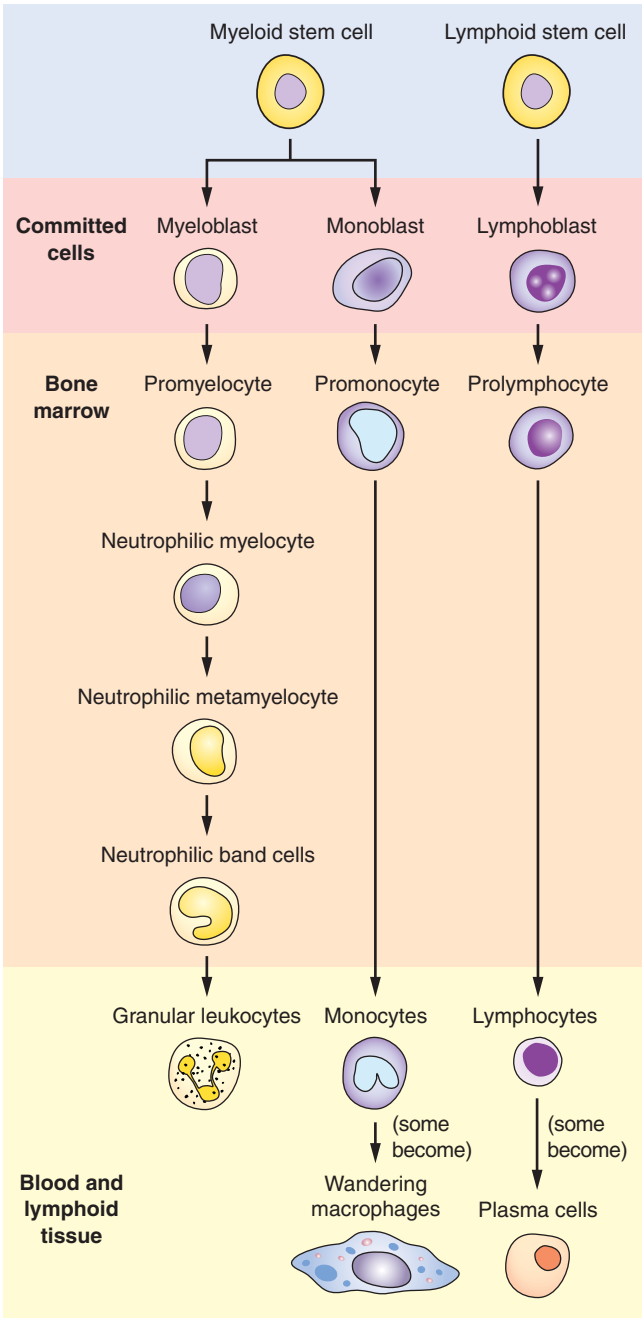


FIGURE 11-3. Leukocytes originate from multipotential stem cells in the bone marrow. Granular leukocytes (neutrophils, eosinophils, basophils) have their origin in the myeloid stem cells and develop through a sequence involving myeloblasts. Monocytes, like granulocytes, are progeny of the myeloid stem cell line, but develop along a pathway involving monoblasts. Only lymphocytes originate from the lymphoid stem cell line. They develop through a sequence involving lymphoblasts and are released from the bone marrow as prolymphocytes, which undergo further differentiation in the lymphoid organs.

Lymphoid Tissues

The body's lymphatic system consists of the lymphatic vessels, lymphoid tissue and lymph nodes, thymus, and spleen (see Chapter 15). Although both precursor B and T lymphocytes begin their development in the bone marrow, they migrate to peripheral lymphoid structures to complete the differentiation process. B lymphocytes mature in the bone marrow, differentiate into plasma cells, and then move to the lymph nodes, where they continue to proliferate and produce antibodies. T lymphocytes leave the bone marrow as precursor T lymphocytes travel to the thymus, where they differentiate into $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells, after which many of them move to lymph nodes, where they undergo further proliferation.

Lymph nodes consist of organized collections of lymphoid tissue located along the lymphatic vessels.[2–4] Typically grayish white and ovoid or bean shaped, they range in size from 1 mm to about 1 to 2 cm in diameter. A fibrous capsule and radiating trabeculae provide a supporting structure, and a delicate reticular network contributes to internal support (Fig. 11-4). The parenchyma of the lymph node is divided into an outer cortex and an inner medulla. The cortex contains well-defined B-cell and T-cell domains. The superficial outer cortex contains

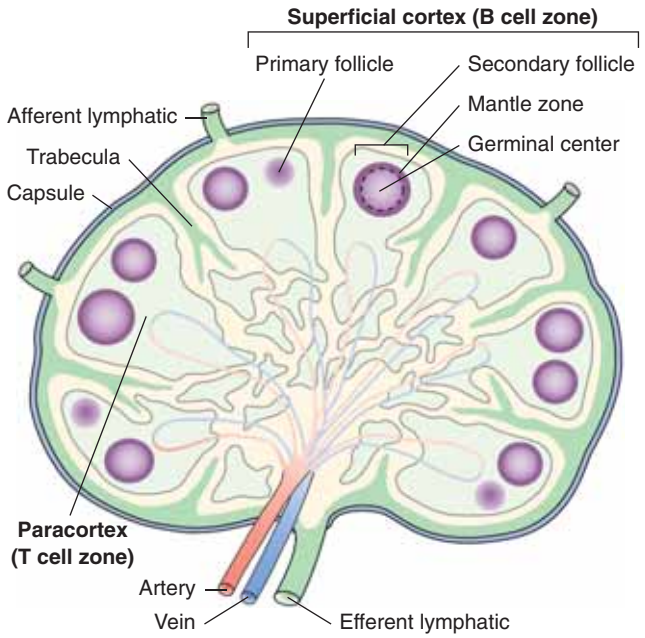


FIGURE 11-4. Structures of normal lymph node.

aggregates of cells called *follicles*. Follicles are the B-cell zones of the lymph nodes. There are two types of follicles: immunologically inactive follicles, called *primary follicles,* and active follicles that contain germinal centers, called *secondary follicles*. Germinal centers contain large lymphocytes (centroblasts) and small lymphocytes with cleaved nuclei (centrocytes). The mantle zone is the small layer of B cells surrounding the germinal centers. The cortex around the follicles is called the *paracortex*. This region contains most of the T cells in the lymph nodes. Like normal lymphocytes, malignant B and T cells tend to home to particular nodal sites, leading to characteristic patterns of involvement. For example, follicular lymphomas (to be discussed) develop in the B-cell areas of the lymph node, whereas T-cell lymphomas typically grow in the paracortical T-cell zones.

The alimentary canal, respiratory passages, and genitourinary systems are guarded by accumulations of lymphoid tissue that are not enclosed in a capsule. This form of lymphoid tissue is called *diffuse lymphoid tissue* or *mucosa-associated lymphoid tissue* (MALT) because of its association with mucous membranes. Lymphocytes are found in the subepithelium of these tissues. Lymphomas can arise from MALT as well as lymph node tissue.

In summary, the hematopoietic system consists of the different types of blood cells generated from the pluripotent stem cells in the bone marrow. These cells differentiate into committed cell lines that develop into red blood cells, platelets, and leukocytes. The development of the different types of blood cells is supported by chemical messengers called *colony-stimulating factors.*

Leukocytes or white blood cell development begins with the myeloid stem cells that develop into granulocyte and monocyte cell lines, and the lymphoid stem cells that develop into the lymphocyte cell line. The immature precursor cells for each of the cell lines are called *blast cells.* The blast cells progress through subsequent maturational stages before becoming mature granulocytes, monocytes, or lymphocytes. The names of these developmental stages are often used in describing blood cell changes that occur in hematopoietic disorders.

The lymphatic system consists of a network of lymphatic vessels, nodes, and tissues where B and T lymphocytes complete their differentiation. Lymph nodes, which are the site where many lymphomas originate, exhibit an outer cortex and an inner medulla. The cortex contains well-defined B-cell and T-cell domains. The B-cell–dependent superficial cortex consists of two types of follicles: immunologically inactive follicles, called *primary follicles,* and active follicles that contain germinal centers, called *secondary follicles.* Most of the T cells are contained in the paracortex, the area between the medullary and outer superficial cortices.

Nonneoplastic Disorders of White Blood Cells

The number of leukocytes, or white blood cells, in the peripheral circulation normally ranges from 4500 to 10,500 cells/μL (4.5 to 10.5 × 10^9/L).[6] The nonneoplastic disorders of white blood cells include a deficiency of leukocytes (i.e., leukopenia) and proliferative disorders (i.e., leukocytosis) in which there are increased numbers of leukocytes.

Neutropenia (Agranulocytosis)

The term *leukopenia* describes a decrease in the absolute number of leukocytes in the blood. The disorder may affect any of the specific types of white blood cells, but most often affects the neutrophils, which are the predominant type of granulocyte. *Neutropenia* refers specifically to an abnormally low number of neutrophils and is commonly defined as a circulating neutrophil count of less than 1500/μL.[4,7–9] It can be further graded as mild (1000/μL), moderate (500 to 1000/μL), or severe (<500/μL) based on an absolute number of neutrophils circulating in the blood. *Agranulocytosis* denotes a virtual absence of neutrophils. In *aplastic anemia,* all of the myeloid stem cells are affected, resulting in anemia, thrombocytopenia, and agranulocytosis.

Pathogenesis

The reduction in the number of granulocytes in the blood (neutropenia) can be seen in a wide variety of conditions, including the effects of drugs, neoplasms, and autoimmune disorders (Chart 11-1). Neutropenia is also

CHART 11-1 Principal Causes of Neutropenia

Congenital

Alloimmune neonatal neutropenia (transfer of maternal antibodies)
Cyclic neutropenia
Kostmann syndrome (severe congenital neutropenia)

Acquired

Autoimmune
- Primary (rare, usually occurs in children and runs a benign course)

Secondary
- Systemic lupus erythematosus
- Felty syndrome in persons with rheumatoid arthritis

Infection related
- Many types of infections agents, but most commonly viruses
- Mechanisms include increased consumption of neutrophils, production of autoantibodies, direct infiltration of hematopoietic cells, bone marrow suppression

Drug related
- Immune-mediated reactions in which drugs act as haptens (e.g., penicillin, propylthiouracil, aminopyrine)
- Accelerated apoptosis (clozapine [antipsychotic agent])
- Cancer chemotherapeutic drugs (bone marrow depression)

Radiation therapy to bone marrow
Hematologic malignancies

a feature of a group of rare inherited disorders such as Kostmann syndrome.[8]

Congenital Neutropenia. A decreased production of granulocytes is a feature of a group of hereditary hematologic disorders, including cyclic neutropenia and Kostmann syndrome. *Periodic* or *cyclic neutropenia* is an autosomal dominant disorder with variable expression that begins in infancy and persists for decades. It is characterized by periodic neutropenia that develops approximately every 21 days and lasts approximately 2 to 3 days.[8] Although the cause is undetermined, it is thought to result from impaired feedback regulation of granulocyte production and release. Severe congenital neutropenia, also known as *Kostmann syndrome,* is a rare inherited form of neutropenia.[7–9] The condition occurs sporadically or as an autosomal recessive disorder, causing severe neutropenia while preserving the erythroid and megakaryocyte cell lineages that result in red blood cell and platelet production. The syndrome is usually recognized at birth or shortly thereafter. Infants with the syndrome have almost no neutrophils present that develop beyond the promyelocyte stage (see Fig. 11-3). Treatment includes the administration of G-CSF. Before the advent of effective therapy, almost all patients died in early childhood.

Acquired Neutropenia. A number of conditions, including aplastic anemia and treatment with cancer chemotherapeutic drugs and irradiation, may cause suppression of bone marrow stem cells, with decreased production of all blood cell types. Overgrowth of neoplastic cells in cases of nonmyelogenous leukemia and lymphoma also may suppress the function of neutrophil precursors. In splenomegaly, neutrophils may be trapped in the spleen along with other blood cells. Autoimmune disorders or idiosyncratic drug reactions may cause increased and premature destruction of neutrophils. In Felty syndrome, a variant of rheumatoid arthritis, there is increased destruction of neutrophils in the spleen. Infections by viruses or bacteria may drain neutrophils from the blood faster than they can be replaced, thereby depleting the neutrophil storage pool in the bone marrow.[8]

Many cases of neutropenia are drug related. Chemotherapeutic drugs used in the treatment of cancer (e.g., alkylating agents, antimetabolites) cause predictable dose-dependent suppression of bone marrow function. The term *idiosyncratic* is used to describe drug reactions that are different from the effects observed in most persons and that cannot be explained in terms of allergy. A number of drugs, such as chloramphenicol (an antibiotic), phenothiazines (antipsychotic agents), propylthiouracil (used in the treatment of hyperthyroidism), and phenylbutazone (used in the treatment of arthritis), may cause idiosyncratic depression of bone marrow function.[7–9] Many idiosyncratic cases of drug-induced neutropenia are thought to be caused by immunologic mechanisms, with the drug or its metabolites acting as antigens (i.e., haptens) to incite the production of antibodies reactive against the neutrophils.

Clinical Course

The clinical features of neutropenia usually depend on the severity of neutropenia and the cause of the disorder. Neutropenia from any cause places persons at risk for infection by gram-positive and gram-negative bacteria and by fungi. The risk of infection is related to the severity of the neutropenia. Persons with chronic benign neutropenia are often free of infection despite low neutrophil counts.

Neutrophils provide the first line of defense against organisms that inhabit the skin and gastrointestinal tract. Thus, skin infections and ulcerative necrotizing lesions of the mouth are common types of infection in neutropenia. The most frequent site of serious infection is the respiratory tract, a result of bacteria or fungi that frequently colonize the airways. Untreated infections can be rapidly fatal, particularly if the neutrophil count is less than 250/μL. In the presence of severe neutropenia, the usual signs of inflammatory response to infection may be absent. Nevertheless, fever in the person with neutropenia should always be assumed to be of infectious origin.

Antibiotics are used to treat infections in those situations in which neutrophil destruction can be controlled or the neutropoietic function of the bone marrow can be recovered. Hematopoietic growth

factors such as recombinant human G-CSF may be used to stimulate the maturation and differentiation of the granulocytic cell line.[8,9]

Infectious Mononucleosis

Infectious mononucleosis is a self-limiting lymphoproliferative disorder caused by the Epstein-Barr virus (EBV), a member of the herpesvirus family.[10–14] The term *EBV-associated infectious mononucleosis* is often used to designate infectious mononucleosis caused by EBV as opposed to non–EBV-associated clinical syndromes of infectious mononucleosis caused by other agents. Infectious mononucleosis may occur at any age, but occurs principally in adolescents and young adults in developed countries. EBV is one of the most successful viruses in evading the immune system, infecting about 90% of humans and persisting for the lifetime of the person. EBV spreads from person to person primarily through contact with infected oral secretions. Transmission requires close contact with infected persons. Thus, the virus spreads readily among young children in crowded conditions, where there is considerable sharing of oral secretions. Kissing is also an effective mode of transmission, hence the term "kissing disease."[12]

Pathogenesis

Infectious mononucleosis is largely transmitted through oral contact with EBV-contaminated saliva. The virus initially penetrates the nasopharyngeal, oropharyngeal, and salivary epithelial cells. It then spreads to the underlying oropharyngeal lymphoid tissue and, more specifically, to B lymphocytes, all of which have receptors for EBV. Infection of the B cells may take one of two forms—it may kill the infected B cell, or the virus may incorporate itself into the cell's genome. The B cells that harbor the EBV genome proliferate in the circulation and produce the well-known *heterophil* antibodies that are used for the diagnosis of infectious mononeucleosis.[10–12] A heterophil antibody is an immunoglobulin that reacts with antigens from another species—in this case, sheep red blood cells.

The normal immune response is important in controlling the proliferation of the EBV-infected B cells and cell-free virus. Most important in controlling the proliferation of EBV-infected B cells are the $CD8^+$ cytotoxic T cells and NK cells. These virus-specific T cells appear as large, atypical lymphocytes that are characteristic of the infection (Fig. 11-5). In otherwise healthy persons, the humoral and cellular immune responses serve to control viral shedding by limiting the number of infected B cells rather than eliminating them.

Although infected B cells and free virions disappear from the blood after recovery from the disease, the virus remains in a few transformed B cells in the oropharyngeal region and is shed in the saliva. Once infected with the virus, persons remain asymptomatically infected for life, and a few such persons intermittently shed EBV. Immunosuppressed persons shed the virus more frequently. Asymptomatic shedding of EBV by healthy persons is thought to account for most of the spread of infectious mononucleosis, despite the fact that it is not a highly contagious disease.

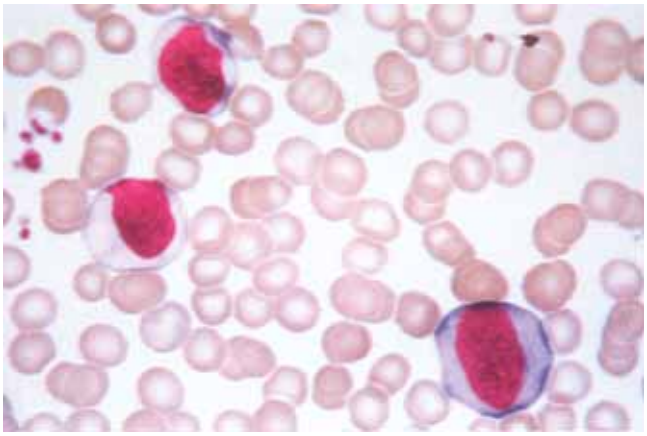


FIGURE 11-5. Infectious mononucleosis. Atypical lymphocytes are characteristic. (From Schwarting R., McKenzie S., Rubin R. [2008]. Hematopathology. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 908]. Philadelphia: Lippincott Williams & Wilkins.)

Clinical Course

The onset of infectious mononucleosis usually is insidious. The incubation period lasts 4 to 8 weeks.[13,14] A prodromal period, which lasts for several days, follows and is characterized by malaise, anorexia, and chills. The prodromal period precedes the onset of fever, pharyngitis, and lymphadenopathy. Occasionally, the disorder comes on abruptly with a high fever. Most persons seek medical attention for severe pharyngitis, which usually is most severe on days 5 to 7 and persists for 7 to 14 days. The lymph nodes are typically enlarged throughout the body, particularly in the cervical, axillary, and groin areas. Hepatitis and splenomegaly are common manifestations of the disease and are thought to be immune mediated. Hepatitis is characterized by hepatomegaly, nausea, anorexia, and jaundice. Although discomforting, it usually is a benign condition that resolves without causing permanent liver damage. The spleen may be enlarged two to three times its normal size, and rupture of the spleen is an infrequent complication. In less than 1% of cases, mostly in the adult age group, complications of the central nervous system (CNS) develop. These complications include cranial nerve palsies, encephalitis, meningitis, transverse myelitis, and Guillain-Barré syndrome.

The peripheral blood usually shows an increase in the number of leukocytes, with a white blood cell count between 12,000 and 18,000 cells/μL, 60% of which are lymphocytes.[12] The rise in white blood cells begins during the first week, continues during the second week of the infection, and then returns to normal around the fourth week. Although leukocytosis is common, leukopenia may be seen in some persons during the first 3 days of illness. Atypical lymphocytes are common, constituting more than 20% of the total lymphocyte count. Heterophil antibodies usually appear during the second or third week and decline after the acute illness has subsided. They may, however, be detectable for up to 9 months after onset of the disease.

Most persons with infectious mononucleosis recover without incident. The acute phase of the illness usually lasts for 2 to 3 weeks, after which recovery occurs rapidly. Some degree of debility and lethargy may persist for 2 to 3 months. Treatment is primarily symptomatic and supportive. It includes bed rest and analgesics such as aspirin to relieve the fever, headache, and sore throat.[13]

In persons with immunodeficiency disorders that lead to defects in cellular immunity (e.g., human immunodeficiency virus [HIV] infection, immunosuppressant-treated recipients of organ or bone marrow transplants), EBV infection may contribute to the development of lymphoproliferative disorders (e.g., non-Hodgkin lymphoma).[10,11] These persons have impaired T-cell immunity and are unable to control the proliferation of EBV-infected B cells.

In summary, neutropenia, which represents a marked reduction in the absolute number of neutrophils, is one of the major disorders of the white blood cells. It can occur as a congenital or acquired disorder. Congenital neutropenia consists primarily of cyclic neutropenia, which is characterized by cyclic (18- to 24-day) oscillations of peripheral neutrophils, and severe congenital neutropenia or Kostmann syndrome, which is associated with severe bacterial infections. The acquired neutropenias encompass a wide spectrum of causative processes, including immunologically mediated bone marrow suppression or neutrophil injury and destruction; infection-mediated mechanisms, including increased peripheral utilization; and drug-mediated mechanisms, particularly those related to the use of cancer chemotherapeutic agents. Because the neutrophil is essential to host defenses against bacterial and fungal infections, severe and often life-threatening infections are common in persons with neutropenia.

Infectious mononucleosis is a self-limited lymphoproliferative disorder caused by the B-lymphotropic Epstein-Barr virus, a member of the herpesvirus family. The highest incidence of infectious mononucleosis is found in adolescents and young adults, and it is seen more frequently in the upper socioeconomic classes of developed countries. The virus is usually transmitted in the saliva. The disease is characterized by fever, generalized lymphadenopathy, sore throat, and the appearance in the blood of atypical lymphocytes and several antibodies, including the well-known heterophil antibodies that are used in the diagnosis of infectious mononucleosis. Most persons with infectious mononucleosis recover without incident. Treatment is largely symptomatic and supportive.

Neoplastic Disorders of Hematopoietic and Lymphoid Origin

The neoplastic disorders of hematopoietic and lymphoid origin represent the most important of the white blood cell disorders. They include the somewhat overlapping categories of the lymphoid neoplasms that arise from sites of lymphocyte differentiation and proliferation. They can be divided into two broad categories based on the origin of the tumor cells: lymphoid neoplasms and myeloid neoplasms. The clinical features of these neoplasms are largely determined by their site of origin, the progenitor cell from which they originated, and the molecular events involved in their transformation into a malignant neoplasm.

Myeloid neoplasms arise from the hematopoietic stem cells and normally give rise to monoclonal proliferations that replace normal bone marrow cells. They include the acute and chronic myelogenous leukemias.[4,7] The lymphoid neoplasms encompass a group of entities that vary widely in their clinical presentation and behaviors. They include the B- and T-cell leukemias and lymphomas (non-Hodgkin and Hodgkin lymphomas) that originate in the peripheral lymphoid structures such as the lymph nodes, where B and T lymphocytes undergo differentiation and proliferation. The plasma cell dyscrasias originate in the lymph nodes, where B cells differentiate into plasma cells.

Leukemias

The leukemias are malignant neoplasms of cells originally derived from precursor myeloid or lymphoid tissue cells. The term *leukemia* (i.e., "white blood") was first used by Virchow to describe a reversal of the usual ratio of red blood cells to white blood cells. Because blood cells circulate throughout the body, these neoplasms are often disseminated from the onset. The leukemic cells may also infiltrate the liver, spleen, lymph nodes, and other tissues throughout the body, causing enlargement of these organs.

Leukemia is the most common cause of cancer in children and adolescents. It accounts for about one of three cancers in children.[15] Although it commonly is thought

Leukemias

- Leukemias are malignant neoplasms arising from the transformation of a single blood cell line derived from hematopoietic stem cells.
- The leukemias are classified as acute and chronic lymphocytic (lymphocytes) or myelogenous (granulocytes, monocytes) leukemias according to their cell lineage.
- Because leukemic cells are immature and poorly differentiated, they proliferate rapidly and have a long life span, they do not function normally, they interfere with the maturation of normal blood cells, and they circulate in the bloodstream, cross the blood-brain barrier, and infiltrate many body organs.

of as a childhood disease, leukemia is diagnosed 10 times more frequently in adults than children.[15]

Classification

The leukemias commonly are classified according to their predominant cell type (i.e., lymphocytic or myelocytic) and whether the condition is acute or chronic. Biphenotypic leukemias demonstrate characteristics of both lymphoid and myeloid lineages. A rudimentary classification system divides leukemia into four types: acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelocytic leukemia, and chronic myelocytic leukemia.[16] The *lymphocytic leukemias* involve immature lymphocytes and their progenitors that originate in the bone marrow but infiltrate the spleen, lymph nodes, CNS, and other tissues. The *myelogenous leukemias,* which involve the pluripotent myeloid stem cells in bone marrow, interfere with the maturation of all blood cells, including the granulocytes, erythrocytes, and thrombocytes.

Etiology and Molecular Biology

The causes of leukemia are largely unknown and likely differ among the different types of leukemia. The incidence of acute leukemia among persons who have been exposed to high levels of radiation is unusually high. An increased number of acute lymphocytic leukemia cases have been recorded after the atomic bomb explosions at Hiroshima and Nagasaki and the Chernobyl accident.[17–19] An increased incidence of leukemia also is associated with exposure to benzene and the use of antitumor drugs (e.g., mechlorethamine, procarbazine, cyclophosphamide).[17–19] Leukemia may occur as a second cancer after aggressive chemotherapy for other cancers, such as Hodgkin lymphoma. The existence of a genetic predisposition to development of acute leukemia is suggested by the increased leukemia incidence among a number of congenital disorders, including Down syndrome, neurofibromatosis, and Fanconi anemia.[17,18] In individuals with Down syndrome, the incidence of acute leukemia is 10 to 20 times that of the general population. There also are numerous reports of multiple cases of acute leukemia occurring within the same family.

The molecular biology of leukemia suggests that the event or events causing the disorders exert their effects through disruption or dysregulation of genes that normally regulate blood cell development, blood cell homeostasis, or both. Most commonly, these are structural changes classified as translocations, in which a part of one (e.g., 8) chromosome becomes located on another chromosome (e.g., 21) and vice versa; inversions, in which part of a chromosome (e.g., 16) is upside down and now in reverse order, but still attached to the original chromosome; and deletions, in which part of a chromosome (e.g., 7) has been lost (see Chapter 6). It is the disruption or dysregulation of specific genes and gene products occurring at the site of these chromosome aberrations that contributes to the development of leukemia.[20] In many instances, these genes and their products have been shown to be directly or indirectly involved in the normal development or maintenance of the hematopoietic system. Thus, it would appear that leukemia results, at least in part, from disruption in the activity of genes that normally regulate blood cell development. Advances in the understanding of the molecular biology of leukemia are beginning to provide a more complete understanding of the molecular complexity of leukemia for the purposes of diagnosis, classification, treatment, and monitoring of clinical outcomes.

One of the more studied translocations is the Philadelphia chromosome, which was the first chromosomal abnormality identified in cancer. The Philadelphia chromosome translocation represents a reciprocal translocation between the long arm of chromosome 22 and the long arm of chromosome 9.[4,7] During the translocation, a large portion of 22q is translocated to 9q, and a smaller piece of 9q is moved to 22q (Fig. 11-6). The portion of 9q that is translocated contains *ABL,* a proto-oncogene that is the cellular homolog of the Abelson murine leukemic virus. The *ABL* gene is received at a specific site on 22q called the *breakpoint cluster* (BCR). The resulting *BCR-ABL* fusion gene codes for a novel protein that allows affected cells to bypass the regulated signals that control normal cell growth and differentiation, and instead undergo malignant transformation to become leukemic cells. The Philadelphia chromosome translocation is found in more than 90% of persons with chronic myelogenous leukemia and in some persons with acute leukemia.[7] The recent development of tyrosine kinase

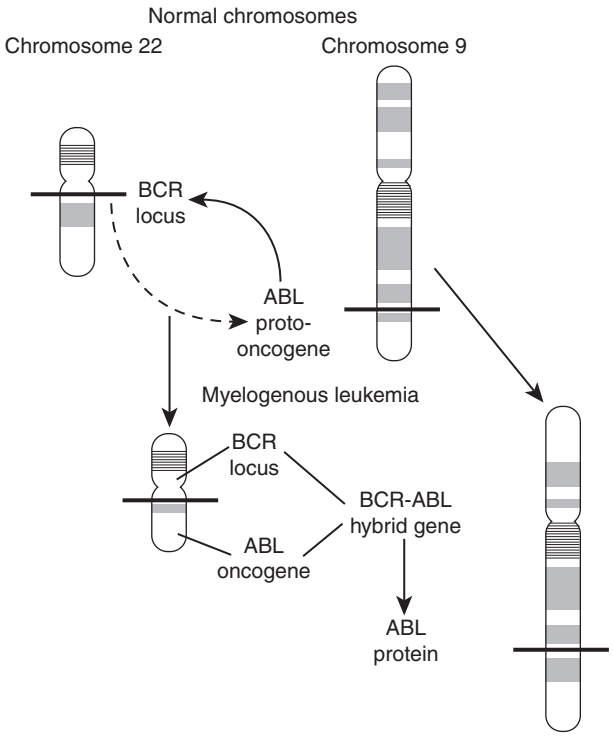


FIGURE 11-6. The Philadelphia (Ph) chromosome is formed by breaks at the ends of the long arms of chromosomes 9 and 22, allowing the *ABL* proto-oncogene on chromosome 9 to be translocated to the breakpoint cluster region (*BCR*) on chromosome 22. The result is a new fusion gene coding for the BCR-ABL protein, which is presumably involved in the pathogenesis of chronic myelogenous leukemia.

inhibitors (e.g., imatinib mesylate) has contributed to the targeted approach for treatment of leukemias that display the Philadelphia chromosome translocation.[21]

Acute Leukemias

The acute leukemias are cancers of the hematopoietic progenitor cells.[17,22,23] They usually have a sudden and stormy onset with signs and symptoms related to depressed bone marrow function. There are two types of acute leukemia: acute lymphocytic (lymphoblastic) leukemia (ALL) and acute myeloid (myelogenous) leukemia (AML). ALL is the most common cancer in children and adults. It accounts for three of four cases of childhood cancer, with AML accounting for most of the remaining cases.[22] AML is mainly a disease of older adults, but is also seen in children and young adults.

ALL encompasses a group of neoplasms composed of precursor B (pre-B) or T (pre-T) lymphocytes referred to as *lymphoblasts* (see Fig. 11-3). Most cases (about 85%) of ALL are of pre–B-cell origin.[7] Approximately 90% of persons with ALL have numeric and structural changes in the chromosomes of their leukemic cells. They include hyperploidy (i.e., more than 50 chromosomes), polyploidy (i.e., three or more sets of chromosomes), and chromosomal translocations and deletions. Many of these chromosomal aberrations serve to dysregulate the expression and function of transcription factors required for normal hematopoietic cell development.

The AMLs are a diverse group of neoplasms affecting myeloid precursor cells in the bone marrow.[4,7,24,25] Most are associated with acquired genetic alterations that inhibit terminal myeloid differentiation. As a result, normal marrow elements are replaced by an accumulation of relatively undifferentiated blast cells with a resultant suppression of the remaining progenitor cells that leads to anemia, neutropenia, and thrombocytopenia. Specific chromosomal abnormalities, including translocations, are seen in a large number of AMLs. One subtype of AML, acute promyelocytic leukemia, which represents 10% of adult cases of AML, is associated with a (15;17) chromosomal translocation.[26] This translocation results in the fusion of the retinoic acid receptor α (RARA) gene on chromosome 17 with the PML gene on chromosome 15. This change in the retinoic acid receptor produces a block in myeloid differentiation at the promyelocytic stage (see Fig. 11-3), probably by inhibiting the action of normal RARA receptors. This block can be overcome by pharmacologic preparations of retinoic acid (a vitamin A analog), causing the neoplastic promyelocytes to differentiate into neutrophils and die.

Manifestations. Although ALL and AML are distinct disorders, they typically present with similar clinical features. Both are characterized by an abrupt onset of symptoms, including fatigue resulting from anemia; low-grade fever, night sweats, and weight loss due to the rapid proliferation and hypermetabolism of the leukemic cells; bleeding due to a decreased platelet count; and bone pain and tenderness due to bone marrow expansion.[17] Infection results from neutropenia, with the risk of infection rising steeply as the neutrophil count falls below 500 cells/μL. Generalized lymphadenopathy, splenomegaly, and hepatomegaly caused by infiltration of leukemic cells occur in all acute leukemias but are more common in ALL.

In addition to the common manifestations of acute leukemia (i.e., fatigue, weight loss, fever, easy bruising), infiltration of malignant cells in the skin, gums, and other soft tissues is particularly common in the monocytic form of AML. The leukemic cells may also cross the blood-brain barrier and establish sanctuary in the CNS. CNS involvement is more common in ALL than AML, and is more common in children than adults. Signs and symptoms of CNS involvement include cranial nerve palsies, headache, nausea, vomiting, papilledema, and occasionally seizures and coma.

Leukostasis is a condition in which the circulating blast count is markedly elevated (usually 100,000 cells/μL). The high number of circulating leukemic blasts increases blood viscosity and predisposes to the development of leukoblastic emboli with obstruction of small blood vessels in the pulmonary and cerebral circulations. Occlusion of the pulmonary vessels leads to vessel rupture and infiltration of lung tissue, resulting in sudden shortness of breath and progressive dyspnea. Cerebral leukostasis leads to diffuse headache and lethargy, which can progress to confusion and coma. Once identified, leukostasis requires immediate and effective treatment to lower the blast count rapidly. Initial treatment uses apheresis to remove excess blast cells, followed by chemotherapy to stop leukemic cell production in the bone marrow.[17]

Hyperuricemia occurs as the result of increased proliferation or increased breakdown of purine nucleotides (i.e., one of the components of nucleic acids) secondary to the leukemic cell death that results from chemotherapy. It may increase before and during treatment. Prophylactic therapy with allopurinol, a drug that inhibits uric acid synthesis, is routinely administered to prevent renal complications secondary to uric acid crystallization in the urine filtrate.

Diagnosis and Treatment. A definitive diagnosis of acute leukemia is based on blood and bone marrow studies; it requires the demonstration of leukemic cells in the peripheral blood, bone marrow, or extramedullary tissue. Bone marrow biopsy may be used to determine the molecular characteristics of the leukemia, the degree of bone marrow involvement, and the morphology and histology of the disease. Cytogenetic studies, which are used to determine chromosomal abnormalities, are one of the most powerful prognostic indicators in acute leukemia. In ALL, the staging includes a lumbar puncture to assess CNS involvement. Imaging studies that include computed tomography (CT) scans of the chest, abdomen, and pelvis may also be obtained to identify additional sites of disease.

Several types of treatment may be used for treatment of ALL and AML. The major therapy is chemotherapy. Treatment of ALL in childhood represents one of the great success stories in oncology. During the past decade, advances in ALL therapy have led to 5-year survival rates

of greater than 80% in children.[27] Other age groups tend to do less well, with only about 30% to 40% of adults achieving long-term survival. Chemotherapy leads to remission in over 50% of persons with AML, but the overall survival rate is less than 30%.[4] Bone marrow or stem cell transplantation may be considered for persons with ALL and AML who have failed to respond to other forms of therapy.[17] Because of the risk of complications, bone marrow transplantation is not usually recommended for patients older than 50 to 55 years of age.

Chronic Leukemias

In contrast to acute leukemias, chronic leukemias are malignancies involving proliferation of more fully differentiated myeloid and lymphoid cells. As with acute leukemia, there are two major types of chronic leukemia: chronic lymphocytic leukemia (CLL) and chronic myeloid (myelogenous) leukemia (CML).[28,29] CLL accounts for about one third of all leukemias.[47] It is mainly a disorder of older persons. The average age at time of diagnosis is approximately 72 years. It is rarely seen in people younger than 40 years of age, and is extremely rare in children.[28] CML accounts for 10% to 15% of all leukemias. As with CLL, it is predominantly a disorder of older adults, with an average age of approximately 67 years at the time of diagnosis.[29]

Chronic Lymphocytic Leukemia. CLL, a clonal malignancy of B lymphocytes, is the most common form of leukemia in adults in the Western world. In the past, CLL was viewed as a homogeneous disease of immature, immune-incompetent, minimally self-renewing B cells, which accumulated because of faulty apoptotic mechanisms. CLL is now becoming viewed as two related entities based on aggressiveness of the disease.[30] Some persons with CLL survive for many years without therapy and eventually succumb to unrelated diseases, whereas others have a rapidly fatal disease despite aggressive therapy. The two entities are thought to reflect differences in immunoglobulin variable (V)-gene mutations, expression of cell surface CD markers (e.g., CD38), and presence of the zeta-associated protein (ZAP-70).[28] ZAP-70 is an intracellular protein that promulgates activation signals delivered to T cells and NK cells by their surface receptors for antigens. It is rarely present in normal B cells but is found in persons with CLL. Persons whose CLL cells have mutated forms of the immunoglobulin gene generally have a more indolent form of the disease; these cells express low levels of the surface antigen and do not express the ZAP-70. Conversely, persons with CLL cells having few or no unmutated V genes and high levels of ZAP-70 expression often do less well.

The clinical signs and symptoms of CLL are largely related to the progressive infiltration of the bone marrow and lymphoid tissues by neoplastic lymphocytes and to secondary immunologic defects. Persons with the indolent form of CLL are often asymptomatic at the time of diagnosis, and the increase in lymphocytes is noted on a complete blood count obtained for another, unrelated disorder. As the disease progresses, lymph nodes gradually increase in size and new nodes are involved, sometimes in unusual areas such as the scalp, orbit, pharynx, pleura, gastrointestinal tract, liver, prostate, and gonads. Persons with the aggressive form of CLL experience a more rapid sequence of clinical deterioration characterized by increasing lymphadenopathy, hepatosplenomegaly, fever, abdominal pain, weight loss, progressive anemia, and thrombocytopenia, with a rapid rise in lymphocyte count.

Hypogammaglobulinemia is common in CLL, especially in persons with advanced disease. An increased susceptibility to infection reflects an inability to produce specific antibodies and abnormal activation of complement. The most common infectious organisms are those that require opsonization for bacterial killing, such as *Streptococcus pneumoniae, Staphylococcus aureus,* and *Haemophilus influenzae.*

The diagnostic hallmark of CLL is isolated increase in lymphocytes. The white blood cell count is usually greater than 20,000/μL and may be elevated to several hundred thousand. Usually, 75% to 98% are lymphocytes. Tests to determine the presence of mutated forms of the immunoglobulin gene (which currently can be detected only in research laboratories) and expression of the CD38 surface antigen and the ZAP-70 protein may be used to determine whether the leukemia is the indolent or aggressive type. Treatment of CLL usually depends on the presence of prognostic indicators.[28] Persons with the low-risk or indolent form of CLL usually do not require specific treatment for many years after diagnosis and eventually die of apparently unrelated causes. Many persons with intermediate-risk disease may remain stable for many years as well, whereas others may develop complications and need treatment within a few months. Most persons with high-risk CLL require combination chemotherapy at the time of diagnosis. In younger patients with aggressive disease, an allogeneic ablative (destruction of bone marrow cells by irradiation or chemotherapy) or nonmyeloablative stem cell transplant is a treatment option.

Chronic Myelogenous Leukemia. CML is a disorder of the pluripotent hematopoietic progenitor cell. It is characterized by excessive proliferation of marrow granulocytes, erythroid precursors, and megakaryocytes. The CML cells harbor a distinctive cytogenic abnormality, the previously described *Philadelphia chromosome.*[4,7] It is generally believed that CML develops when a single, pluripotent hematopoietic stem cell acquires a Philadelphia chromosome. Although CML originates in the pluripotent stem cells, granulocyte precursors remain the dominant leukemic cell type.

The clinical course of CML is commonly divided into three phases: (1) a chronic phase of variable length, (2) a short accelerated phase, and (3) a terminal blast crisis phase. The onset of the chronic phase is usually slow, with nonspecific symptoms such as weakness and weight loss. The most characteristic laboratory finding at the time of presentation is leukocytosis with immature granulocyte cell types in the peripheral blood. Anemia and, eventually, thrombocytopenia develop. Anemia causes weakness, easy fatigability, and exertional dyspnea. Splenomegaly is often

present at the time of diagnosis; hepatomegaly is less common; and lymphadenopathy is relatively uncommon. Persons in the early chronic phase of CML generally are asymptomatic, but without effective treatment most will enter the accelerated phase within 4 years.[31]

The accelerated phase of CML is characterized by enlargement of the spleen and progressive symptoms. Splenomegaly often causes a feeling of abdominal fullness and discomfort. An increase in basophil count and more immature cells in the blood or bone marrow confirm transformation to the accelerated phase. During this phase, constitutional symptoms such as low-grade fever, night sweats, bone pain, and weight loss develop because of rapid proliferation and hypermetabolism of the leukemic cells. Bleeding and easy bruising may arise from dysfunctional platelets. Generally, the accelerated phase is short (6 to 12 months).

The terminal blast crisis phase of CML represents evolution to acute leukemia and is characterized by an increasing number of myeloid precursors, especially blast cells, in the blood (Fig. 11-7). Constitutional symptoms become more pronounced during this period, and splenomegaly may increase significantly. Isolated infiltrates of leukemic cells can involve the skin, lymph nodes, bones, and CNS. With very high blast counts (>100,000 cells/μL), symptoms of leukostasis may occur. The prognosis for patients who are in the blast crisis phase is poor, with a median survival of 3 months.[31]

A diagnostic feature of CML is an elevated white blood count, with a median count of 150,000/μL at the time of diagnosis, although in some cases it is only modestly increased. The hallmark of the disease is the presence of the BCR-ABL gene product, which can be detected in the peripheral blood. The treatment of CML is evolving rapidly. An inhibitor of the BCR-ABL tyrosine kinase, imatinib mesylate, induces complete remission in a high fraction of persons with stable-phase CML.[32,33] The only available curative treatment for CML is allogeneic bone marrow or stem cell transplantation.

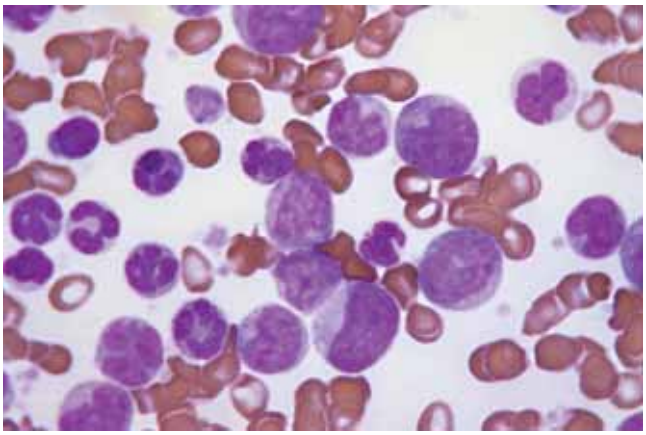


FIGURE 11-7. Peripheral blood showing blast crisis in chronic myelogenous leukemia. (From Centers for Disease Control and Prevention. [2008]. *Public health image library.* [Online] Available: http://www.phil.cdc.gov/phil/home.asp.)

Malignant Lymphomas

- The lymphomas represent malignancies that arise in the peripheral lymphoid tissues.
- Non-Hodgkin lymphomas represent a group of heterogeneous lymphocytic cancers that are multicentric in origin and spread to various tissues throughout the body, including the bone marrow.
- Hodgkin lymphoma is a group of cancers characterized by Reed-Sternberg cells that begins as a malignancy in a single lymph node and then spreads to contiguous lymph nodes.
- Both types of lymphomas are characterized by manifestations related to uncontrolled lymph node and lymphoid tissue growth, bone marrow involvement, and constitutional symptoms (fever, fatigue, weight loss) related to the rapid growth of abnormal lymphoid cells and tissues.

Malignant Lymphomas

The lymphomas are a diverse group of solid tumors composed of neoplastic lymphoid cells that vary with respect to molecular features, genetics, clinical presentation, and treatment. Two groups of lymphomas are recognized: non-Hodgkin lymphomas (NHLs) and Hodgkin lymphoma.[34,35]

Non-Hodgkin Lymphomas

The NHLs represent a clinically diverse group of either B-cell or T-cell neoplasms. In both men and women, the incidence rates for NHL increased approximately 50% between 1978 and the late 1990s, but have stabilized since that time.[36] Age-adjusted incidence rates of NHL in the United States and Canada are among the highest in the world. They represent about 4% of all new cases of cancer diagnosed in the United States each year, making them the fifth most common cause of cancer death in the United States.[34]

As with most other malignancies, the cause of NHL is largely unknown. However, impairment of the immune system and infectious agents may play a role. There is evidence of EBV infection in essentially all people with Burkitt lymphoma, which is endemic to some parts of Africa.[4,7] A second virus, the human T-cell lymphotropic virus (HTLV-1), which is endemic in the southwestern islands of Japan, has been associated with adult T-cell leukemia/lymphoma. The NHLs are also seen with increased frequency in persons infected with HIV, in those who have received chronic immunosuppressive therapy after organ transplantation, and in individuals with acquired or congenital immunodeficiencies.[37,38] There is also a reported

association between chronic *Helicobacter pylori* infection and low-grade MALT lymphoma of the stomach.

Non-Hodgkin lymphomas can originate from malignant transformation of either the T or B cells during their differentiation in the peripheral lymphoid tissues.[4,7] Although the NHLs can originate in any of the lymphoid tissues, they most commonly originate in the lymph nodes. Like normal lymphocytes, transformed B and T cells tend to home in to particular lymph node sites, leading to characteristic patterns of involvement. For example, B-cell lymphomas tend to proliferate in the B-cell areas of the lymph node, whereas T-cell lymphomas typically grow in the paracortical T-cell areas[4,7] (see Fig. 11-4). All have the potential to spread to various lymphoid tissues throughout the body, especially the liver, spleen, and bone marrow.

The classification of NHLs remains controversial and is still evolving. A commonly used classification is the World Health Organization (WHO) system[4,7,35,39] (Chart 11-2). The WHO system classifies lymphomas in terms of cell type (B or T cell), level of maturation (e.g., immature or mature), and anatomic sites (e.g., MALT lymphoma of the stomach).[4] The NHLs are actually a complex group of almost 40 distinct entities, based on the appearance of the lymphoma cells, the presence of surface markers (e.g., antigens, CD markers), and genetic features.[4,5,19] In addition, the specific types of lymphomas are sometimes grouped together into low-grade, aggressive, and very aggressive categories.

Mature B-Cell Lymphomas. Mature (peripheral) B-cell lymphomas are the most common type of lymphoma in the Western world. The most common of the mature B-cell lymphomas are the follicular lymphomas (22%) and diffuse large B-cell lymphomas (31%). Small lymphocytic lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma, and MALT lymphoma together account for 28% of NHLs.[4]

Follicular lymphomas are derived from germinal center B cells and consist of a mixture of centroblasts and centrocytes. Follicular lymphomas are a particularly common neoplasm in the United States, where they constitute about one third of all adult NHLs, with a peak incidence at 60 years of age. The lymphoma predominantly affects lymph nodes. Other sites of involvement include the spleen, bone marrow, peripheral blood, head and neck region, gastrointestinal tract, and skin. Most persons have advanced disease at presentation and an indolent clinical course, with a median survival of 6 to 10 years.[7,35] Over time, approximately one of three follicular lymphomas transforms into a fast-growing diffuse large B-cell lymphoma.

Diffuse large B-cell lymphomas are a heterogeneous group of aggressive germinal or postgerminal center neoplasms. The disease occurs in all age groups but is most prevalent between 60 and 70 years of age. The cause of diffuse large B-cell lymphoma is unknown, but may involve EBV or HIV infections. It is a rapidly evolving, multifocal, nodal and extranodal tumor. Manifestations are typically seen at the time of presentation. As a group, diffuse large B-cell lymphomas are rapidly fatal if untreated. However, with intensive combination chemotherapy, complete remission can be achieved in 60% to 80% of persons and approximately 40% to 50% remain disease free after several years and can be considered cured.[7,35]

Burkitt lymphoma, one of the most rapidly growing tumors of the NHLs, is also a disorder of germinal center B cells. Endemic Burkitt lymphoma is the most common childhood cancer (peak age 3 to 7 years) in Central Africa, often beginning in the jaw.[4] It occurs in regions of Africa where both EBV and malarial infection are common. Virtually 100% of patients with African Burkitt lymphoma have evidence of previous EBV infection, and their tumors carry the EBV genome and express EBV-encoded antigens.[4] Malarial infections in this population have been shown to cause T-cell immunodeficiencies, and it is postulated that this association may be the link between EBV infection and the development of lymphoma. A sporadic or nonendemic form of Burkitt lymphoma occurs less frequently in other parts of the world. The classic presentation of endogenous Burkitt lymphoma is a destructive tumor in the jaw and other facial bones, whereas the sporadic form typically presents with abdominal masses. Both forms of Burkitt lymphoma respond to aggressive chemotherapy, with a cure rate of up to 90%.[4]

Mantle cell lymphomas constitute less than 10% of NHLs and have their origin in the naive B cell. After the precursor stage, B cells undergo immunoglobulin (Ig) gene rearrangements and develop into surface IgM- and IgD-positive naive B cells. These cells give rise to mantle cell lymphoma. Mantle cell lymphomas do not occur in children, but affect older persons (median age, 60 years).

CHART 11-2 WHO Classification of Selected Non-Hodgkin Lymphomas

B-Cell Lymphomas

Precursor B-cell lymphomas
- B-cell lymphoblastic lymphoma

Mature B-cell lymphomas
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Follicular lymphoma
- Small lymphocytic lymphoma
- Lymphoplasmacytic lymphoma
- Mantle cell lymphoma
- Mucosa-associated lymphoid tissue (MALT) lymphoma
- Burkitt lymphoma

T-Cell Lymphomas

Precursor T-cell lymphomas
- T-cell lymphoblastic lymphoma

Mature T- (and natural killer) cell lymphomas
- Anaplastic large cell lymphoma
- Peripheral T-cell lymphoma (unspecified)

*Developed from the World Health Organization. [Online] Available: http://www.who.int/ classifications/apps/icd/meetings/tokyomeeting/B_6-3%20Annex1.pdf.

They have a rapid rate of progression, and only one in five persons survives at least 5 years.[34]

Marginal zone lymphomas involve late-stage memory B cells that reside in the marginal zone or outermost compartment of the lymph node follicle. Variants of marginal node lymphoma include splenic marginal zone lymphoma and MALT lymphomas of the stomach and other mucosal surfaces. *MALT lymphomas* constitute 5% to 10% of all B-cell NHLs.[4] Most MALT lymphomas involve the stomach or other mucosal sites, including the respiratory system. MALT lymphomas tend to remain localized for prolonged periods and to follow an indolent course. Extranodal marginal B-cell lymphomas of the MALT type are curable by radiation or surgery when localized. MALT lymphomas that occur in the stomach secondary to *H. pylori* infection often respond to treatment with appropriate antimicrobial agents.

Clinical Manifestations. The manifestations of NHL depend on lymphoma type (i.e., indolent or aggressive) and the stage of the disease. Persons with indolent or slow-growing lymphomas usually present with painless lymphadenopathy, which may be isolated or widespread. Involved lymph nodes may be present in the retroperitoneum, mesentery, and pelvis. The indolent lymphomas are usually disseminated at the time of diagnosis, and bone marrow involvement is frequent. With or without treatment, the natural course of the disease may fluctuate over 5 to 10 or more years. Many low-grade lymphomas eventually transform into more aggressive forms of lymphoma/leukemia.

Persons with intermediate or more aggressive forms of lymphoma usually present with accompanying constitutional symptoms such as fever, drenching night sweats, or weight loss. Frequently, there is increased susceptibility to bacterial, viral, and fungal infections associated with hypogammaglobulinemia and a poor humoral antibody response, rather than the impaired cellular immunity seen with Hodgkin lymphoma. Because of their high growth fraction, these lymphomas tend to be sensitive to radiation and chemotherapy. Hence, with intensive combination chemotherapy, complete remission can be achieved in 60% to 80% of cases.[40]

Diagnosis and Treatment. A lymph node biopsy is used to confirm the diagnosis of NHL and immunophenotyping to determine the lineage and clonality. Lymphomas can be grouped according to surface markers or phenotypic markers (e.g., CD20).[40] Staging of the disease is important in selecting a treatment for persons with NHL. Bone marrow biopsy, blood studies, chest and abdominal CT scans, magnetic resonance imaging (MRI), positron emission tomography (PET), gallium scans, and bone scans may be used to determine the stage of the disease.[38] Newer technologies, such as deoxyribonucleic acid (DNA) microarray analysis, which identifies genes that are either overexpressed or underexpressed by tumor cells, may be used to distinguish persons further into distinct risk groups.[39]

Treatment of NHL depends on the histologic type, stage of the disease, and clinical status of the person. For early-stage disease involving a single or limited node involvement, localized radiation may be used as a single treatment modality. However, because most people who present with indolent lymphoma have disseminated disease at the time of diagnosis, combination chemotherapy, combined adjuvant radiation therapy, or both are recommended. Persons with lymphomas that carry a risk of CNS involvement usually receive CNS prophylaxis with high doses of chemotherapeutic agents or cranial irradiation.

Hodgkin Lymphoma

Hodgkin lymphoma, previously known as *Hodgkin disease*, is a specialized form of lymphoma that features the presence of an abnormal cell called a *Reed-Sternberg cell*.[4,7,41,42] Because of improved treatment methods, death rates have decreased by more than 60% since the early 1970s. Distribution of the disease is bimodal; it occurs more frequently in two separate groups, the first in early adulthood (15 to 40 years) and the second in older adulthood (55 years of age or older).[35,42] About 10% to 15% of cases are diagnosed in children and teenagers.[42]

Hodgkin lymphoma differs from NHL in several respects. First, HL usually arises in a single node or chain of nodes and spreads first to anatomically contiguous lymphoid tissues; whereas, NHL frequently originates at extranodal sites and spreads in an unpredictable fashion. Therefore, the staging of HL is much more important in guiding therapy than it is for NHL. Second, HL also has distinctive morphological features. It is characterized by the presence of large, atypical, mononuclear tumor cells, called *Reed-Sternberg cells* (Fig. 11-8). These cells release factors that induce the accumulation of reactive lymphocytes, macrophages, and granulocytes, which typically make up greater than 90% of the tumor's cells.[7]

The origin of the neoplastic Reed-Sternberg cell of Hodgkin lymphoma has been difficult to study, in large part because these cells do not express many of the markers found on lymphocytes. It is only recently that methods have been developed that allow for the microanalysis

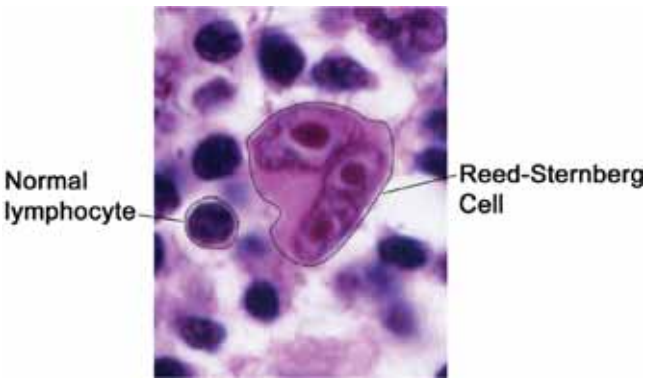


FIGURE 11-8. Classic Reed-Sternberg cell; photograph shows normal lymphocyte compared with Reed-Sternberg cell. (From National Cancer Institute. [Online] Available: http://visualsonline.cancer.gov/details.cfm?imageid=7172.)

of these cells and their variants. These studies have shown that the Reed-Sternberg cells of most individual cases harbor identical immunoglobulin genes that show evidence of mutation, establishing the cell of origin as a germinal center or postgerminal center B cell.

As with NHLs, the cause of Hodgkin lymphoma is largely unknown. Although exposure to carcinogens and viruses as well as genetic and immune mechanisms have been proposed as causes, none has been proved to be involved in the pathogenesis of the disease. It appears that people with a history of infectious mononucleosis are at increased risk for development of Hodgkin lymphoma.[4,7,35]

Classification. The WHO classification proposed classifying Hodgkin lymphoma into two major categories: nodular lymphocyte-predominant Hodgkin lymphoma and classic Hodgkin lymphoma.[4,41,42] Nodular lymphocyte-predominant Hodgkin lymphoma represents only a small portion of all cases of Hodgkin lymphoma and is a unique form that generally exhibits a nodular growth pattern, with or without diffuse areas and with rare Reed-Sternberg cells called "popcorn" or "L&H" (lymphohistiocytic) cells. It is often localized rather than disseminated at the time of diagnosis, exhibits a slowly progressive course, and has an overall survival rate greater than 80%.[4]

Classic Hodgkin lymphoma is characterized by clonal proliferation of typical mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells with invariable expression of CD30. Four variants of classic Hodgkin lymphoma have been described: nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted. The nodular sclerotic type is the most common and is often found in adolescent and young adult women, 15 to 35 years of age.[4] Lymphocyte-rich Hodgkin lymphoma is a newly defined entity, and lymphocyte-depleted Hodgkin lymphoma is rarely diagnosed. At present, all subtypes of classic Hodgkin lymphoma are treated in the same manner.[41]

Clinical Manifestations. Most persons with Hodgkin lymphoma present with painless enlargement of a single node or group of nodes. The initial lymph node involvement typically is above the level of the diaphragm (i.e., in the neck, supraclavicular area, or axilla). Mediastinal masses are frequent and are sometimes discovered on routine chest radiography. There may be complaints of chest discomfort with cough or dyspnea. Involvement of subdiaphragmatic lymph nodes at the time of presentation is unusual and more common in elderly men. Additional symptoms that suggest Hodgkin lymphoma include fevers, chills, night sweats, and weight loss. Pruritus and intermittent fevers associated with night sweats are classic symptoms of Hodgkin lymphoma.

Other symptoms such as fatigue and anemia are indicative of disease spread. In the advanced stages of Hodgkin lymphoma, the liver, spleen, lungs, digestive tract, and, occasionally, CNS may be involved. As the disease progresses, the rapid proliferation of abnormal lymphocytes leads to an immunologic defect, particularly in cell-mediated responses, rendering the person more susceptible to viral, fungal, and protozoal infections. Anergy, or the failure to develop a positive response to skin tests such as the tuberculin test, is common early in the course of the disease.

Diagnosis and Treatment. A definitive diagnosis of Hodgkin lymphoma requires that the Reed-Sternberg cell be present in a biopsy specimen of lymph node tissue. CT scans of the chest and abdomen commonly are used to assess for involvement of mediastinal, abdominal, and pelvic lymph nodes.[41] If with initial screening the extent of lymph node involvement cannot be determined, PET imaging may be helpful.

Persons with Hodgkin lymphoma are staged according to the number of lymph nodes involved, whether the lymph nodes are on one or both sides of the diaphragm, and whether there is disseminated disease involving the bone marrow, liver, lung, or skin. The staging of Hodgkin lymphoma is of great clinical importance because the choice of treatment and the prognosis ultimately are related to the distribution of the disease. In addition, patients are designated stage A if they lack constitutional symptoms and stage B if 10% weight loss over 6 months or night sweats are present.

Irradiation and chemotherapy are used in treating the disease. Most people with localized disease are treated with radiation therapy. A combined approach using radiation and chemotherapy is used in persons with advanced disease. As the accuracy of staging techniques, delivery of radiation, and curative efficacy of combination chemotherapy regimens have improved, the survival of people with Hodgkin lymphoma also has improved. With modern treatment methods, a 5-year cure rate of 85% can be achieved.[42]

Plasma Cell Dyscrasias

Plasma cell dyscrasias are characterized by expansion of a single clone of immunoglobulin-producing plasma cells and a resultant increase in serum levels of a single monoclonal immunoglobulin or its fragments. The plasma cell dyscrasias include multiple myeloma, lymphoplasmacytic lymphoma, and monoclonal gammopathy of undetermined significance. *Monoclonal gammopathy of undetermined significance* (MGUS) is characterized by the presence of the monoclonal immunoglobulin in the serum without other findings of multiple myeloma. MGUS is considered a premalignant condition.[4,7,43–45] Approximately 2% per year of persons with MGUS will go on to develop a plasma cell dyscrasia (multiple myeloma or lymphoplasmacytic lymphoma). The strong link between MGUS and multiple myeloma suggests that a first oncogenic event produces MGUS and a second event results in multiple myeloma.[4]

Multiple Myeloma

Multiple myeloma is a B-cell malignancy of terminally differentiated plasma cells. It accounts for 1% of all

cancers and 10% of all hematologic malignancies in Caucasians and 20% in African Americans.[46] It occurs most frequently in persons older than 60 years of age, with the median age of patients with multiple myeloma being 71 years.

The cause of multiple myeloma is unknown. Risk factors are thought to include chronic immune stimulation, autoimmune disorders, exposure to ionizing radiation, and occupational exposure to pesticides or herbicides (e.g., dioxin). Myeloma has been associated with exposure to Agent Orange during the Vietnam War. A number of viruses have been associated with the pathogenesis of myeloma. There is a 4.5-fold increase in the likelihood of development of multiple myeloma for persons with HIV infection.[47]

Pathogenesis. Multiple myeloma is characterized by proliferation of malignant plasma cells in the bone marrow and osteolytic bone lesions throughout the skeletal system. As with other hematopoietic malignancies, it is now recognized that multiple myeloma is associated with chromosomal abnormalities, including deletions of 13q and translocations involving the IgG locus on chromosome 14.[7] Changes also occur in the bone marrow microenvironment, including the induction of angiogenesis, the suppression of cell-mediated immunity, and the development of paracrine signaling loops involving cytokines such as IL-6 and vascular endothelial growth factor (VEGF). Other growth factors that are implicated in multiple myeloma include granulocyte CSF, interferon-α, and IL-10.

One of the characteristic features resulting from the proliferating neoplastic plasma cells in multiple myeloma is the unregulated production of an abnormal monoclonal paraprotein referred to as the *M protein* because it is detected as an M spike on protein electrophoresis. In most cases the M protein is either IgG or IgA.[44] In some cases, the plasma cells produce only the light chains of the immunoglobulin molecule. Because of their low molecular weigh, the light chains are readily excreted in the urine, where they are termed *Bence Jones proteins*. More commonly, however, malignant plasma cells produce both complete immunoglobulins and free light chains; therefore, both M proteins and Bence Jones proteins are present. The excess light chains are directly toxic to renal tubular structures and are an important aspect of the pathophysiology of multiple myeloma.

Manifestations. The main sites involved in multiple myeloma are the bones and bone marrow (Fig. 11-9). In addition to the abnormal proliferation of marrow plasma cells, there is proliferation and activation of osteoclasts, which leads to bone resorption and destruction. This increased bone resorption predisposes the individual to pathologic fractures and hypercalcemia. Very high concentrations of paraproteins may cause a hyperviscosity of body fluids. The light-chain component may break down into amyloid, a proteinaceous substance deposited between cells, causing heart failure and nephropathy. Renal involvement, generally called *myeloma nephrosis*, is a distinctive feature of multiple

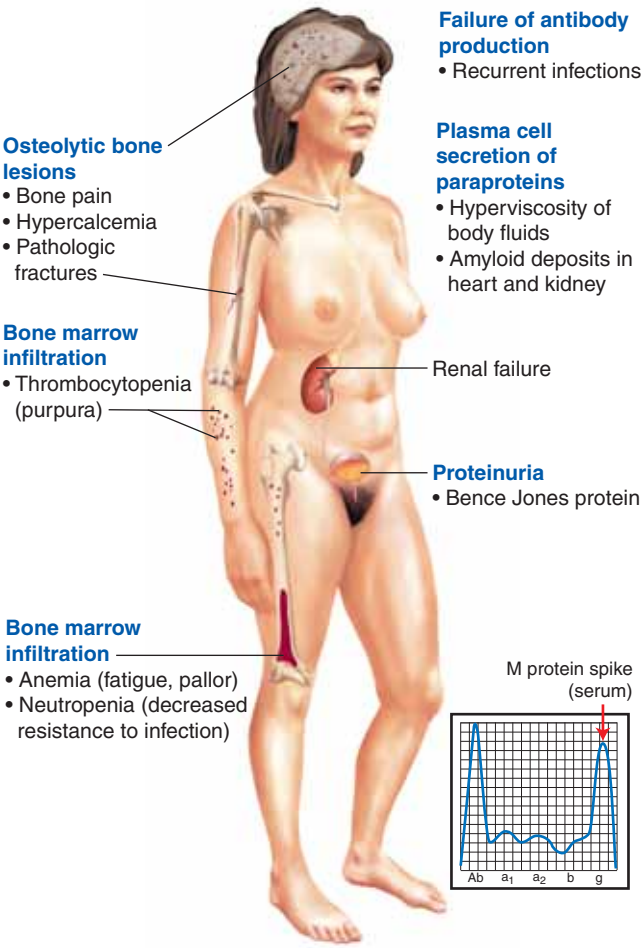


FIGURE 11-9. Clinical features of multiple myeloma.

myeloma. Although multiple myeloma is characterized by excessive production of monoclonal immunoglobulin, levels of normal immunoglobulins are usually depressed. This contributes to a general susceptibility to recurrent bacterial infections.

The malignant plasma cells also can form plasmacytomas (plasma cell tumors) in bone and soft tissue sites. The most common site of soft tissue plasmacytomas is the gastrointestinal tract. The development of plasmacytomas in bone tissue is associated with bone destruction and localized pain. Osteolytic lesions and compression fractures may be seen in the axial skeleton and proximal long bones. Occasionally, the lesions may affect the spinal column, causing vertebral collapse and spinal cord compression.

Bone pain is one of the first symptoms to occur in approximately three fourths of all individuals diagnosed with multiple myeloma. Bone destruction also impairs the production of erythrocytes, leukocytes, and thrombocytes. This predisposes the patient to anemia, recurrent infections, and thrombocytopenic purpura. Many patients experience weight loss and weakness. Renal insufficiency occurs in 50% of patients. Neurologic manifestations caused by neuropathy or spinal cord compression also may be present.

Diagnosis and Treatment. Diagnosis of multiple myeloma is based on clinical manifestations, blood tests, and bone marrow examination. The classic triad of bone marrow plasmacytosis (>10% plasma cells), lytic bone lesions, and either the serum M-protein spike or the presence of Bence Jones proteins in the urine is definitive for a diagnosis of multiple myeloma. Bone radiographs are important in establishing the presence of bone lesions. Anemia is almost universal. Other laboratory features include hypercalcemia, an elevated erythrocyte sedimentation rate, and signs of kidney failure. The strongest predictors of outcome are low serum β_2-microglobulin (a small subunit of the major histocompatibility complex I molecule) and C-reactive protein levels.

The treatment of multiple myeloma is rapidly changing.[45] Recently, thalidomide or lenalidomide (a second-generation thalidomide drug) combined with dexamethasone (a corticosteroid) has emerged as an active agent for use in the initial treatment of multiple myeloma.[44] Another agent, a reversible 26S proteosome inhibitor (bortezomib), was recently approved for treatment of multiple myeloma. High-dose chemotherapy with autologous stem cell transplantation is now considered appropriate front-line therapy for patients younger than 70 years of age newly diagnosed with multiple myeloma. Allogeneic transplantation offers prolonged disease-free outcomes and potential cure, but at a high cost of treatment-related mortality. Because of this, "mini-transplants" using non–marrow-ablative chemotherapy may be used to provide sufficient immune suppression to allow donor engraftment and subsequent graft-versus-tumor effect.

In summary, the neoplastic disorders of hematopoietic and lymphoid origin include the leukemias, lymphomas, and multiple myeloma. The leukemias are malignant neoplasms of the hematopoietic precursor cells that originate in the bone marrow. They are classified according to cell type (i.e., lymphocytic or myelocytic) and whether the disease is acute or chronic. The lymphocytic leukemias involve immature lymphocytes and their progenitors that originate in the bone marrow but infiltrate the spleen, lymph nodes, CNS, and other tissues. The myelogenous leukemias involve the pluripotent myeloid stem cells in bone marrow and interfere with the maturation of all blood cells, including the granulocytes, erythrocytes, and thrombocytes.

The acute leukemias (i.e., ALL, which primarily affects children, and AML, which primarily affects adults) have a sudden and stormy onset with symptoms of depressed bone marrow function (anemia, fatigue, bleeding, and infections); bone pain; and generalized lymphadenopathy, splenomegaly, and hepatomegaly. The chronic leukemias, which largely affect adults, have a more insidious onset. CLL often has the most favorable clinical course, with many persons living long enough to die of other, unrelated causes. The course of CML is slow and progressive, with transformation to a course resembling that of AML.

The lymphomas (NHL and Hodgkin lymphoma) represent malignant neoplasms of cells native to lymphoid tissue that have their origin in the secondary lymphoid structures such as the lymph nodes and mucosa-associated lymphoid tissues. The NHLs are a group of neoplastic disorders that originate in the lymphoid tissues, usually the lymph nodes. The NHLs are multicentric in origin and spread early to various lymphoid tissues throughout the body, especially the liver, spleen, and bone marrow. Hodgkin lymphoma is characterized by painless and progressive enlargement of a single node or group of nodes. It is believed to originate in one area of the lymphatic system and, if unchecked, spreads throughout the lymphatic network.

Multiple myeloma is a plasma cell dyscrasia characterized by expansion of a single clone of immunoglobulin-producing plasma cells and a resultant increase in serum levels of a single monoclonal immunoglobulin or its fragments. The main sites involved in multiple myeloma are the bones and bone marrow. In addition to the abnormal proliferation of marrow plasma cells, there is proliferation and activation of osteoclasts, which leads to bone resorption and destruction and predisposes to increased risk for pathologic fractures and development of hypercalcemia. Paraproteins secreted by the plasma cells may cause hyperviscosity of body fluids and may break down into amyloid, a proteinaceous substance deposited between cells that can cause heart failure and neuropathy. Bone marrow involvement leads to increased risk of infection due to suppressed humoral and cell-mediated immunity and anemia due to impaired red cell production.

REVIEW EXERCISES

1. Many of the primary immunodeficiency disorders, in which there is a defect in the development of immune cells of T- or B-lymphocyte origin, can be cured with allogeneic stem cell transplantation from an unaffected donor.

A. Explain why stem cells are used rather than mature lymphocytes. You might want to refer to Figure 11-5.

B. Describe how the stem cells would go about the process of repopulating the bone marrow.

2. A mother brings her 4-year-old son into the pediatric clinic because of irritability, loss of appetite, low-grade fever, pallor, and complaints that his legs hurt. Blood tests reveal anemia, thrombocytopenia, and an elevated leukocyte count with atypical lymphocytes. A diagnosis of acute lymphocytic leukemia (ALL) is confirmed with bone marrow studies.

A. What is the origin of the anemia, thrombocytopenia, elevated leukocyte count, and atypical lymphocytes seen in this child?

B. Explain the cause of the child's fever, pallor, increased bleeding, and bone pain.
C. The parents are informed that the preferred treatment for ALL consists of aggressive chemotherapy with the purpose of achieving a remission. Explain the rationale for using chemotherapy to treat leukemia.
D. The parents are told that the child will need intrathecal chemotherapy administered by a lumbar puncture. Why is this treatment necessary?

3. A 36-year-old man presents to his health care clinic with fever, night sweats, weight loss, and a feeling of fullness in his abdomen. Subsequent lymph node biopsy reveals a diagnosis of non-Hodgkin lymphoma (NHL).

A. Although lymphomas can originate in any of the lymphoid tissues of the body, most originate in the lymph nodes, and most (80% to 85%) are of B-cell origin. Hypothesize as to why B cells are more commonly affected than T cells.
B. A newly developed monoclonal antibody, rituximab, is being used in the treatment of NHL. Explain how this agent exerts its effect and why it is specific for B-cell lymphomas.

REFERENCES

1. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 429–456). Philadelphia: Elsevier Saunders.
2. Ross M.H., Pawline W. (2006). *Histology: A text and atlas* (5th ed., pp. 253–266, 272–275). Philadelphia: Lippincott Williams & Wilkins.
3. Fey M.F. (2007). Normal and malignant hematopoiesis. *Annals of Oncology* 18(Suppl1), 9–13.
4. Schwarting R., McKenzie S., Rubin R. (2008). Hematopathology. In Rubin R., Strayer D.E. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed. pp. 893–927). Philadelphia: Lippincott Williams & Wilkins.
5. Kaushansky K. (2006). Lineage-specific hematopoietic growth factors. *New England Journal of Medicine* 354(19), 2034–2045.
6. Fischbach F. (2004). *A manual of laboratory and diagnostic tests* (7th ed., p. 48). Philadelphia: Lippincott Williams & Wilkins.
7. Kumar V., Abbas A.K., Fausto N., Aster J.C. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 589–638). Philadelphia: Saunders Elsevier.
8. Schwartzberg L.S. (2006). Neutropenia: Etiology and pathogenesis. *Clinical Cornerstone* 8(Suppl 5), S5–S11.
9. Berliner N., Horwitz M., Loughran T.P. (2004). Congenital and acquired neutropenia. *Hematology* 63–79.
10. Cohen J.I. (2000). Epstein-Barr virus infection. *New England Journal of Medicine* 343, 481–492.
11. McAdam A.J., Sharpe A.H. (2010). Infectious diseases. In Kumar V., Abbas A.K., Fausto N., Aster J.C. *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 355–357). Philadelphia: Saunders Elsevier.
12. Schwartz D.A., Genta R.M., Bennett D.P., et al. (2008). Infectious and parasitic diseases. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 285–386). Philadelphia: Lippincott Williams & Wilkins.
13. Godshall S.E., Kirscher J.T. (2000). Infectious mononucleosis: Complexities of a common syndrome. *Postgraduate Medicine* 107, 175–186.
14. Ebell M.H. (2004). Epstein-Barr virus infectious mononucleosis. *American Family Physician* 70, 1279–1287, 1289–1290.
15. American Cancer Society. (2008). *Cancer facts & figures 2008*. Atlanta: American Cancer Society.
16. American Cancer Society. (2007). *Leukemia—Acute lymphocytic*. Atlanta: American Cancer Society.
17. Faderi S., Jeha S., Kantajian H.M. (2003). The biology and therapy of adult acute lymphoblastic leukemia. *Cancer* 98, 1337–1354.
18. Viele C.S. (2003). Diagnosis, treatment, and nursing care of acute leukemia. *Seminars in Oncology Nursing* 19(2), 98–108.
19. Belson M., Kingsley B., Holmes A. (2007). Risk factors for acute leukemia in children. *Environmental Health Perspectives* 115(1), 138–145.
20. Bloomfield C.D., Caligiuri M.A. (2001). Biology of leukemias. In DeVita V.T. Jr., Hellman S., Rosenberg S.A. (Eds.), *Cancer: Principles and practice of oncology* (6th ed., pp. 2390–2402). Philadelphia: Lippincott Williams & Wilkins.
21. Kurzrock R., Kantarjian H.M., Druker B.J., et al. (2003). Philadelphia chromosome–positive leukemias: From basic mechanisms to molecular therapeutics. *Annals of Internal Medicine* 138, 819–830.
22. Jabbour E.J., Faderl S., Kantarjian H.M. (2005). Adult acute lymphoblastic leukemia. *Mayo Clinic Proceedings* 80, 1517–1527.
23. Pui C., Reiling M.V., Downin J.R. (2004). Acute lymphoblastic leukemia. *New England Journal of Medicine* 350, 1535–1548.
24. American Cancer Society. (2007). *Leukemia—Acute myeloid (myelogenous)*. Atlanta: American Cancer Society.
25. Stone R.M., O'Donnell R.R., Sekeres M.A. (2004). Acute myeloid leukemia. *Hematology* 98–117.
26. Lo-Coco F., Ammatuna E. (2006). The biology of acute promyelocytic leukemia and its on diagnosis and treatment. *Hematology* 156–160.
27. Pui C.-H., Evans W.E. (2006). Treatment of acute lymphoblastic leukemia. *New England Journal of Medicine* 354, 166–178.
28. American Cancer Society. (2007). *Leukemia—Chronic lymphocytic*. Atlanta: American Cancer Society.
29. American Cancer Society. (2007). *Leukemia—Chronic myeloid (myelogenous)*. Atlanta: American Cancer Society.
30. Chiorazzi N., Rai K.R., Farrarini M. (2005). Chronic lymphocytic leukemia. *New England Journal of Medicine* 352, 804–815.
31. Breed C.D. (2003). Diagnosis, treatment, and nursing care of patients with chronic leukemia. *Seminars in Oncology Nursing* 19(2), 109–117.
32. Vlahorvic G., Crawford J. (2003). Activation of tyrosine kinases in cancer. *Oncologist* 8, 531–538.
33. Goldman J.M., Melo J.V. (2003). Chronic myeloid leukemia: Advances in biology and new approaches to treatment. *New England Journal of Medicine* 349, 1451–1464.
34. American Cancer Society. (2007). *Non-Hodgkin lymphoma*. Atlanta: American Cancer Society.
35. Rademaker J. (2007). Hodgkin's and non-Hodgkin's lymphoma. *Radiologic Clinics of North America* 45, 69–83.
36. Canadian Cancer Society, National Cancer Institute Canada, Statistics Canada, et al. (2008). *Canadian cancer statistics 2008*. [Online] Available: http://www.cancer.ca. Accessed February 18, 2009.
37. Armitage J.O. (2005). Staging of non-Hodgkin lymphoma. *CA: A Cancer Journal for Clinicians* 55, 368–376.

38. American Cancer Society. (2007). *Non-Hodgkin lymphoma*. Atlanta: American Cancer Society.
39. Cheson B.D. (2004). What is new in lymphoma? *CA: A Cancer Journal for Clinicians* 54, 260–272.
40. Reiser M., Diehl V. (2002). Current treatment of follicular non-Hodgkin's lymphoma. *European Journal of Cancer* 38, 1167–1172.
41. Yung L., Linch D. (2003). Hodgkin's lymphoma. *Lancet* 361, 943–951.
42. American Cancer Society. (2008). *Hodgkin lymphoma*. Atlanta: American Cancer Society.
43. Kyle R.A., Rajkumar S.V. (2004). Multiple myeloma. *New England Journal of Medicine* 351, 1860–1873.
44. Rajkumar S., Kyle R.A. (2005). Multiple myeloma: Diagnosis and treatment. *Mayo Clinic Proceedings* 80, 1371–1382.
45. Nau K.C., Lewis W.D. (2008). Multiple myeloma: Diagnosis and treatment. *American Family Physician* 78(7), 853–860.
46. Katzel J.A. (2007). Multiple myeloma: Charging toward a bright future. *CA: A Cancer Journal for Clinicians* 57, 301–318.
47. Zaidi A.A., Vesole D.H. (2001). Multiple myeloma: An old disease with a new hope for the future. *CA: A Cancer Journal for Clinicians* 51, 273–285.

Hemostasis and Blood Coagulation
Components of Hemostasis
Platelets
The Coagulation System
Endothelium
Clot Formation and Dissolution
Vessel Spasm
Platelet Plug Formation
The Coagulation Cascade
Clot Retraction
Clot Dissolution
Hypercoagulability States
Increased Platelet Function
Increased Clotting Activity
Inherited Disorders
Acquired Disorders
Bleeding Disorders
Platelet Disorders
Thrombocytopenia
Impaired Platelet Function
Coagulation Disorders
Inherited Disorders
Acquired Disorders
Bleeding Associated with Vascular Disorders
Disseminated Intravascular Coagulation

Chapter 12

Disorders of Hemostasis

The term *hemostasis* refers to the stoppage of blood flow. The normal process of hemostasis is regulated by a complex array of activators and inhibitors that maintain blood fluidity and prevent blood from leaving the vascular compartment. Hemostasis is normal when it seals a blood vessel to prevent blood loss and hemorrhage. It is abnormal when it causes inappropriate blood clotting or when clotting is insufficient to stop the flow of blood from the vascular compartment. Disorders of hemostasis fall into two main categories: the inappropriate formation of clots within the vascular system (thrombosis) and the failure of blood to clot in response to an appropriate stimulus (bleeding).

Hemostasis and Blood Coagulation

Hemostasis is a multistep process that transforms blood into a semisolid clot with erythrocytes trapped in its fibrin meshwork (Fig. 12-1). It involves platelets, plasma clotting factors, naturally occurring anticoagulants, and the inherent properties of the endothelial lining of blood vessels.

Components of Hemostasis

Platelets

Platelets, also called *thrombocytes,* are large fragments from the cytoplasm of bone marrow cells called *megakaryocytes.*[1–4] There are normally 150,000 to 400,000 platelets in each microliter (μL) of blood.[1] The life span of a platelet is only 8 to 9 days. Platelets do not leave the blood as white blood cells do, but at any time about one third of them are in storage in blood-filled spaces in the spleen. These stored platelets can be released from the spleen into the circulation as needed. Platelet production is controlled by a protein called *thrombopoietin* that causes proliferation and maturation of megakaryocytes.[2] The sources of thrombopoietin include the liver, kidney, smooth muscle, and bone marrow. Its production and release are regulated by the number of platelets in the circulation.

Although platelets lack a nucleus, they have many of the structural and functional characteristics of a whole

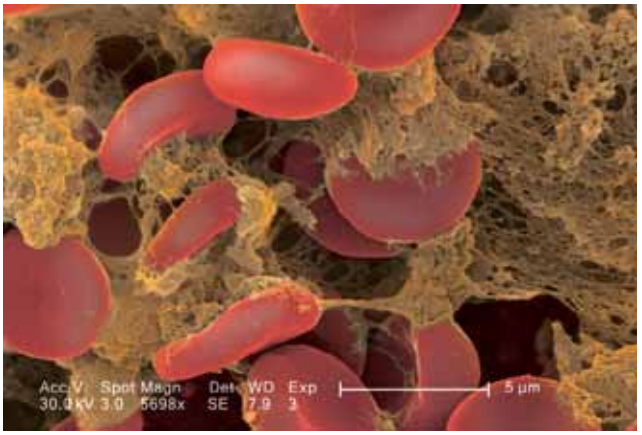


FIGURE 12-1. A scanning electron micrograph depicting a number of red cells enmeshed in a fibrinous matrix on the luminal surface of an indwelling catheter (magnification × 5698). (From the Centers for Disease Control and Prevention Public Images Library, Courtesy Janice Carr.)

cell.[1–4] They contain an outer cell membrane, microtubular structures, and inner organelles (Fig. 12-2). The platelet cell membrane, which plays an important role in platelet adhesion and the coagulation process, is covered with a surface coat of glycocalyx, consisting of glycoproteins, glycosaminoglycans, and several coagulation factors adsorbed from the plasma.[2] One of the important glycoproteins is glycoprotein IIb/IIIa (gpIIb/IIIa), which binds fibrinogen and acts to connect many platelets together to form large aggregates. Phospholipids, which are also present in the platelet membrane, provide critical binding sites for calcium and coagulation factors in the intrinsic coagulation pathway.[2,3] The cell membrane is supported by a network of microtubules, actin filaments, myosin, and actin-binding proteins. They are arranged circumferentially and are responsible for maintaining the platelet's disk shape.

Hemostasis

- Hemostasis is an orderly, stepwise process that begins when a loss of endothelial integrity causes platelet activation.
- Upon activation, platelets undergo adhesion, granule release, and aggregation to form a primary platelet plug.
- The formation of the secondary hemostatic plug requires activation of the coagulation cascade, which terminates with thrombin converting fibrinogen into insoluble fibrin, which helps to form an insoluble hemostatic clot.
- The final step of the process involves fibrinolysis or clot dissolution, which prevents excess clot formation.

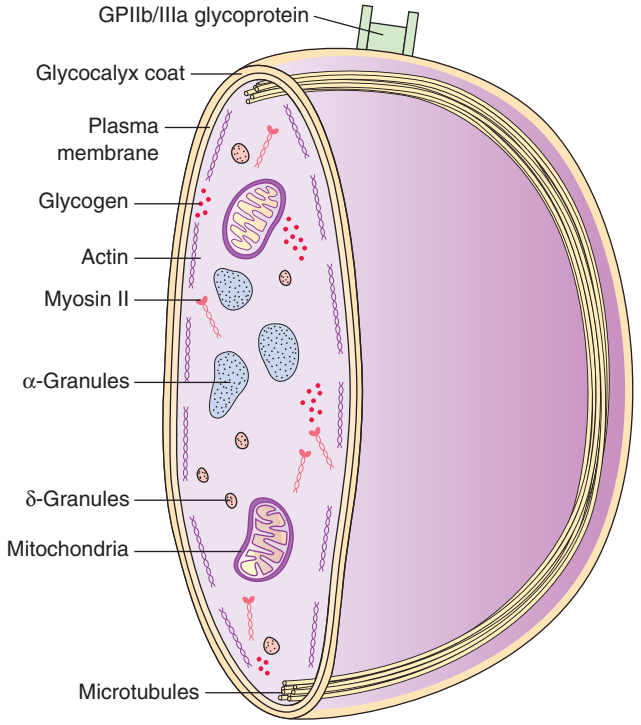


FIGURE 12-2. Platelet structure.

The central part of the platelet contains mitochondria, enzymes needed for synthesis of adenosine triphosphate (ATP) and the prostaglandin thromboxane A_2 (TXA_2), glycogen, and two specific types of granules (α- and δ-granules) that release mediators for hemostasis.[2–4] The α-granules contain fibrinogen, coagulation factors, plasminogen, plasminogen activator inhibitor, and platelet-derived growth factors. The contents of these granules play an important role in platelet aggregation, blood coagulation, and the initial phase of vessel repair. The release of growth factors causes vascular endothelial cells, smooth muscle cells, and fibroblasts to proliferate and grow. The δ-granules, or dense granules, mainly contain adenosine diphosphate (ADP), ATP, ionized calcium, serotonin, and histamine, which facilitate platelet adhesion and vasoconstriction at the site of vessel injury.

The Coagulation System

The coagulation system uses plasma proteins that are present as inactive procoagulation factors. Each of the procoagulation or coagulation factors, identified by Roman numerals, performs a specific step in the coagulation process. The activation of one procoagulation factor or proenzyme is designed to activate the next factor in the sequence (i.e., cascade effect). Because most of the inactive procoagulation factors are present in the blood at all times, the multistep process ensures that a massive episode of intravascular clotting does not occur by chance. It also means that abnormalities of the clotting process occur when one or more of the factors are deficient or when conditions lead to inappropriate activation of any of the steps.

Most of the coagulation factors are proteins synthesized in the liver. Vitamin K is necessary for the synthesis of factors VII, IX, and X; prothrombin; and protein C. Calcium (factor IV) is required in all but the first two steps of the clotting process. The body usually has sufficient amounts of calcium for these reactions. Inactivation of the calcium ion prevents blood from clotting when it is removed from the body. The addition of citrate to blood stored for transfusion purposes prevents clotting by chelating ionic calcium.

A clot is not meant to be a permanent solution to vessel injury; thus, blood clotting is accompanied by processes designed to control the coagulation process and dissolve the clot once bleeding has been controlled. Blood coagulation is regulated by several natural anticoagulants, including antithrombin III and proteins C and S, which act as anticoagulants by inactivating some of the clotting factors (to be discussed). The plasma also contains a plasma protein called *plasminogen* that when activated is converted to plasmin, an enzyme capable of digesting the fibrin strands of the clot. In addition to removing clots that are no longer needed, plasmin functions continually to prevent clots from forming inappropriately.

Endothelium

The blood vessels themselves play an important role in preventing and controlling the formation of blood clots. Blood vessels are lined with endothelial cells that modulate several, and frequently opposite, stages of normal hemostasis. Under most circumstances endothelial cells maintain an environment that promotes blood flow by blocking platelet adhesion and activation, by inhibiting the coagulation process, and by lysing blood clots. It should be noted, however, that the endothelium can be activated by infectious agents, hemodynamic factors, plasma mediators, and cytokines that are liberated during the inflammatory process.

An intact endothelial surface prevents platelets and plasma coagulation factors from interacting with the underlying thrombogenic subendothelial extracellular matrix. Moreover, if platelets are activated, they are inhibited from adhering to the surrounding uninjured endothelium by endothelial prostacyclin (prostaglandin I_2 [PGI_2]) and nitric oxide (see Chapter 18). Both mediators are potent vasodilators and inhibitors of platelet aggregation. Endothelial cells also elaborate an enzyme called *adenosine diphosphatase* that degrades ADP and further inhibits platelet aggregation. The anticoagulant effects of endothelial cells are mediated by membrane-bound heparin and thrombomodulin, both of which inactivate thrombin. Endothelial cells also synthesize tissue plasminogen activator, promoting fibrinolytic activity that clears fibrin deposits from endothelial cell surfaces.

Although endothelial cells exhibit properties that inhibit blood clotting, they also are capable of exhibiting numerous procoagulant properties in response to injury and activation. An important function of activated endothelial cells is the synthesis of von Willebrand factor (to be discussed), which participates in platelet adhesion and blood clotting.

Clot Formation and Dissolution

Hemostasis is divided into five stages: (1) vessel spasm, (2) formation of the platelet plug, (3) blood coagulation or development of an insoluble fibrin clot, (4) clot retraction, and (5) clot dissolution.[1] During the process of hemostasis, hairlike fibrin strands glue the aggregated platelets together and intertwine to form the structural basis of the blood clot. In the presence of fibrin, plasma becomes gel-like and traps red blood cells and other formed elements in the blood (Fig. 12-1). Hemostasis is complete when fibrous tissue grows into the clot and seals the hole in the vessel.

Vessel Spasm

Vessel spasm is initiated by endothelial injury and caused by local and humoral mechanisms. It is a transient event, usually lasting less than 1 minute, that results from neural reflexes and humoral factors released from the traumatized tissue and blood platelets.[1] For smaller vessels, release of the vasoconstrictor TXA_2 is responsible for much of the vessel spasm.

Platelet Plug Formation

The platelet plug, the second line of defense, is initiated as platelets come in contact with the vessel wall. Small breaks in the vessel wall are often sealed with the platelet plug rather than a blood clot. Platelet plug formation involves adhesion, granule release, and aggregation of platelets.[3] Platelets are attracted to a damaged vessel wall, become activated, and change from smooth disks to spiny spheres, exposing glycoprotein receptors on their surfaces. Platelet adhesion requires a protein molecule called *von Willebrand factor* (vWF). This factor is produced by both megakaryocytes and endothelial cells and circulates in the blood as a carrier protein for coagulation factor VIII. Adhesion to the vessel subendothelial layer occurs when the platelet membrane receptor binds to vWF at the injury site, linking the platelet to exposed collagen fibers.

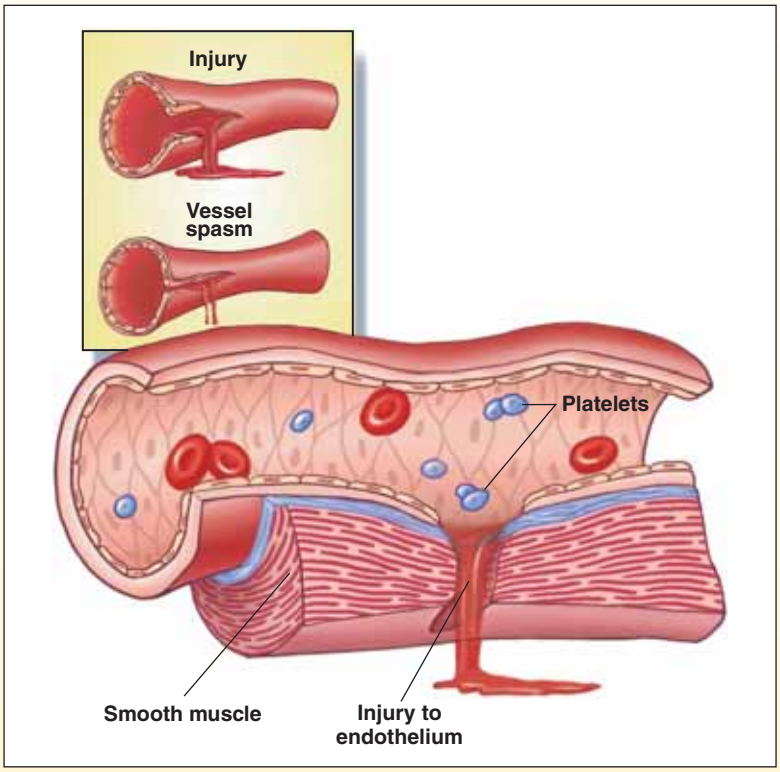
Degranulation and release of the contents of both the α- and δ-granules occur soon after platelet adhesion. The release of the δ-granule contents is particularly important because calcium is required for the coagulation component of hemostasis, and ADP is a mediator of platelet aggregation.[3] The binding of ADP to the platelet membrane induces a conformation change of the gpIIb/III a receptors, allowing them to bind fibrinogen and form aggregates. Besides ADP, platelets secrete the prostaglandin TXA_2, which is an important stimulus for platelet aggregation. The combined actions of ADP and TXA_2 lead to the expansion of the enlarging platelet aggregate, which is called the *primary hemostatic platelet plug*. Conversion of the primary platelet plug into a definitive clot (known as a *secondary hemostatic plug*) occurs as the coagulation pathway is activated on the surface of the aggregated platelets and fibrinogen is converted to fibrin, thereby creating a fibrin meshwork that cements the platelets and other blood components together.

UNDERSTANDING → Hemostasis

Hemostasis, which refers to the stoppage of blood flow, is divided into five stages: (1) vessel spasm, (2) formation of the platelet plug, (3) development of a blood clot as a result of the coagulation process, (4) clot retraction, and (5) clot dissolution. The process involves the interaction of substrates, enzymes, protein cofactors, and calcium ions that circulate in the blood or are released from platelets and cells in the vessel wall.

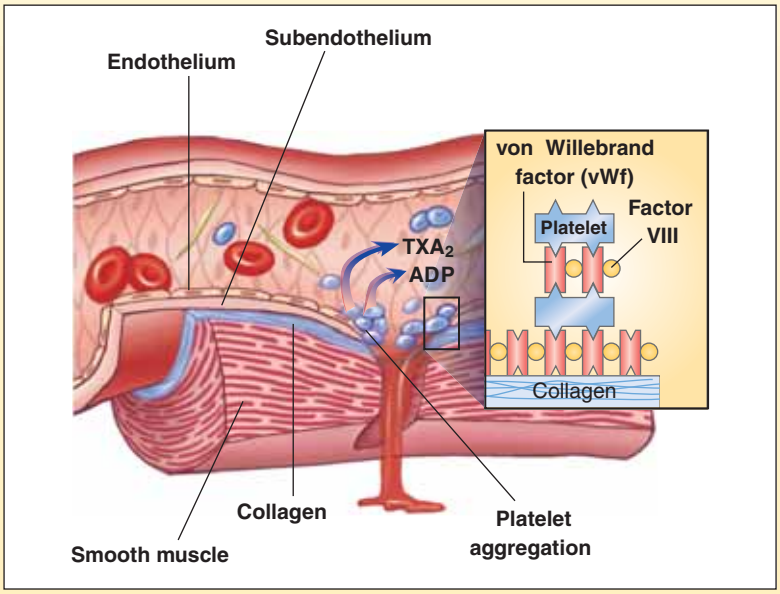
1

Vessel Spasm. Injury to a blood vessel causes vascular smooth muscle in the vessel wall to contract. This instantaneously reduces the flow of blood from the vessel rupture. Both local nervous reflexes and local humoral factors such as thromboxane A_2 (TXA_2), which is released from platelets, contribute to the vasoconstriction.



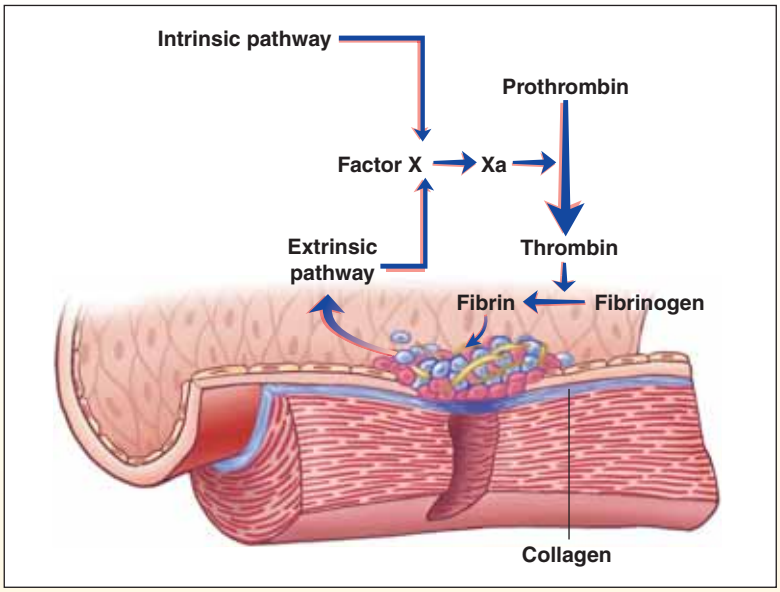
2

Formation of the Platelet Plug. Seconds after vessel injury, von Willebrand factor, released from the endothelium, binds to platelet receptors, causing adhesion of the platelets to the exposed collagen fibers (*inset*). As the platelets adhere to the collagen fibers on the damaged vessel wall, they become activated and release adenosine diphosphate (ADP) and TXA_2. The ADP and TXA_2 attract additional platelets, leading to platelet aggregation.



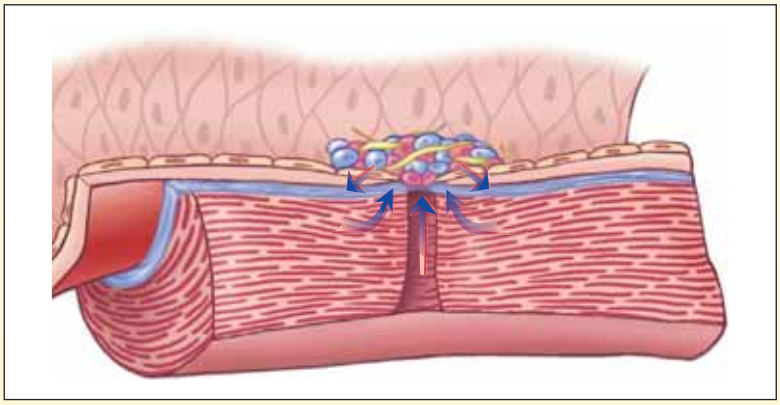
3

Blood Coagulation. Blood coagulation is a complex process involving the sequential activation of various factors in the blood. There are two coagulation pathways: (1) the intrinsic pathway begins in the circulation and is initiated by activation of circulating factor XII, and (2) the extrinsic pathway is activated by a cellular lipoprotein called *tissue factor* that becomes exposed when tissues are injured. Both pathways lead to the activation of factor X, conversion of prothrombin to thrombin, and conversion of fibrinogen to the insoluble fibrin threads that hold the clot together.



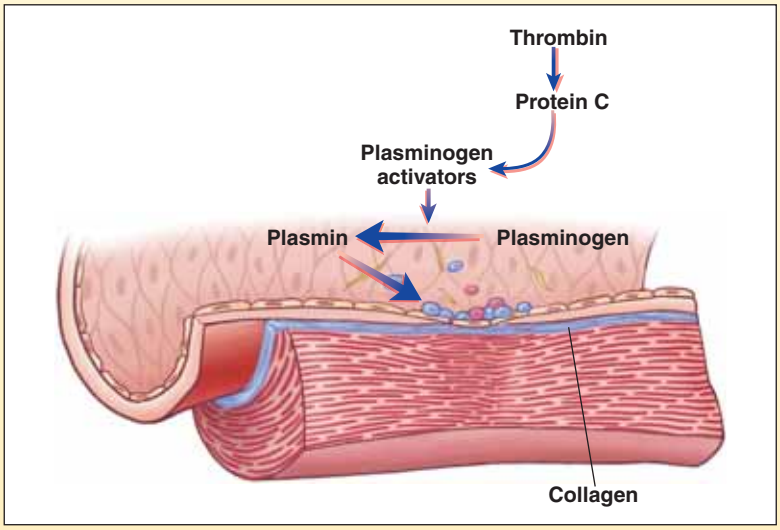
4

Clot Retraction. Within a few minutes after a clot is formed, the actin and myosin in the platelets that are trapped in the clot begin to contract in a manner similar to that in muscles. As a result, the fibrin strands of the clot are pulled toward the platelets, thereby squeezing serum (plasma without fibrinogen) from the clot and causing it to shrink.



5

Clot Dissolution or Lysis. Clot dissolution begins shortly after a clot is formed. It begins with activation of plasminogen, an inactive precursor of the proteolytic enzyme, plasmin. When a clot is formed, large amounts of plasminogen are trapped in the clot. The slow release of a very powerful activator called tissue plasminogen activator (t-PA) from injured tissues and vascular endothelium converts plasminogen to plasmin, which digests the fibrin strands, causing the clot to dissolve.



Platelet aggregation inhibitors, including aspirin, clopidogrel (Plavix), and ticlopidine (Ticlid), can be used to prevent platelet aggregation and clot formation in persons who are at risk for myocardial infarction, stroke, or peripheral artery disease.[5,6] Low-dose aspirin therapy inhibits prostaglandin synthesis, including TXA_2. Clopidogrel and ticlopidine achieve their antiplatelet effects by inhibiting the ADP pathway in platelets. Unlike aspirin, these drugs have no effect on prostaglandin synthesis. Drugs that act as gpIIb/IIIa receptor inhibitors (tirofiban, eptifibatide, abciximab) have been developed for use in the treatment of persons with acute coronary syndromes (see Chapter 19).[6]

The Coagulation Cascade

The coagulation cascade is the third component of the hemostatic process. It is a stepwise process resulting in the conversion of the soluble plasma protein fibrinogen into insoluble fibrin strands. The fibrin strands create a meshwork that cements platelets and other blood components together to form the clot.

The coagulation process results from the activation of what have traditionally been designated the *intrinsic* and the *extrinsic* pathways[1,3] (Fig. 12-3). The intrinsic pathway, which is a relatively slow process, begins in the circulation with the activation of factor XII (Hageman factor). The extrinsic pathway, which is a much faster process, begins with trauma to the blood vessel or surrounding tissues and the release of an adhesive lipoprotein called *tissue factor* (also known as thromboplastin or factor III) from the subendothelial cells. The terminal steps in both pathways are the same: the activation of factor X and the conversion of prothrombin to thrombin. Thrombin then acts as an enzyme to convert fibrinogen to fibrin, the material that stabilizes a clot. The intrinsic system is activated as blood comes in contact with collagen in the injured vessel wall; the extrinsic system is activated when blood is exposed to tissue extracts. However, this classification is largely artificial since both systems are needed for normal hemostasis, and many interrelations exist between them.[7] Moreover, each system is activated when blood passes out of the vascular system.

Clinical laboratories assess the function of the two limbs of the coagulation pathway through two standard assays: the *prothrombin time* (PT) and the *partial thromboplastin* time (PTT). The PT assesses the function of the extrinsic pathway (factors VII, X, II, V, and fibrinogen); whereas, the PTT assesses the function of the intrinsic pathway (factors XII, XI, IX, VII, X, V, II, and fibrinogen).[3]

Once initiated, the coagulation cascade must be restricted to the local site of vascular injury to prevent clotting from occurring in the entire vascular system. Several natural anticoagulants function to control clotting—antithrombin III, proteins C and S, and tissue factor pathway inhibitor.[4] Antithrombin III inhibits the activity of thrombin and factors IXa, Xa, XIa, and XIIa (see Fig. 12-3). It is activated by binding to heparin-like molecules on endothelial cells. Proteins C and S are two vitamin K–dependent plasma proteins that inactivate the cofactors Va and VIIIa. Tissue factor pathway inhibitor is a protein secreted by the endothelium that inactivates factor Xa and tissue factor VIIa complexes.

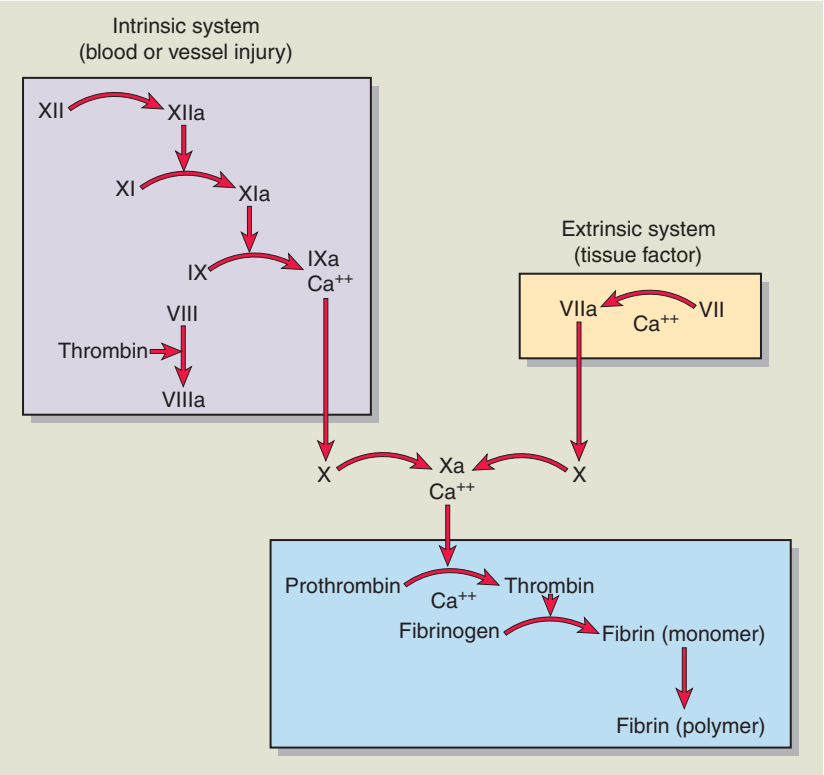


FIGURE 12-3. The intrinsic and extrinsic coagulation pathways. The terminal steps in both pathways are the same. Calcium, factors X and V, and platelet phospholipids combine to form prothrombin activator, which then converts prothrombin to thrombin. This interaction causes conversion of fibrinogen into the fibrin strands that create the insoluble blood clot.

The anticoagulant drugs warfarin and heparin are used to prevent thromboembolic disorders, such as deep vein thrombosis and pulmonary embolism.[6] Warfarin acts by decreasing prothrombin and other procoagulation factors. It alters vitamin K in a manner that reduces its ability to participate in the synthesis of the vitamin K–dependent coagulation factors in the liver. Warfarin is readily absorbed after oral administration. Its maximum effect takes 36 to 72 hours because of the varying half-lives of different clotting factors that remain in the circulation. Heparin is naturally formed and released in small amounts by mast cells in connective tissue surrounding capillaries. Heparin binds to antithrombin III, causing a conformational change that increases the ability of antithrombin III to inactivate thrombin, factor Xa, and other clotting factors. By promoting the inactivation of clotting factors, heparin ultimately suppresses the formation of fibrin. Pharmacologic preparations of heparin are extracted from animal tissues. Heparin is unable to cross the membranes of the gastrointestinal tract and must be given by injection, usually by intravenous infusion. Low–molecular-weight heparins have been developed that inhibit activation of factor X, but have little effect on thrombin and other coagulation factors. The low–molecular-weight heparins are given by subcutaneous injection and require less frequent administration and monitoring compared with the standard (unfractionated) heparin.

Clot Retraction

Clot retraction normally occurs within 20 to 60 minutes after a clot has formed, contributing to hemostasis by squeezing serum from the clot and joining the edges of the broken vessel. Platelets, through the action of their actin and myosin filaments, also contribute to clot retraction. Clot retraction therefore requires large numbers of platelets, and failure of clot retraction is indicative of a low platelet count.

Clot Dissolution

The dissolution of a blood clot begins shortly after its formation; this allows blood flow to be reestablished and permanent tissue repair to take place.[1] The process whereby the strands of the clot are dissolved is called *fibrinolysis*. As with clot formation, clot dissolution requires a sequence of steps controlled by activators and inhibitors. Plasminogen, the proenzyme for the fibrinolytic process, normally is present in the blood in its inactive form. It is converted to its active form, plasmin, by plasminogen activators (PAs) formed in the vascular endothelium, liver, and kidneys. The plasmin formed from plasminogen digests the fibrin strands of the clot and certain clotting factors, such as fibrinogen, factor V, factor VIII, prothrombin, and factor XII. The most important of the plasminogen activators is *tissue-type plasminogen activator* (tPA), which is synthesized principally by endothelial cells and is most active when attached to fibrin. The affinity of tPA for fibrin makes it a useful therapeutic agent, since it largely confines its activity to sites of recent thrombosis.[3] Another plasminogen activator called *urokinase-type plasminogen activator* (uPA) is present in the tissues and can activate plasminogen in the fluid phase.

As with other potent physiologic systems, the activity of plasmin is tightly controlled. Excess circulating plasmin is rapidly inactivated by α_2-antiplasmin, which limits the fibrinolytic process to the local clot rather than occurring throughout the entire circulation.[3] Endothelial cells further modulate the coagulation/anticoagulation process by releasing PA inhibitors, which block fibrinolysis and confer an overall procoagulation effect. The PA inhibitors are increased by certain cytokines and probably play a role in the intravascular thrombosis accompanying severe inflammation.

In summary, hemostasis is a multistep process that transforms blood into a semisolid clot with erythrocytes trapped in its fibrin meshwork. It involves platelets, plasma clotting factors, naturally occurring anticoagulants, and the endothelial cells that line blood vessels. The process of hemostasis is divided into five phases: vessel spasm, which constricts the size of the vessel and reduces blood flow; platelet adherence and formation of the platelet plug; formation of the fibrin clot, which cements the platelet plug together; clot retraction, which pulls the edges of the injured vessel together; and clot dissolution, which involves the action of plasmin to dissolve the clot and allow blood flow to be reestablished and tissue healing to take place. Blood coagulation requires the stepwise activation of coagulation factors, carefully controlled by activators and inhibitors.

Hypercoagulability States

Hypercoagulability represents an exaggerated form of hemostasis that predisposes to thrombosis and blood vessel occlusion. There are two general forms of hypercoagulability states: conditions that create increased platelet function and conditions that cause accelerated activity of the coagulation system. Chart 12-1 summarizes conditions commonly associated with hypercoagulability states. Arterial thrombi are usually due to turbulence and composed largely of platelet aggregates, whereas venous thrombi are usually due to stasis of flow and composed largely of platelet aggregates and fibrin complexes that result from activation of the coagulation cascade.

Increased Platelet Function

Increased platelet function predisposes to platelet adhesion, formation of platelet clots, and the disruption of blood flow. The causes of increased platelet function include an increase in platelet numbers and disturbances in blood flow, damage to the vascular endothelium, and increased sensitivity of platelets to factors that cause adhesiveness and aggregation.

CHART 12-1 Conditions Associated with Hypercoagulability States

Increased Platelet Function

Increased platelet numbers
- Reactive disorder (iron-deficiency anemia, splenectomy, cancer, chronic inflammatory conditions)
- Myeloproliferative disorders (polycythemia vera)

Endothelial injury
- Atherosclerosis
- Elevated blood lipid and cholesterol levels
- Smoking

Accelerated Activity of the Clotting System

Inherited disorders (primary)
- Mutation in the factor V gene (factor V Leiden)
- Mutation in the prothrombin gene

Acquired (secondary)
- Prolonged bed rest or immobility
- Oral contraceptive agents and pregnancy
- Myocardial infarction
- Heart failure
- Malignant diseases
- Antiphospholipid antibody syndrome

The term *thrombocytosis* is used to describe elevations in the platelet count above 1,000,000/μL.[8] An increase in platelet counts can occur as a reactive disorder associated with iron-deficiency anemia, especially in children; splenectomy; cancer; and chronic inflammatory conditions such as rheumatoid arthritis and Crohn disease. Usually the only clinically apparent signs are those of the underlying disease. Myeloproliferative disorders such as polycythemia vera (see Chapter 14) produce excess platelets that may predispose to thrombosis or, paradoxically, bleeding when the rapidly produced platelets are defective.

Atherosclerotic plaques disturb blood flow, causing endothelial damage and promoting platelet adherence. Platelets that adhere to the vessel wall release growth factors that cause proliferation of smooth muscle and thereby contribute to the development of atherosclerosis (discussed in Chapter 18). Smoking, elevated levels of blood lipids and cholesterol, hemodynamic stress, and diabetes mellitus predispose to vessel damage, platelet adherence, and eventual thrombosis.

Hypercoagulability States

- Hypercoagulability states increase the risk of clot or thrombus formation in either the arterial or venous circulations.
- Arterial thrombi are associated with conditions that produce an increase in platelet numbers or turbulence in blood flow with platelet adhesion.
- Venous thrombi are associated with inherited or acquired conditions that cause a decrease in anticoagulation factors or produce a stasis of blood, thereby causing an increase in procoagulation factors.

Increased Clotting Activity

Thrombus formation due to activation of the coagulation system can result from primary (genetic) or secondary (acquired) disorders affecting the coagulation components of the blood clotting process (i.e., an increase in procoagulation factors or a decrease in anticoagulation factors).

Inherited Disorders

Of the inherited causes of hypercoagulability, mutations in the factor V gene and prothrombin gene are the most common.[4,9] In persons with inherited defects in factor V, the mutant factor Va cannot be inactivated by protein C; as a result, an important antithrombotic counterregulatory mechanism is lost. Approximately 2% to 5% of Caucasians carry a specific factor V mutation (referred to as the *Leiden mutation*, because of the Dutch city where it was first discovered).[3] The defect predisposes to venous thrombosis, and among persons with recurrent deep vein thrombosis, the frequency of the mutation may be as high as 60%.[3] It is one of the most common causes of primary and recurrent thromboembolism in pregnancy and is also associated with abruptio placentae (premature placental separation) and fetal growth disturbance.[9]

A single nucleotide change in the prothrombin gene, which affects 1% to 2% of the population, is associated with elevated prothrombin levels and an almost threefold increase in venous thromboses.[4] Another hereditary defect results in high circulating levels of homocysteine, which predisposes to venous and arterial thrombosis by activating platelets and altering antithrombotic mechanisms.[4]

Acquired Disorders

Unlike the hereditary disorders, the conditions that predispose to acquired or secondary thrombotic disorders are often multiple. In some situations, such as prolonged bed rest and immobility, stasis of blood and accumulation of activated clotting factors and platelets are most common. Hyperviscosity syndromes (e.g., polycythemia) and deformed red blood cells in sickle cell disease increase the resistance to flow and cause small vessel stasis. Hypercoagulability is associated with oral contraceptive use and the hyperestrogenic state of pregnancy, probably related to the increased synthesis of coagulation factors and reduced synthesis of antithrombin III.[10] The incidence of stroke, thromboemboli, and myocardial infarction is greater in women who use oral contraceptives, particularly those older than 35 years of age and those who are heavy smokers. In disseminated cancer, release of procoagulant tumor products predisposes to thrombosis. Smoking and obesity promote hypercoagulability for unknown reasons.

Antiphospholipid Syndrome. Another cause of increased venous and arterial thrombosis is the *antiphospholipid syndrome*. The condition is associated with a family

of autoantibodies directed against several negatively charged phospholipids that results in increased coagulation activity. How antiphospholipid antibodies lead to hypercoagulability is unclear, but possible explanations include direct platelet activation, endothelial cell activation or injury, or interference with the phospholipid-binding proteins involved in the regulation of blood coagulation (e.g., tissue factor, prothrombin, antithrombin III, and protein C).[11,12] Common features of the disorder include recurrent thrombosis, repeated fetal loss, and thrombocytopenia. The disorder can be manifest as a primary condition occurring in isolation with signs of hypercoagulability or as a secondary condition most often associated with connective tissue disorders, particularly systemic lupus erythematosus.

Persons with the disorder present with a variety of clinical manifestations, typically those characterized by recurrent venous and arterial thrombi. Cardiac valvular vegetations associated with thrombi adherence and thrombocytopenia due to excessive platelet consumption may also occur. Venous thrombosis, especially in the deep leg veins, occurs in up to 50% of persons with the syndrome, half of whom develop pulmonary emboli. Arterial thromboses are less common than venous thromboses and most frequently manifest with features of ischemia and infarction. The cerebral arteries are the most commonly affected. Other sites for arterial thrombosis are the coronary arteries of the heart and the retinal, renal, and peripheral arteries. Women with the disorder commonly have a history of recurrent pregnancy losses after the 10th week of gestation because of ischemia and thrombosis of the placental vessels. These women also have increased risk of giving birth to a premature infant owing to pregnancy-associated hypertension and uteroplacental insufficiency.

In most persons with antiphospholipid syndrome, the thrombotic events occur as a single episode at one anatomic site. In some persons recurrences may occur months or years later and mimic the initial event. Occasionally, someone may present with multiple vascular occlusions involving many organ systems. This rapid-onset condition is termed *catastrophic antiphospholipid syndrome* and is associated with a high mortality rate.

Treatment of the syndrome focuses on removal or reduction in factors that predispose to thrombosis, including advice to stop smoking and counseling against use of estrogen-containing oral contraceptives by women. The acute thrombotic event is treated with anticoagulants (heparin and warfarin) and immune suppression in refractory cases. Aspirin and anticoagulant drugs may be used to prevent future thrombosis.[13]

In summary, hypercoagulability causes excessive clotting and contributes to thrombus formation. It results from conditions that foster an increase in platelet numbers or function or accelerated activity of the coagulation system. Thrombocytosis, an elevation in the platelet count, can occur as a reactive process (secondary thrombocytosis) or an essential process (primary thrombocytosis). Increased platelet function usually results from disorders such as atherosclerosis that damage the vascular endothelium and disturb blood flow or from conditions such as smoking that increase sensitivity of platelets to factors that promote adhesiveness and aggregation.

Factors that cause accelerated activity of the coagulation system include blood flow stasis, resulting in an accumulation of coagulation factors, and alterations in the components of the coagulation system (i.e., an increase in procoagulation factors or a decrease in anticoagulation factors). The antiphospholipid syndrome, another cause of venous and arterial clotting, manifests as a primary disorder or a secondary disorder associated with systemic lupus erythematosus. It is associated with antiphospholipid antibodies, which promote thrombosis that can affect many organs.

Bleeding Disorders

Bleeding disorders or impairment of blood coagulation can result from defects in any of the factors that contribute to hemostasis. Bleeding can occur as a result of disorders associated with platelet number or function, coagulation factors, and blood vessel integrity.

Platelet Disorders

Bleeding due to platelet disorders reflects a failure of activated platelets to bring about hemostasis through the formation of a platelet plug at the site of injury to the blood vessel wall that causes physical or biochemical disruption of the endothelium.

Bleeding Disorders

- Bleeding disorders are caused by defects associated with platelets, coagulation factors, and vessel integrity.
- Disorders of platelet plug formation include a decrease in platelet numbers due to inadequate platelet production (bone marrow dysfunction), excess platelet destruction (thrombocytopenia), abnormal platelet function (thrombocytopathia), or defects in von Willebrand factor.
- Impairment of the coagulation stage of hemostasis is caused by a deficiency in one or more of the clotting factors.
- Disorders of blood vessel integrity result from structurally weak vessels or vessel damage due to inflammation and immune mechanisms.

Thrombocytopenia

Thrombocytopenia refers to a decrease in the number of circulating platelets to a level less than 100,000/μL.[14] The greater the decrease in the platelet count, the greater the risk of bleeding. However, spontaneous bleeding usually does not occur until the platelet count falls below 20,000/μL.

The anatomic sites of bleeding in persons with thrombocytopenia are the intercellular junctions in the postcapillary venules.[15] Key molecules in the junctions include adhesive proteins and associated intracellular binding components (see Chapter 1). Different vascular beds with varying functions require different types of junctions. For example, the regulatory control of capillary permeability in the skin and mucosal surfaces is far different from that in the brain. Common sites for spontaneous bleeding from platelet disorders are the skin and mucous membranes of the nose, mouth, gastrointestinal tract, and uterine cavity. Cutaneous bleeding is seen as purple areas of bruising (purpura) and pinpoint hemorrhages (petechiae) in dependent areas where the capillary pressure is higher. Petechiae are seen almost exclusively in conditions of platelet deficiency, and not platelet dysfunction. They are also seen in conditions of poor collagen synthesis and impaired formation of capillary intercellular junctions (Fig. 12-4). Because tight regulation of capillary permeability in the brain is essential to prevent intercellular leakage, nontraumatic intracranial bleeding is relatively rare, even in persons with severe thrombocytopenia.[15]

The major causes of thrombocytopenia are decreased platelet production, decreased platelet survival, splenic sequestration, and dilution.[14] Decreased platelet production due to loss of bone marrow function may occur because of congenital anemia (e.g., Wiskott-Aldrich syndrome [see Chapter 16]) or acquired anemia (e.g., aplastic anemia [see Chapter 13]), bone marrow infiltration by malignant cells (e.g., leukemia), or bone marrow depression (e.g., radiation therapy, chemotherapy). Infection with human immunodeficiency virus (HIV) or cytomegalovirus may suppress the production of megakaryocytes, the platelet precursors.

Reduced platelet survival is caused by a variety of immune and nonimmune mechanisms. Platelet destruction may be caused by antiplatelet antibodies. The antibodies may be directed against platelet self-antigens or against antigens on the platelets from blood transfusions or pregnancy. In acute disseminated intravascular clotting or thrombotic thrombocytopenic purpura, excessive platelet consumption leads to a deficiency.

Production of platelets may be normal, but excessive pooling of platelets in the spleen may occur. When necessary, hypersplenic thrombocytopenia may be treated with splenectomy. Massive blood or plasma transfusions may cause a dilutional thrombocytopenia because blood stored for more than 24 hours has no viable platelets.

FIGURE 12-4. Leg of a 9-year-old boy with petechiae due to a vitamin C deficiency. (From Duggan C.P., Westra S.J., Rosenberg A.E. [2007]. Case 23-2007: A 9-year-old body with bone pain, rash, and gingival hyperplasia. *New England Journal of Medicine* 357, 395.)

Immune Thrombocytopenic Purpura. Immune thrombocytopenic purpura (ITP), an autoimmune disorder, results in platelet antibody formation and excess destruction of platelets. The thrombocytopenia that occurs in ITP is thought to result from multiple mechanisms, including antiplatelet antibodies against glycoproteins (IIb/IIIa and Ib/IX) in the platelet membrane. The platelets, which are made more susceptible to phagocytosis because of the antibody, are destroyed in the spleen.[16] The disorder can occur in the absence of any known risk factors (primary or idiopathic ITP) or as a secondary disorder due to an underlying disorder, and as an acute (duration of 6 months or less) or chronic disorder. Secondary forms of ITP may be associated with acquired immunodeficiency syndrome (AIDS), systemic lupus erythematosus, antiphospholipid syndrome, chronic lymphocytic leukemia, lymphoma, hepatitis C, and drugs such as heparin and quinidine.

About half of the cases of ITP occur as an acute primary disorder in children, affecting both boys and girls.[17] The disorder occurs in young children (5 years of age) and usually follows a viral infection. It is characterized by sudden onset of petechiae and purpura and is usually a self-limited disorder requiring no treatment. Most children recover in a few weeks. In contrast, primary ITP is often a chronic disorder in adults with an insidious onset that seldom follows an infection. It is a disease of young people, with a peak incidence between the ages of 18 and 40 years, and is seen three times as often in women as in men.

Manifestations of ITP include a history of bruising, bleeding from gums, epistaxis (i.e., nosebleed), melena, and abnormal menstrual bleeding in those with moderately reduced platelet counts. Because the spleen is the site of platelet destruction, splenic enlargement may occur. The condition may be discovered incidentally or as a result of signs of bleeding, often into the skin (i.e., purpura and petechiae) or oral mucosa. About half of adults with primary ITP present with a platelet count of less than 10,000/μL and are at risk for internal hemorrhage.[17]

Diagnosis of ITP usually is based on severe thrombocytopenia (platelet counts <20,000 to 30,000/μL) and exclusion of other causes. Tests for the platelet-bound antibodies are available but lack specificity (e.g., they react with platelet antibodies from other sources). The secondary form of ITP sometimes mimics the idiopathic form of the disorder; therefore, the diagnosis is made only after excluding other known causes of thrombocytopenia.

The decision to treat ITP is based on the platelet count and the degree of bleeding. Many persons with ITP do well without treatment. Corticosteroids are usually used as initial therapy. Other effective initial treatments include intravenous immune globulin. However, this treatment is expensive and the beneficial effect lasts only 1 to 2 weeks. Because the spleen is the major site of antibody formation and platelet destruction, splenectomy is the traditional second-line treatment for persons who relapse or do not respond to drugs.[17] Immunosuppressive therapy may be used for persons who are refractory to other forms of treatment.

Drug-Induced Thrombocytopenia. Some drugs, such as quinine, quinidine, and certain sulfa-containing antibiotics, may induce thrombocytopenia.[18] These drugs act as haptens to induce an antigen–antibody response and formation of immune complexes that cause platelet destruction by complement-mediated lysis (see Chapter 15). In persons with drug-associated thrombocytopenia, there is a rapid fall in the platelet count within 2 to 3 days of resuming a drug or 7 or more days (i.e., the time needed to mount an immune response) after starting a drug for the first time. The platelet count rises rapidly after the drug is discontinued.

The anticoagulant drug heparin has been increasingly implicated in thrombocytopenia and, paradoxically, in thrombosis. The complications typically occur 5 days after the start of therapy and result from heparin-dependent antiplatelet antibodies that cause aggregation of platelets and their removal from the circulation. The antibodies often bind to vessel walls, causing complications such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke.[19] The treatment of heparin-induced thrombocytopenia requires the immediate discontinuation of heparin therapy and the use of alternative anticoagulants to prevent thrombosis recurrence. The newer low–molecular-weight heparin has been shown to be effective in reducing the incidence of heparin-induced complications compared with the older, high–molecular-weight form of the drug.

Thrombotic Microangiopathies. The term *thrombotic microangiopathies* encompasses a spectrum of clinical syndromes that include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS).[14] As originally described, TTP is associated with a combination of manifestations that includes fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and transient neurologic abnormalities. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia, but is distinguished from TTP by the dominance of acute renal failure and absence of neurologic manifestations. Fundamental to both conditions is the widespread formation of hyaline thrombi in the microcirculation that are composed primarily of dense aggregates of platelets surrounded by fibrin. The consumption of platelets leads to thrombocytopenia, and the narrowing of the blood vessels by the platelet-rich thrombi results in the microangiopathic hemolytic anemia.

The pathogenesis of TTP is elusive but likely results from introduction of platelet—aggregating substances into the circulation. The underlying cause of many cases is the deficiency of an enzyme (designated ADAMTS 13) that degrades very high–molecular–weight multimers of vWF, allowing them to accumulate and cause platelet aggregation and adhesion to the endothelium.[4,14] The enzyme deficiency may be inherited or acquired as a result of antibody directed against the enzyme. Although TTP usually occurs in previously healthy persons, it may also complicate collagen vascular diseases (rheumatoid arthritis and systemic lupus erythematosus), drug-induced hypersensitivities, cancer chemotherapy, bone marrow transplantation, infections such as HIV, and pregnancy.[4]

TTP occurs at virtually every age, but is most common in women in the fourth and fifth decades. It may be chronic and recurrent, but more frequently the onset is abrupt and the outcome may be fatal. Widespread vascular occlusions result from thrombi in the arterioles and capillaries of many organs, including the heart, brain, and kidneys. The clinical manifestations include purpura, petechiae, vaginal bleeding, and neurologic symptoms ranging from headache to seizures and altered consciousness. Anemia is universal and may be marked. About half of patients have azotemia due to renal failure.[4]

Emergency treatment for TTP includes *plasmapheresis,* a procedure that involves removal of plasma from withdrawn blood and replacement with fresh-frozen plasma. Plasma infusion provides the deficient enzyme. With plasmapheresis and plasma infusion treatment, there is a complete recovery in 80% of cases.[4]

Although clinically similar to TTP, there is no underlying enzyme deficiency in HUS, because ADAMTS 13 levels are normal. HUS in children and the elderly usually occurs subsequent to infectious gastroenteritis caused by *Escherichia coli* O157:H7[14] (see Chapter 29). The organism elaborates a toxin that damages endothelial cells, which initiates platelet activation and aggregation. Affected individuals often present with bloody diarrhea, which is followed a few days later by HUS. With supportive care and plasma exchange, recovery is possible, but irreversible renal damage and death can occur in severe cases.[14]

Impaired Platelet Function

Impaired platelet function (also called *thrombocytopathia*) may result from inherited disorders of adhesion (e.g., von Willebrand disease) or acquired defects caused by drugs, disease, or surgery involving extracorporeal circulation (i.e., cardiopulmonary bypass). Defective platelet function is also common in uremia, presumably because of unexcreted waste products.

The use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is the most common cause of impaired platelet function. Aspirin produces irreversible acetylation of platelet cyclooxygenase activity and consequently the synthesis of TXA_2, which is required for platelet aggregation. The effect of aspirin on platelet aggregation lasts for the life of the platelet—usually approximately 8 to 9 days. In contrast to the effects of aspirin, the inhibition of cyclooxygenase by other NSAIDs is reversible and lasts only for the duration of drug action. Aspirin (81 mg daily) commonly is used to prevent formation of arterial thrombi and reduce the risk for heart attack and stroke.

Coagulation Disorders

Blood coagulation defects can result from deficiencies or impaired function of one or more of the clotting factors, including vWF. Deficiencies can arise because of inherited disease or because of defective synthesis or increased consumption of the clotting factors. Bleeding resulting from clotting factor deficiencies typically occurs after injury or trauma. Large bruises, hematomas, and prolonged bleeding into the gastrointestinal or urinary tracts or joints are common.

Inherited Disorders

Hemophilia A and von Willebrand disease are two of the most common inherited disorders of bleeding. Hemophilia A (factor VIII deficiency) affects 1 in 5000 male live births and von Willebrand disease more than 1 in 1000 persons.[20] Hemophilia B, a deficiency of factor IX, occurs in approximately 1 in 20,000 persons, accounting for 15% of people with hemophilia.[4] It is genetically and clinically similar to hemophilia A.

Hemophilia A and von Willebrand disease are caused by defects involving the factor VIII–vWF complex. Von Willebrand factor, which is synthesized by the endothelium and megakaryocytes, is required for platelet adhesion to the subendothelial matrix of the blood vessel. It also serves as the carrier for factor VIII and is important for the stability of factor VIII in the circulation by preventing its proteolysis. Factor VIII coagulant protein, the functional portion, is produced by the liver and endothelial cells. Thus, factor VIII and vWF, synthesized separately, come together and circulate in the plasma as a unit that serves to promote clotting and adhesion of platelets to the vessel wall.

Von Willebrand Disease. Von Willebrand disease is a relatively common hereditary bleeding disorder characterized by a deficiency or defect in vWF. It affects both men and women and is typically diagnosed in adulthood.[21,22] In most cases, it is transmitted as an autosomal dominant disorder, but several rare autosomal recessive variants have been identified.[14]

As many as 20 variants of von Willebrand disease have been described.[4] These variants can be grouped into two categories: types 1 and 3, which are associated with reduced levels of vWF, and type 2, which is characterized by defects in vWF.[4] Type 1, an autosomal dominant disorder, accounts for approximately 75% of cases and is relatively mild. Type 2, also an autosomal dominant disorder, accounts for about 20% of cases and is associated with mild to moderate bleeding. Type 3, which is a relatively rare autosomal recessive disorder, is associated with extremely low levels of functional vWF and correspondingly severe clinical manifestations.

Persons with von Willebrand disease have a compound defect involving platelet function and the coagulation pathway. Clinical manifestations include spontaneous bleeding from the nose, mouth, and gastrointestinal tract; excessive menstrual flow; and a prolonged bleeding time in the presence of a normal platelet count. Most cases (i.e., types 1 and 2) are mild and the disorder is diagnosed when surgery or dental extraction results in prolonged bleeding. In severe cases (i.e., type 3), life-threatening gastrointestinal bleeding and joint hemorrhage may be similar to that seen in hemophilia.

The bleeding associated with von Willebrand disease is usually mild, and no treatment is routinely administered other than avoidance of aspirin. Desmopressin acetate (DDAVP), a synthetic analog of the hormone vasopressin, is used in the treatment of type 1 von Willebrand disease and for establishing hemostasis during surgical or dental procedures.[21,23] DDAVP stimulates the endothelial cells to release stored vWF and plasminogen activator. The drug is available as an intranasal spray. A vWF-containing factor VIII concentrate may be used for treatment of persons with excessive bleeding.[21]

Hemophilia A. Hemophilia A is an X-linked recessive disorder that primarily affects males. Although it is a hereditary disorder, there is no family history of the disorder in approximately 30% of newly diagnosed cases, suggesting that it has arisen as a new mutation in the factor VIII gene.[14] Approximately 90% of persons with hemophilia produce insufficient quantities of the factor and 10% produce a defective form. The percentage of normal factor VIII activity in the circulation depends on the genetic defect and determines the severity of hemophilia (i.e., 6% to 30% in mild hemophilia, 2% to 5% in moderate hemophilia, and 1% or less in severe forms of hemophilia). In mild or moderate forms of the disease, bleeding usually does not occur unless there is a local lesion or trauma such as surgery or a dental procedure. The mild disorder may not be detected in childhood. In severe hemophilia, bleeding usually occurs in childhood (e.g., it may be noticed at the time of circumcision) and is spontaneous and severe, often occurring several times a month.

Characteristically, bleeding occurs in soft tissues, the gastrointestinal tract, and the hip, knee, elbow, and ankle joints. Spontaneous joint bleeding usually begins when a child begins to walk. Often, a target joint is prone to repeated bleeding. The bleeding causes inflammation of the synovium, with acute pain and swelling. Without proper treatment, chronic bleeding and inflammation cause joint fibrosis and contractures, resulting in major disability. Muscle hematomas may be present in 30% of episodes, and intracranial hemorrhage, although uncommon, is an important cause of death.[23]

The prevention of trauma is important in persons with hemophilia. Aspirin and other NSAIDs that affect platelet function should be avoided. Factor VIII replacement therapy (either recombinant or heat-treated concentrates from human plasma) administered at home has reduced the typical musculoskeletal damage. It is initiated when bleeding occurs or as prophylaxis with repeated bleeding episodes. The newer recombinant products and continuous-infusion pumps may allow prevention rather than therapy for hemorrhage. The development of inhibitory antibodies to recombinant factor VIII is still a major complication of treatment; 10% to 15% of treated persons produce high titers of antibodies that bind to and inhibit factor VIII. The rate of antibody production for plasma-derived products is approximately the same.

Current factor VIII products (both plasma derived and recombinant) are considered very safe as a result of technological advances of the last two decades.[24] Until the mid-1980s, before routine screening of blood for HIV antibodies was instituted, thousands of patients with hemophilia received plasma-derived factor VIII that was contaminated with HIV, and many developed AIDS.[14] Effective donor screening and development of purification and viral inactivation procedures now provide a safer product. A number of recombinant factor VIII preparations are available. These products were made with the use of blood-derived additives of human or animal origin, such as albumin. These additives were needed to keep the cells viable so they could produce the factor VIII protein. With mild hemophilia A, the person's endogenously produced factor VIII can be released by the administration of DDAVP.[25] In persons with moderate to severe factor VIII deficiency, the stored levels of factor VIII are insufficient, and DDAVP treatment is ineffective.

The cloning of the factor VIII gene and progress in gene delivery systems have led to the hope that hemophilia A may be cured by gene replacement therapy. Carrier detection and prenatal diagnosis can now be done by analysis of direct gene mutation or DNA linkage studies.

Acquired Disorders

Coagulation factors II, V, VII, IX, X, XI, and XII; prothrombin; and fibrinogen are synthesized in the liver. In liver disease, synthesis of these clotting factors is reduced, and bleeding may result. Of the coagulation factors synthesized in the liver, factors II, VII, IX, and X and prothrombin require the presence of vitamin K for normal activity. In vitamin K deficiency, the liver produces the clotting factor, but in an inactive form. Vitamin K is a fat-soluble vitamin that is continuously being synthesized by intestinal bacteria. This means that a deficiency in vitamin K is not likely to occur unless intestinal synthesis is interrupted or absorption of the vitamin is impaired. Vitamin K deficiency can occur in the newborn infant before the establishment of the intestinal flora; it can also occur as a result of treatment with broad-spectrum antibiotics that destroy intestinal flora. Because vitamin K is a fat-soluble vitamin, its absorption requires bile salts. Vitamin K deficiency may result from impaired fat absorption caused by liver or gallbladder disease.

Bleeding Associated with Vascular Disorders

Bleeding resulting from vascular disorders, sometimes called *nonthrombocytopenic purpura,* is relatively common and results in mild bleeding disorders.[14] These disorders may occur because of structurally weak vessel walls or because of damage to vessels by inflammation or immune responses. Most often they are characterized by easy bruising and the spontaneous appearance of petechiae and purpura of the skin and mucous membranes. In persons with bleeding disorders caused by vascular defects, the platelet count and results of other tests for coagulation factors are normal.

Among the vascular disorders that cause bleeding are hemorrhagic telangiectasia, vitamin C deficiency (scurvy), Cushing disease, and senile purpura. Hemorrhagic telangiectasia is an uncommon autosomal dominant disorder that is characterized by thin-walled, dilated capillaries and arterioles. Vitamin C is a reversible reducing agent that is an essential cofactor for the hydroxylation of proline in collagen synthesis. A severe vitamin C deficiency results in poor collagen synthesis and failure of capillary cells to be cemented together properly, which causes a fragile vascular wall (Fig. 12-4). Cushing disease causes protein wasting and loss of vessel tissue support because of excess cortisol (see Chapter 32). Senile purpura (i.e., bruising in elderly persons) is caused by impaired collagen synthesis due to the aging process.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a paradox in the hemostatic sequence that is characterized by widespread coagulation and bleeding.[26–29] It is not a primary disease but a complication of many different disorders. DIC begins with massive activation of the coagulation sequence, which leads fibrin deposition and formation of thrombi in the microcirculation of the body (Fig. 12-5). The widespread deposition of fibrin leads to tissue ischemia and hemolytic anemia from fragmentation of red cells as they squeeze through the narrowed microvasculature. As a consequence of the thrombotic process, there is consumption of platelets and coagulation factors and the activation of plasminogen that leads to a hemorrhagic diathesis.

The disorder can be initiated by activation of the intrinsic or extrinsic pathway, or both. Activation through the extrinsic pathway occurs with liberation of tissue factors and is associated with obstetric complications, trauma, bacterial sepsis, and cancers. The intrinsic pathway may be activated through extensive endothelial damage, with activation of factor XII. Endothelial damage may be caused by viruses, infections, immune mechanisms, stasis of blood, or temperature extremes. Impaired anticoagulation pathways are also associated with reduced levels of antithrombin and the protein C anticoagulant system in DIC. There is increasing evidence that the underlying cause of DIC is infection or inflammation, and the

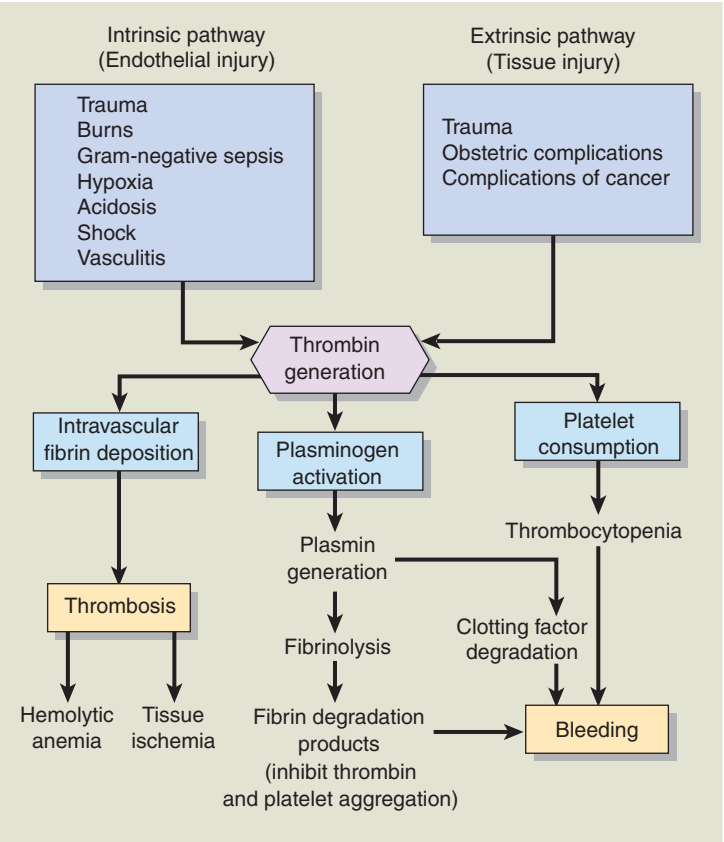


FIGURE 12-5. Pathophysiology of disseminated intravascular coagulation.

cytokines (tumor necrosis factor, interleukin-1, and others) liberated in the process are the pivotal mediators.[27,28] These cytokines not only mediate inflammation, but also can increase the expression of tissue factor on endothelial cells and simultaneously decrease the expression of thrombomodulin. Thrombomodulin, a glycoprotein that is present on the cell membrane of endothelial cells, binds thrombin and acts as an additional regulatory mechanism in coagulation. The net effect is a shift in balance toward a procoagulant state.[26]

Common clinical conditions that may cause DIC include obstetric disorders, accounting for 50% of cases; massive trauma; shock; sepsis; and malignant disease.[14] Chart 12-2 summarizes the conditions associated with DIC. The factors involved in the conditions that cause DIC are often interrelated. In obstetric complications, tissue factors released from necrotic placental or fetal tissue or amniotic fluid may enter the circulation, inciting DIC. The hypoxia, shock, and acidosis that may coexist also contribute by causing endothelial injury. Gram-negative bacterial infections result in the release of endotoxins, which activate both the extrinsic pathway by release of tissue factor and the intrinsic pathway through endothelial damage. Endotoxins also inhibit the activity of protein C. Antigen–antibody complexes associated with infection can activate platelets through complement fragments.[14]

Although coagulation and formation of microemboli characterize DIC, its acute manifestations usually are more directly related to the bleeding problems that occur.

CHART 12-2 Conditions That Have Been Associated with Disseminated Intravascular Coagulation

Obstetric Conditions
- Abruptio placentae
- Dead fetus syndrome
- Preeclampsia and eclampsia
- Amniotic fluid embolism

Cancers
- Metastatic cancer
- Acute promyelocytic leukemia

Infections
- Acute bacterial infections (e.g., meningococcal meningitis)
- Histoplasmosis, Aspergillosis
- Rickettsial infections (e.g., Rocky Mountain spotted fever)
- Parasitic infections (e.g., malaria)
- Sepsis/septic shock

Trauma or Surgery
- Burns
- Massive trauma
- Surgery involving extracorporeal circulation
- Snake bite
- Heatstroke

Hematologic Conditions
- Blood transfusion reactions

The bleeding may be present as petechiae, purpura, oozing from puncture sites, or severe hemorrhage. Uncontrolled postpartum bleeding may indicate DIC. Microemboli may obstruct blood vessels and cause tissue hypoxia and necrotic damage to organ structures, such as the kidneys, heart, lungs, and brain. As a result, common clinical signs may be due to renal, circulatory, or respiratory failure; acute bleeding ulcers; or convulsions and coma. A form of hemolytic anemia may develop as red cells are damaged passing through vessels partially blocked by thrombus.

The treatment of DIC is directed toward managing the primary disease, replacing clotting components, and preventing further activation of clotting mechanisms. Transfusions of fresh-frozen plasma, platelets, or fibrinogen-containing cryoprecipitate may correct the clotting factor deficiency. Heparin may be given to decrease blood coagulation, thereby interrupting the clotting process. Heparin therapy is controversial, however, and the risk of hemorrhage may limit its use to severe cases. It typically is given as a continuous intravenous infusion that can be interrupted promptly if bleeding is accentuated. Tissue factor pathway inhibitors, antithrombin, protein C concentrates, and anti-inflammatory cytokines such as interleukin-10 are being evaluated in clinical trials as potential therapies.[27]

In summary, bleeding disorders or impairment of blood coagulation can result from defects in any of the factors that contribute to hemostasis: platelets, coagulation factors, or vascular integrity. The number of circulating platelets can be decreased (i.e., thrombocytopenia) because of reduced bone marrow production, excess pooling in the spleen, or immune destruction. Impaired platelet function (i.e., thrombocytopathia) is caused by inherited disorders (von Willebrand disease) or results from drugs or disease. Impairment of blood coagulation can result from deficiencies of one or more of the known clotting factors. Deficiencies can arise because of acquired disorders (i.e., liver disease or vitamin K deficiency) or inherited diseases (i.e., hemophilia A or von Willebrand disease). Bleeding may also occur from structurally weak vessels that result from impaired synthesis of vessel wall components (i.e., vitamin C deficiency, excessive cortisol levels as in Cushing disease, or the aging process) or from damage by genetic mechanisms (i.e., hemorrhagic telangiectasia) or the presence of microthrombi.

Disseminated intravascular coagulation is characterized by widespread coagulation and bleeding in the vascular compartment. It begins with massive activation of the coagulation cascade and generation of microthrombi that cause vessel occlusion and tissue ischemia. Clot formation consumes all available coagulation proteins and platelets, and severe hemorrhage results.

REVIEW EXERCISES

1. A 55-year-old man has begun taking one 81-mg aspirin tablet daily on the recommendation of his physician. The physician had told him that this would help to prevent heart attack and stroke.

A. What is the action of aspirin in terms of heart attack and stroke prevention?
B. The drug clopidogrel (Plavix) is often prescribed along with aspirin to prevent thrombosis in persons with severe atherosclerotic disease who are at risk for myocardial infarction or stroke. Explain the rationale for using the two drugs.

2. The drug desmopressin acetate (DDAVP), which is a synthetic analog of arginine vasopressin, increases the half-life of factor VIII and is sometimes used to treat bleeding in males with mild hemophilia.

A. Explain.

3. A 29-year-old new mother, who delivered her infant 3 days ago, is admitted to the hospital with chest pain and is diagnosed as having venous thrombosis with pulmonary emboli.

A. What factors would contribute to this woman's risk of developing thromboemboli?

4. The new mother is admitted to the intensive care unit and started on low–molecular-weight heparin and warfarin. She is told that she will be discharged in a day or two and will remain on the heparin for 5 days and the warfarin for at least 3 months.

A. Use Figure 12-3 to explain the action of heparin and warfarin. Why is heparin administered for 5 days during the initiation of warfarin treatment?
B. Anticoagulation with heparin and warfarin is not a definitive treatment for clot removal in pulmonary embolism, but a form of secondary prevention. Explain.

REFERENCES

1. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 457–468). Philadelphia: Elsevier Saunders.
2. Ross M.H., Kaye G., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 262–264, 271–272). Philadelphia: Lippincott Williams & Wilkins.
3. Kumar V., Abbas A.K., Fausto N., Aster J.C. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., 115–125). Philadelphia: Saunders Elsevier.
4. Schwarting R., McKenzie S., Rubin R. (2008). Hematopathology. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 880–893). Philadelphia: Lippincott Williams & Wilkins.
5. Messmore H.L., Jeske W.P., Wehrmacher W., et al. (2005). Antiplatelet agents: Current drugs and future trends. *Hematology/Oncology Clinics of North America* 19, 87–117.

6. Zehnder J.L. (2007). Drugs used in disorders of coagulation. In Katzung B.G. (Ed.), *Basic and clinical pharmacology* (10th ed., pp. 542–559). New York: McGraw-Hill.
7. Furie B., Furie B.C. (2008). Mechanisms of thrombus formation. *New England Journal of Medicine* 359(9), 938–949.
8. Schafer, A.I. (2004). Thrombocytosis. *New England Journal of Medicine* 350, 1211–1219.
9. Bloomenthal D., von Dadelszen P., Liston R., et al. (2002). The effect of factor V Leiden carriage on maternal and fetal health. *Canadian Medical Association Journal* 167, 48–54.
10. Chrousos G.P., Zoumakis E.N., Gravania A. (2007). The gonadal hormones and inhibitors. In Katzung B.G. (Ed.), *Basic and clinical pharmacology* (10th ed., p. 658). New York: McGraw-Hill.
11. Levine J.S., Branch D.W., Rausch J. (2002). The antiphospholipid syndrome. *New England Journal of Medicine* 346, 752–763.
12. Hanly J.C. (2003). Antiphospholipid syndrome: An overview. *Canadian Medical Association Journal* 168, 1675–1682.
13. Lim W., Crowther M.A., Eikelboom J.W. (2006). Management of antiphospholipid antibody syndrome. *Journal of the American Medical Association* 295, 1050–1057.
14. Aster J.C. (2008). Hematopoietic and lymphoid systems. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.). *Robbins basic pathology* (8th ed., pp. 468–477). Philadelphia: Saunders Elsevier.
15. Nachman R.L., Rafii S. (2008). Platelets, petechiae, and preservation of the vascular wall. *New England Journal of Medicine* 359(12), 1261–1270.
16. Bromberg M.E. (2006). Immune thrombocytopenia purpura: The changing therapeutic landscape. *New England Journal of Medicine* 355, 1643–1645.
17. Cines D.B., Blanchette V.S. (2002). Immune thrombocytopenic purpura. *New England Journal of Medicine* 346, 995–1008.
18. van den Bemt P.M., Meyboom R.H., Egberts A.C. (2004). Drug-induced immune thrombocytopenia. *Drug Safety* 27, 1243–1252.
19. Franchini M. (2005). Heparin-induced thrombocytopenia: An update. *Thrombosis Journal* 3, 14–18.
20. Mannucci P.M., Tuddenham E.G.D. (2001). The hemophilias: From royal genes to gene therapy. *New England Journal of Medicine* 344, 1773–1779.
21. Mannucci P.M. (2004). Treatment of von Willebrand's disease. *New England Journal of Medicine* 351, 683–694.
22. Soliman D.E., Broadman L.M. (2006). Coagulation defects. *Anesthesiology Clinics* 24, 549–578.
23. Sadler J.V. (2005). New concepts in von Willebrand disease. *Annual Review of Medicine* 56, 173–180.
24. Klinge J., Ananyeva N.M., Hauser C., et al. (2002). Hemophilia A: From basic science to clinical practice. *Seminars in Thrombosis and Hemostasis* 28, 309–322.
25. Mannucci P.M. (1997). Desmopressin (DDAVP) in the treatment of bleeding disorders: The first 20 years. *Blood* 90, 2515–2521.
26. Kitchens C.S. (2009). Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). *Hematolology 2009*, 240–246.
27. Franchini M., Lippi G., Manzato F. (2006). Recent acquisitions in the pathophysiology, diagnosis and treatment of disseminated intravascular coagulation. *Thrombosis Journal* 4, 4–12.
28. Van der Poll T., Jonge E., Levi M. (2001). Regulatory role of cytokines in disseminated intravascular coagulation. *Seminars in Thrombosis and Hemostasis* 27, 639–651.
29. Levi M. (2007). Disseminated intravascular coagulation. *Critical Care Medicine* 35(9), 2191–2195.

The Red Blood Cell
Hemoglobin Synthesis
Red Cell Production
Red Cell Life Span and Destruction
Laboratory Tests
Anemia
Blood Loss Anemia
Hemolytic Anemias
Inherited Disorders of the Red Cell Membrane
Sickle Cell Disease
The Thalassemias
Inherited Enzyme Defects
Acquired Hemolytic Anemias
Anemias of Deficient Red Cell Production
Iron-Deficiency Anemia
Megaloblastic Anemias
Aplastic Anemia
Anemia of Chronic Disease
Polycythemia
Primary Polycythemia
Secondary Polycythemia
Age-Related Changes in Red Blood Cells
Red Cell Changes in the Neonate
Hyperbilirubinemia in the Neonate
Hemolytic Disease of the Newborn
Red Cell Changes in the Elderly

Chapter 13

Disorders of Red Blood Cells

Although the lungs provide the means for gas exchange between the external and internal environments, it is the hemoglobin in the red blood cells that transports oxygen to the tissues. The red blood cells also function as carriers of carbon dioxide and participate in acid-base balance. The function of the red blood cells, in terms of oxygen transport, is discussed in Chapter 21, and acid-base balance is discussed in Chapter 8. This chapter focuses on the red blood cell, anemia, transfusion therapy, polycythemia, and age-related changes in the red blood cells.

The Red Blood Cell

The erythrocytes or mature red blood cells are the most common type of blood cell, being 500 to 1000 times more numerous than other blood cells. The erythrocyte is a nonnucleated, thin, biconcave disk (Fig. 13-1). This unique shape contributes in two ways to the oxygen transport function of the erythrocyte. The biconcave shape provides a larger surface area for oxygen diffusion than would a spherical cell of the same volume, and the thinness of the cell membrane enables oxygen to diffuse rapidly between the exterior and the innermost regions of the cell[1–3] (Fig. 13-2A). Another structural feature that facilitates the transport function of the red blood cell is the flexibility of its membrane. The biconcave shape and flexibility of the red cell membrane are maintained by a complex network of fibrous proteins, especially one called *spectrin* (Fig. 13-3). Spectrin forms an attachment with another protein, called *ankyrin,* that resides on the inner surface of the membrane and is anchored to an integral protein that spans the membrane.[2] This unique arrangement of proteins imparts elasticity and stability to the membrane and allows it to deform easily as it moves through narrow spaces in the vascular network.

The function of the red blood cell, facilitated by the hemoglobin molecule, is to transport oxygen to the tissues. Because oxygen is poorly soluble in plasma, about 95% to 98% is carried bound to hemoglobin. The hemoglobin molecule is composed of two pairs of structurally different alpha (α) and beta (β) polypeptide chains (see

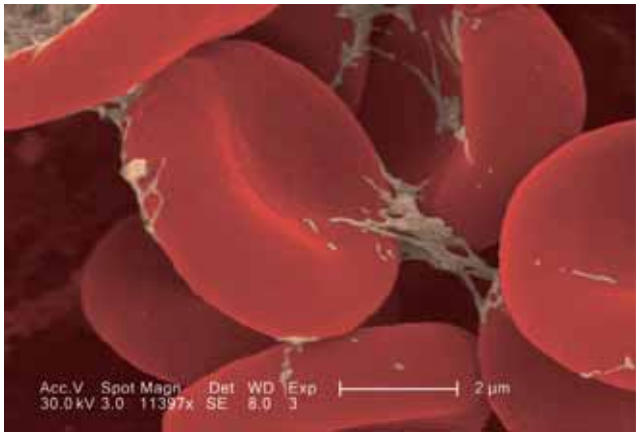


FIGURE 13-1. A highly magnified (×11,397) scanning electron micrograph of a number of red blood cells found enmeshed in a fibrinous matrix on the luminal surface of an indwelling vascular catheter. Note the biconcave shape of each erythrocyte, which increases the surface area of these hemoglobin-filled cells, thus promoting more effective gas exchange. (Centers for Disease Control and Prevention Public Images Library, Courtesy Janice Carr.)

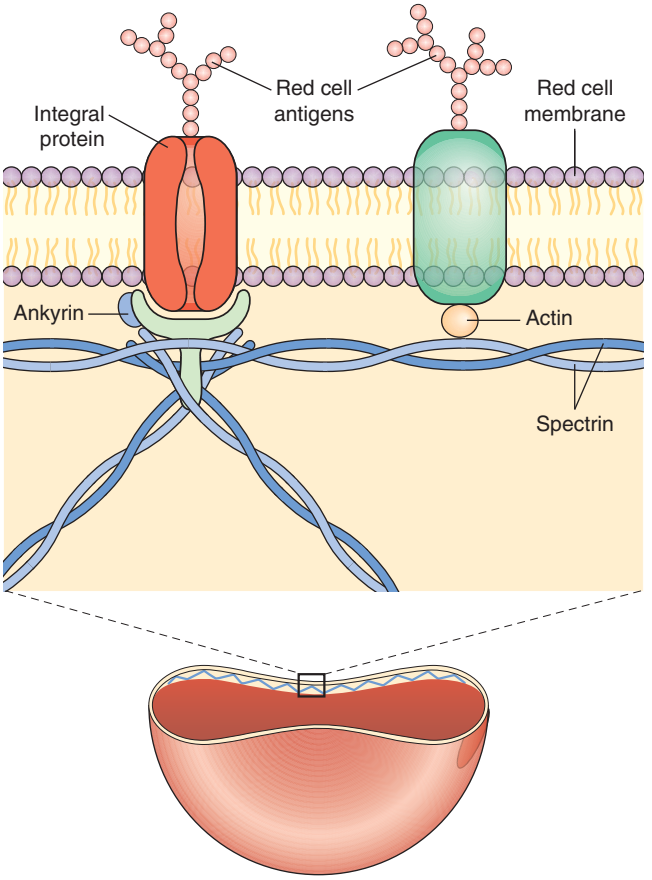


FIGURE 13-3. Cross-sectional side view of the biconcave structure of the red blood cell and diagram showing the cytoskeleton and flexible network of spectrin proteins that attach to the ankyrin protein, a transmembrane protein that resides on the inner surface of the membrane and is anchored to an integral protein that spans the membrane.

Fig. 13-2B). Each of the four polypeptide chains consists of a globin (protein) portion and a heme unit, which surrounds an atom of iron that binds oxygen.[1,3] Thus, each molecule of hemoglobin can carry four molecules of oxygen. Hemoglobin is a natural pigment; because of its iron content, it appears reddish when oxygen is attached and has a bluish cast when deoxygenated. The production of each type of globin chain is controlled by individual structural genes with five different gene loci. Mutations, which can occur anywhere in these five loci, have resulted in over 550 types of abnormal hemoglobin molecules.[1]

There are two major types of normal hemoglobin—adult hemoglobin (HbA) and fetal hemoglobin (HbF). HbA consists of a pair of α chains and a pair of β chains. HbF is the predominant hemoglobin in the fetus from the third through the ninth months of gestation. It has a pair of gamma (γ) chains substituted for the α chains. Because of this chain substitution, HbF has a higher affinity for oxygen than adult hemoglobin. This affinity facilitates the transfer of oxygen across the placenta from the HbA in the mother's blood to the HbF in the fetus's blood. HbF is replaced within 6 months of birth with HbA.

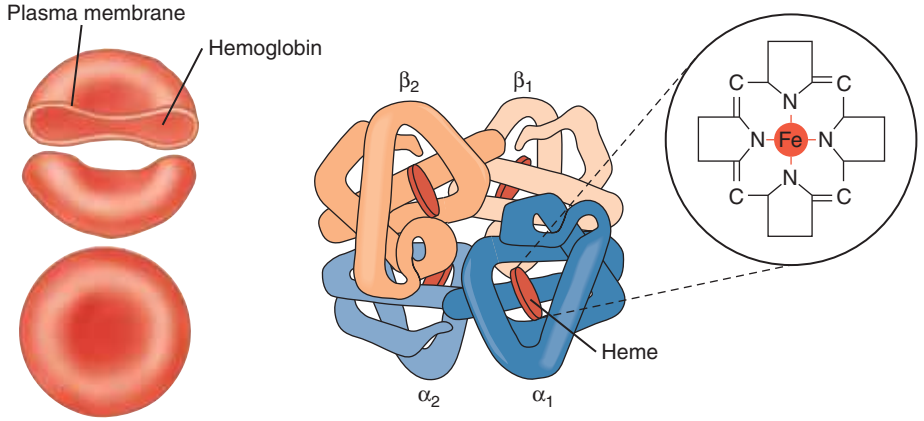


FIGURE 13-2. **(A)** Biconcave structure of the red blood cell as shown in cross-section and in lateral surface view. **(B)** Hemoglobin molecule, showing the four iron (Fe)-containing heme subunits and their structure.

Red Blood Cells

- The function of red blood cells, facilitated by the iron-containing hemoglobin molecule, is to transport oxygen from the lungs to the tissues.
- The production of red blood cells, which is regulated by erythropoietin, occurs in the bone marrow and requires iron, vitamin B_{12}, and folate.
- The red blood cell, which has a life span of approximately 120 days, is broken down in the spleen; the degradation products such as iron and amino acids are recycled.
- The heme molecule, which is released from the red blood cell during the degradation process, is converted to bilirubin and transported to the liver, where it is removed and rendered water soluble for elimination in the bile.

Hemoglobin Synthesis

The rate at which hemoglobin is synthesized depends on the availability of iron for heme synthesis. A lack of iron results in relatively small amounts of hemoglobin in the red blood cells. Body iron is found in several compartments. About 65% of iron is in the form of hemoglobin, with small amounts found in the myoglobin of muscle, the cytochromes, and iron-containing enzymes.[3] The remaining 15% to 30% is stored for later use, mainly in the liver and less in the reticuloendothelial cells of the bone marrow.[3] Iron in the hemoglobin compartment is recycled. When red blood cells age and are destroyed in the spleen, the iron from their hemoglobin is released into the circulation and returned to the bone marrow for incorporation into new red blood cells or to the liver and other tissues for storage.

Dietary sources help to maintain iron stores. Iron, principally derived from meat, is absorbed in the small intestine, especially the duodenum (Fig. 13-4). When body stores of iron are diminished or erythropoiesis is stimulated, absorption is increased. In iron overload, excretion of iron is accelerated. Normally, some iron is sequestered in the intestinal epithelial cells and is lost in the feces as these cells slough off. The iron that is absorbed enters the circulation, where it immediately combines with a β-globulin, *apotransferrin*, to form *transferrin*, which is then transported in the plasma.[3] From the plasma, iron can be deposited in tissue cells such as the liver, where it is stored as *ferritin*, a protein–iron complex, which can easily return to the circulation. Serum ferritin levels, which can be measured in the laboratory, provide an index of body iron stores. Smaller quantities of iron are stored in cells in an extremely insoluble form called *hemosiderin*. This occurs when the total quantity of iron in the body is more than the ferritin storage pool can accommodate.

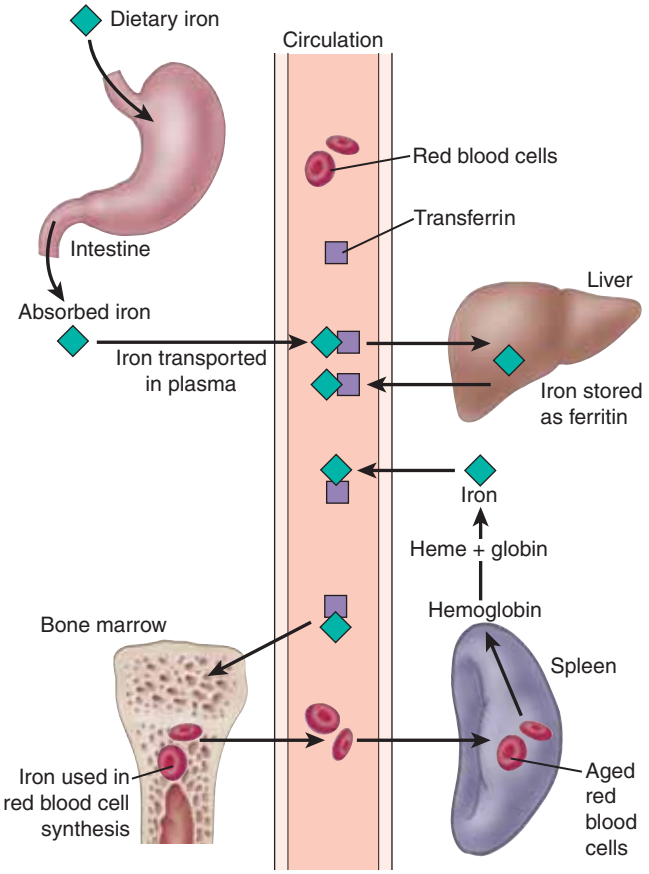


FIGURE 13-4. Diagrammatic representation of the iron cycle, including its absorption from the gastrointestinal tract, transport in the circulation, storage in the liver, recycling from aged red cells destroyed in the spleen, and use in the bone marrow synthesis of red blood cells.

Red Cell Production

Erythropoiesis refers to the production of red blood cells. After birth, red cells are produced in the red bone marrow. Until 5 years of age, almost all bones produce red cells to meet the growth needs of a child, after which bone marrow activity gradually declines.[3] After 20 years of age, red cell production takes place mainly in the membranous bones of the vertebrae, sternum, ribs, and pelvis.[3] With this reduction in activity, the red bone marrow is replaced with fatty yellow bone marrow.

The red blood cells are derived from precursor cells called *proerythroblasts*, which are formed continuously from pluripotent stem cells in the bone marrow[3] (Fig. 13-5). The red cell precursors move through a series of divisions, each producing a smaller cell as they continue to develop into mature red blood cells. Hemoglobin synthesis begins at the early erythroblast stage and continues until the cell becomes a mature erythrocyte. During its transformation from normoblast to reticulocyte, the red blood cell accumulates hemoglobin as the nucleus condenses and is finally lost. The period from stem cell to emergence of the reticulocyte in the circulation normally takes approximately 1 week. Maturation of reticulocyte

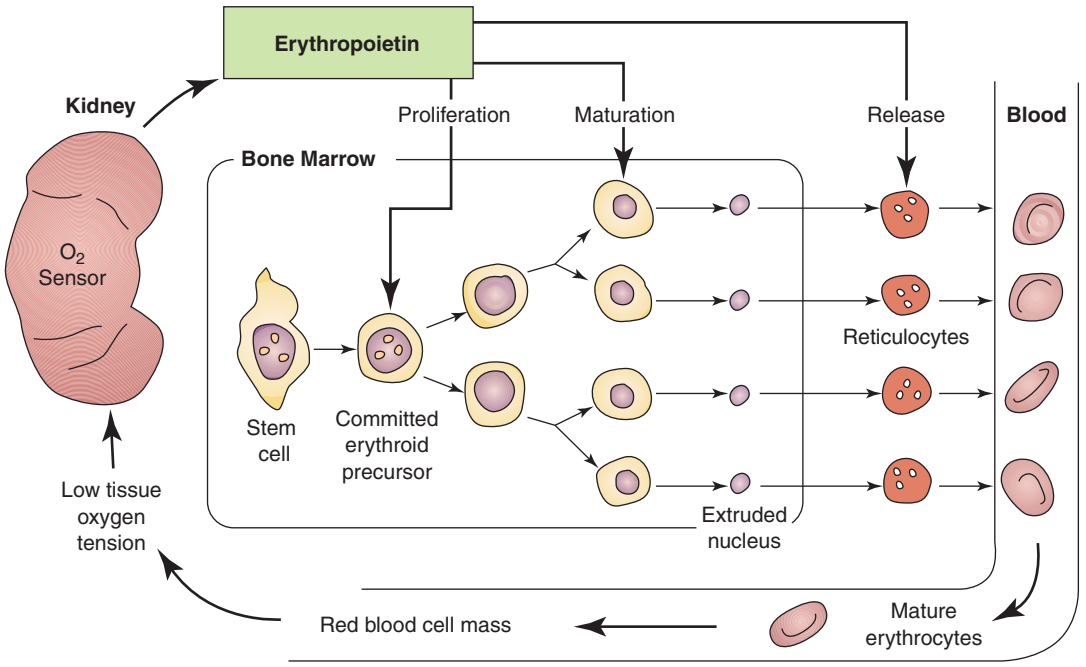


FIGURE 13-5. Red blood cell development involves the proliferation and differentiation of committed bone marrow cells through the erythroblast and normoblast stages to reticulocytes, which are released into the bloodstream and finally become erythrocytes.

to erythrocyte takes approximately 24 to 48 hours. During this process, the red cell loses its mitochondria and ribosomes, along with its ability to produce hemoglobin and engage in oxidative metabolism. Most maturing red cells enter the blood as reticulocytes.

Erythropoiesis is governed for the most part by tissue oxygen needs. Any condition that causes a decrease in the amount of oxygen that is transported in the blood ordinarily produces an increase in the rate of red cell production. The oxygen content of the blood does not act directly on the bone marrow to stimulate red blood cell production. Instead, the decreased oxygen content is sensed by the kidneys, which then produce a hormone called *erythropoietin*.[2,4] Normally, about 90% of all erythropoietin is produced by the kidneys, with the remaining 10% formed in the liver. Erythropoietin acts primarily in later stages of erythropoiesis to stimulate the production of proerythroblasts from stem cells in the bone marrow. In the absence of erythropoietin, as in kidney failure, hypoxia has little or no effect on red blood cell production. Human erythropoietin can be produced by recombinant deoxyribonucleic acid (DNA) technology. It is used for the management of anemia in cases of chronic renal failure, for anemias induced by chemotherapy in persons with malignancies, and in the treatment of anemia in human immunodeficiency virus (HIV)-infected persons treated with zidovudine.[4]

Because red blood cells are released into the blood as reticulocytes, the percentage of these cells is higher when there is a marked increase in red blood cell production. In some severe forms of anemia, the reticulocytes (normally about 1%) may account for as much as 30% of the total red cell count. In some situations, red cell production is so accelerated that numerous erythroblasts appear in the blood.

Red Cell Life Span and Destruction

Mature red blood cells have a life span of approximately 4 months, or 120 days.[3] Even though mature red cells do not have a nucleus, mitochondria, or endoplasmic reticulum, they have cytoplasmic enzymes that are capable of metabolizing glucose and forming small amounts of adenosine triphosphate (ATP). These enzymes also help to preserve the pliability of the cell membrane, maintain transmembrane transport of ions, keep the iron of the cell's hemoglobin in the reduced ferrous form that binds oxygen, and prevent oxidation of the proteins in the red cells. Even so, the metabolic activity in the cell decreases as the red cell ages, and the cell membrane becomes more and more fragile, causing it to rupture as it passes through tight places in the circulation. Many of the aged red cells self-destruct in the spleen as they squeeze through spaces between the trabeculae of the red pulp, which are only about 3 mm wide, in comparison with the 8 mm width of the red cell.[3] The rate of red cell destruction (1% per day) normally is equal to the rate of red cell production, but in conditions such as hemolytic anemia, the cell's life span may be shorter.

The destruction of red blood cells is facilitated by a group of large phagocytic macrophages found in the spleen, liver, bone marrow, and lymph nodes. These phagocytic cells recognize old and defective red cells and then ingest and destroy them in a series of enzymatic reactions. During these reactions, the amino acids from the globulin chains and iron from the heme units are

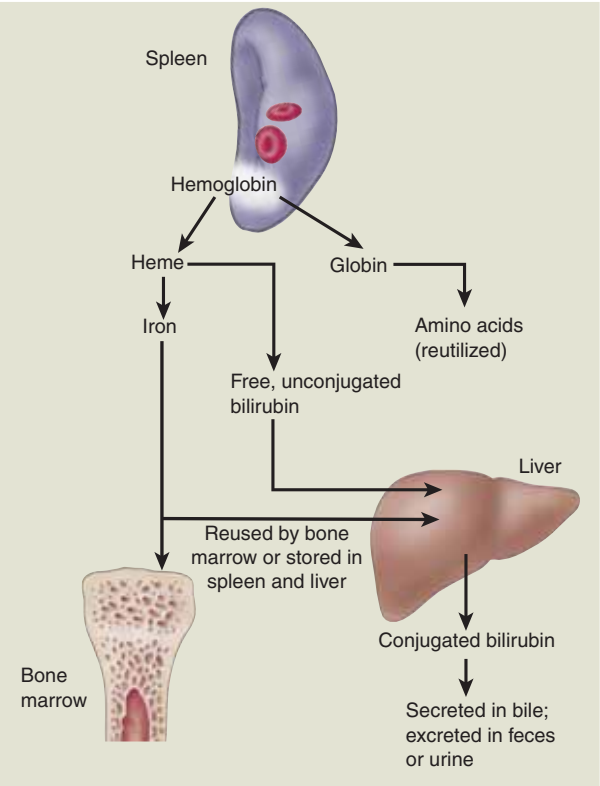


FIGURE 13-6. Destruction of red blood cells and fate of hemoglobin.

salvaged and reused (Fig. 13-6). The bulk of the heme unit is converted to bilirubin, the pigment of bile, which is insoluble in plasma and attaches to plasma proteins for transport. Bilirubin is removed from the blood by the liver and conjugated with glucuronide to render it water soluble so that it can be excreted in the bile. The plasma-insoluble form of bilirubin is referred to as *unconjugated bilirubin* and the water-soluble form as *conjugated bilirubin*. Serum levels of conjugated and unconjugated bilirubin can be measured in the laboratory and are reported as direct and indirect, respectively. If the rate of red cell destruction and consequent bilirubin production exceed the liver's ability to remove it from the blood, unconjugated bilirubin accumulates in the blood. This results in a yellow discoloration of the skin, called *jaundice*.

When red blood cell destruction takes place in the circulation, as in *hemolytic anemia*, the hemoglobin remains in the plasma where it binds to a hemoglobin-binding protein called *haptoglobin*.[1] Other plasma proteins, such as albumin, can also bind hemoglobin. With extensive intravascular destruction of red blood cells, hemoglobin levels may exceed the hemoglobin-binding capacity of haptoglobin and other plasma proteins. When this occurs, free hemoglobin appears in the blood (i.e., hemoglobinemia) and is excreted in the urine (i.e., hemoglobinuria). Because excessive red blood cell destruction can occur in hemolytic transfusion reactions, urine samples are tested for free hemoglobin after a transfusion reaction.

Laboratory Tests

Red blood cells can be studied by means of a sample of blood (Table 13-1). In modern clinical laboratories, specialized blood cell counters rapidly provide accurate measurements of red cell content and cell indices. The *red blood cell count* measures the total number of red blood cells in a microliter (μL) of blood. The *percentage of reticulocytes* (normally approximately 1%) provides an index of the rate of red cell production. The *hemoglobin* (grams per deciliter [dL] or 100 milliliters [mL] of blood) measures the hemoglobin content of the blood. The major components of blood are the red cell mass and plasma volume. The *hematocrit* measures the red cell mass in a 100-mL plasma volume. To determine the hematocrit, a sample of blood is placed in a glass tube, which is then centrifuged to separate the cells and the plasma. The hematocrit may be deceptive because it varies with the quantity of extracellular fluid, rising with dehydration and falling with overexpansion of extracellular fluid volume (Fig. 13-7).

TABLE 13-1 Standard Laboratory Values for Red Blood Cells

Test	Normal Values	Significance
Red blood cell count (RBC)		
Men	4.2–5.4 × 10^6/μL	Number of red cells in the blood
Women	3.6–5.0 × 10^6/μL	
Reticulocytes	1.0%–1.5% of total RBC	Rate of red cell production
Hemoglobin		
Men	14–16.5 g/dL	Hemoglobin content of the blood
Women	12–15 g/dL	
Hematocrit		
Men	40%–50%	Volume of cells in 100 mL of blood
Women	37%–47%	
Mean corpuscular volume	85–100 dL	Size of the red cell
Mean corpuscular hemoglobin concentration	31–35 g/dL	Concentration of hemoglobin in the red cell
Mean cell hemoglobin	27–34 pg/cell	Red cell mass

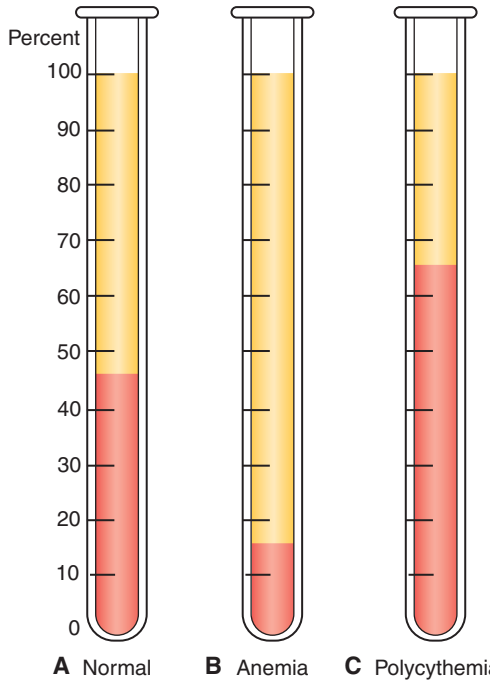


FIGURE 13-7. Hematocrit. The hematocrit measures the percentage of cells in 100 mL of plasma: **(A)** normal, **(B)** decreased in anemia, and **(C)** increased in polycythemia.

Red cell indices are used to differentiate types of anemias by size or color of red cells. The *mean corpuscular volume* (MCV) reflects the volume or size of the red cells.[1] The MCV falls in microcytic (small cell) anemia and rises in macrocytic (large cell) anemia. Some anemias are normocytic (i.e., cells are of normal size or MCV). The *mean corpuscular hemoglobin concentration* (MCHC) is the concentration of hemoglobin in each cell. Hemoglobin accounts for the color of red blood cells. Anemias are described as *normochromic* (normal color or MCHC) or *hypochromic* (decreased color or MCHC). *Mean cell hemoglobin* (MCH) refers to the mass of the red cell and is less useful in classifying anemias.

A stained blood smear provides information about the size, color, and shape of red cells and the presence of immature or abnormal cells. If blood smear results are abnormal, examination of the bone marrow may be indicated. Bone marrow commonly is aspirated with a special needle from the posterior iliac crest or the sternum. The aspirate is stained and observed for number and maturity of cells and abnormal types.

In summary, the red blood cell provides the means for transporting oxygen from the lungs to the tissues. The biconcave shape of the red cell increases the surface area for diffusion of oxygen across the thin cell membrane. A complex cytoskeleton of proteins attached to the interior of the membrane maintains its shape and allows the cell to be deformed while passing through the small capillaries. The red cell contains hemoglobin, a molecule composed of two polypeptide chains each consisting of a globin (protein) portion and a heme unit, which surrounds an iron atom that combines reversibly with oxygen. Red cells develop from stem cells in the bone marrow and are released as reticulocytes into the blood, where they become mature erythrocytes. Red blood cell production is regulated by the hormone erythropoietin, which is produced by the kidney in response to a decrease in oxygen levels.

The life span of a red blood cell is approximately 120 days. Red cell destruction normally occurs in the spleen, liver, and bone marrow. In the process of destruction, the heme portion of the hemoglobin molecule is converted to bilirubin. Bilirubin, which is insoluble in plasma, attaches to plasma proteins for transport in the blood. It is removed from the blood by the liver and conjugated to a water-soluble form so that it can be excreted in the bile.

In the laboratory, automated blood cell counters rapidly provide accurate measurements of red blood cell count and cell indices. A stained blood smear provides information about the size, color, and shape of red cells and the presence of immature or abnormal cells. If blood smear results are abnormal, examination of the bone marrow may be indicated.

Anemia

Anemia is defined as an abnormally low number of circulating red blood cells or level of hemoglobin, or both, resulting in diminished oxygen-carrying capacity.[5,6] Anemia usually results from excessive loss (bleeding) or destruction (hemolysis) of red blood cells or deficient red blood cell production because of a lack of nutritional elements or bone marrow failure. These mechanisms serve as a basis for classifying anemia.

The effects of anemia can be grouped into three categories: (1) manifestations of impaired oxygen transport and the resulting compensatory mechanisms, (2) reduction in red cell indices and hemoglobin levels, and (3) signs and symptoms associated with the pathologic process that is causing the anemia. The manifestations of anemia depend on its severity, the rapidity of its development, underlying pathologic mechanisms, and the person's age and health status. If the onset is slow, the body compensates for the decrease in oxygen-carrying capacity of the blood with increases in plasma volume, cardiac output, and respiratory rate. These changes can largely compensate for the effects of mild to moderate anemia in otherwise healthy individuals but are less effective in those with compromised respiratory or cardiac function.

The redistribution of the blood from cutaneous tissues or a lack of hemoglobin causes pallor of the skin, mucous membranes, conjunctiva, and nail beds. Tachycardia and palpitations may occur as the body tries to compensate with an increase in cardiac output. Anemias

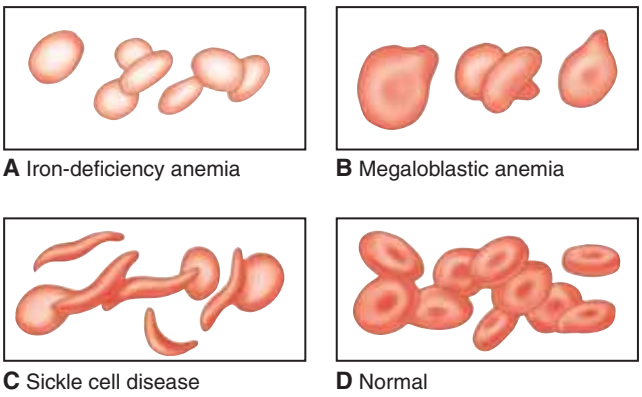


FIGURE 13-8. Red cell characteristics seen in different types of anemia: **(A)** microcytic and hypochromic red cells, characteristic of iron-deficiency anemia; **(B)** macrocytic and misshaped red blood cells, characteristic of megaloblastic anemia; **(C)** abnormally shaped red blood cells seen in sickle cell disease; and **(D)** normocytic and normochromic red blood cells, as a comparison.

caused by premature destruction of red cells (hemolytic anemias) are associated with hyperbilirubinemia, jaundice, and pigment gallstones. Anemias that result from ineffective hematopoiesis (premature death of red blood cells in the bone marrow) are associated with inappropriately high levels of iron absorption from the gut, which can lead to iron overload and eventual damage to endocrine organs and the heart.

Laboratory tests are useful in determining the severity and cause of the anemia. The red cell count and hemoglobin levels provide information about the severity of the anemia, whereas red cell characteristics such as size (normocytic, microcytic, macrocytic), color (normochromic, hypochromic), and shape often provide information about the cause of anemia (Fig. 13-8).

Anemia

- Anemia, which is a deficiency of red cells or hemoglobin, results from excessive loss (blood loss anemia), increased destruction (hemolytic anemia), or impaired production of red blood cells (iron-deficiency, megaloblastic, and aplastic anemias).
- Blood loss anemia is characterized by loss of iron-containing red blood cells from the body; hemolytic anemia involves destruction of red blood cells in the body with iron being retained in the body.
- Manifestations of anemia are caused by the decreased presence of hemoglobin in the blood (pallor), tissue hypoxia due to deficient oxygen transport (weakness and fatigue), and recruitment of compensatory mechanisms (tachycardia and palpitations) designed to increase oxygen delivery to the tissues.

Blood Loss Anemia

The clinical manifestations and red cell changes associated with blood loss anemia depend on the rate of hemorrhage and whether the bleeding loss is internal or external. With rapid blood loss, circulatory shock and circulatory collapse may occur. With more slowly developing anemia, the amount of red cell mass lost may reach 50% without the occurrence of signs and symptoms.[3]

The effects of acute blood loss are mainly due to loss of intravascular volume, which can lead to cardiovascular collapse and shock (see Chapter 20). A fall in the red blood cell count, hematocrit, and hemoglobin is caused by hemodilution resulting from movement of fluid into the vascular compartment. Initially, the red cells are normal in size and color (normocytic, normochromic). The hypoxia that results from blood loss stimulates proliferation of committed erythroid stem cells in the bone marrow. It takes about 5 days for the progeny of hematopoietic stem cells to differentiate fully, an event that is marked by increased reticulocytes in the blood. If the bleeding is controlled and sufficient iron stores are available, the red cell concentration returns to normal within 3 to 4 weeks. External bleeding leads to iron loss and possible iron deficiency, which can hamper restoration of the red cell count.

Chronic blood loss does not affect blood volume but instead leads to iron-deficiency anemia when iron stores are depleted. It is commonly caused by gastrointestinal bleeding and menstrual disorders. Because of compensatory mechanisms, persons are commonly asymptomatic until the hemoglobin level is less than 8 g/dL. The red cells that are produced have too little hemoglobin, giving rise to microcytic hypochromic anemia (see Fig. 13-8).

Hemolytic Anemias

Hemolytic anemia is characterized by the premature destruction of red cells, the retention in the body of iron and the other products of hemoglobin destruction, and a compensatory increase in erythropoiesis.[5,6] Almost all types of hemolytic anemia are distinguished by normocytic and normochromic red cells. Because of the red blood cell's shortened life span, the bone marrow usually is hyperactive, resulting in an increased number of reticulocytes in the circulating blood. As with other types of anemia, the person experiences easy fatigability, dyspnea, and other signs and symptoms of impaired oxygen transport.

Hemolytic anemias are commonly classified according to whether the defect is intrinsic to the red cell or due to some external factor.[5] Intrinsic factors have been described for all components of the red cell, including the cell membrane, enzyme systems, and hemoglobin, most of which are hereditary. Extrinsic or acquired factors include immune mechanisms, mechanical trauma, and infections.

Destruction of red cells can occur within the vascular compartment (intravascular) or within the phagocytic cells of the reticuloendothelial system (extravascular).

Intravascular hemolysis is less common and occurs as a result of mechanical injury caused by defective cardiac valves, complement fixation in transfusion reactions, or exogenous toxic factors. Regardless of cause, intravascular hemolysis leads to hemoglobinemia, hemoglobinuria, and hemosiderinuria. The conversion of the heme pigment to bilirubin can result in unconjugated hyperbilirubinemia and jaundice. Massive intravascular hemolysis can lead to acute tubular necrosis (Chapter 25). Extravascular hemolysis, the most common type of red cell destruction, takes place largely within the phagocytic cells of the spleen and liver. Because extreme changes in shape are necessary for red cells to navigate the splenic sinusoids successfully, reduced deformability makes the passage difficult and leads to splenic sequestration, followed by phagocytosis. Extravascular hemolysis is not associated with hemoglobinemia or hemoglobinuria, but it often produces jaundice. It can also lead to the formation of bilirubin-rich gallstones, also called *pigment stones*.

Inherited Disorders of the Red Cell Membrane

Hereditary spherocytosis, transmitted as an autosomal dominant trait in 75% of the cases, is the most common inherited disorder of the red cell membrane.[5] The disorder is caused by abnormalities of the spectrin and ankyrin membrane proteins that lead to a gradual loss of the membrane surface. The loss of membrane relative to cytoplasm causes the cell to become a tight sphere instead of a concave disk. Although the spherical cell retains its ability to transport oxygen, it is poorly deformable and susceptible to destruction as it passes through the venous sinuses of the splenic circulation. Clinical signs are variable but typically include mild hemolytic anemia, jaundice, splenomegaly, and bilirubin gallstones. A life-threatening aplastic crisis may occur when a sudden disruption of red cell production (often from a viral infection) causes a rapid drop in hematocrit and the hemoglobin level. The disorder usually is treated with splenectomy to reduce red cell destruction, and blood transfusions may be required in a crisis.

Sickle Cell Disease

Sickle cell disease is an inherited disorder in which an abnormal hemoglobin (hemoglobin S [HbS]) leads to chronic hemolytic anemia, pain, and organ failure. The HbS gene is transmitted by recessive inheritance and can manifest as sickle cell trait (i.e., heterozygote with one HbS gene) or sickle cell disease (i.e., homozygote with two HbS genes). Approximately 8% of African Americans are heterozygous for HbS and 0.1% to 0.2% are homozygous.[5] In parts of Africa, where malaria is endemic, the gene frequency approaches 30%, attributed to the slight protective effect it confers against *Plasmodium falciparum* malaria.[5]

The abnormal structure of HbS results from a point mutation in the β chain of the hemoglobin molecule, with an abnormal substitution of a single amino acid, valine, for glutamic acid (Fig. 13-9). In the heterozygote,

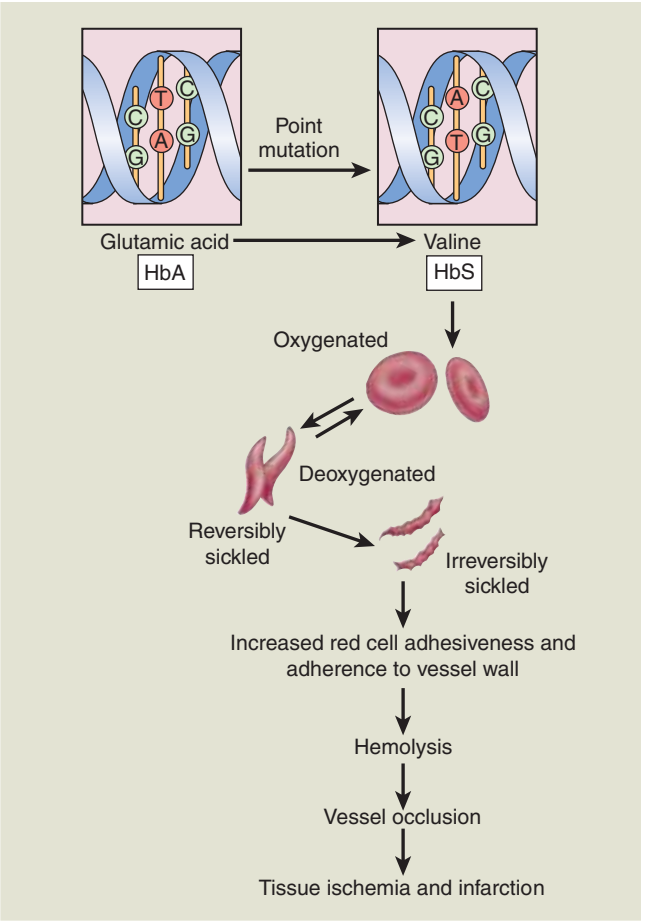


FIGURE 13-9. Mechanism of sickling and its consequences in sickle cell disease.

only approximately 40% of the hemoglobin is HbS, but in the homozygote, 80% to 95% of the hemoglobin is HbS.[5] Variations in proportions exist, and the concentration of HbS correlates with the risk of sickling. HbS polymerizes when deoxygenated, creating a semisolid gel that makes the erythrocyte rigid, distort its shape, and cause structural damage to the red cell membrane. The sickled cell may return to its normal shape with oxygenation in the lungs. However, after repeated episodes of deoxygenation, the cells remain permanently sickled. The person with sickle cell trait who has less HbS has little tendency to sickle and is virtually asymptomatic. Fetal hemoglobin (HbF) inhibits the polymerization of HbS; therefore, most infants with sickle cell disease do not begin to experience the effects of the sickling until after 8 to 10 weeks of age, when the HbF has been replaced by HbS.[6]

There are two major consequences of red blood cell sickling—chronic hemolytic anemia and blood vessel occlusion. Premature destruction of the cells due to the rigid, nondeformable membrane occurs in the spleen, causing hemolysis and anemia from a decrease in red cell numbers. Overall, the mean life span of red cells in persons with sickle cell disease average only 20 days (one sixth of normal).[5] Vessel occlusion disrupts blood flow causing tissue ischemia and a pain crises. Recent evidence

suggests that vessel occlusion is a complex process involving an interaction among the sickled cells, vessel endothelial cells, platelets, and other blood components.[7] The process is initiated by the adherence of sickled cells to the vessel endothelium, causing endothelial cell activation with liberation of inflammatory mediators and substances that increase platelet activation and promote blood coagulation.[5–7]

Factors associated with sickling and vessel occlusion include cold, stress, physical exertion, infection, and illnesses that cause hypoxia, dehydration, or acidosis. The rate of HbS polymerization is affected by the concentration of hemoglobin in the cell. Dehydration increases the hemoglobin concentration and contributes to the polymerization and resultant sickling. Acidosis reduces the affinity of hemoglobin for oxygen, resulting in more deoxygenated hemoglobin and increased sickling. Even such trivial incidents as reduced oxygen tension induced by sleep may contribute to the sickling process.

Clinical Course. Persons who are homozygous for the HbS gene experience severe hemolytic anemia, chronic hyperbilirubinemia, and vaso-occlusive crises. The hyperbilirubinemia that results from the breakdown products of hemoglobin often leads to jaundice and the formation of pigment gallstones.

The complications of sickle cell disease are numerous, with two of the most common being vaso-occlusive pain crisis and acute chest syndrome.[7–9] An acute pain episode results from tissue hypoxia due to vessel occlusion and can occur suddenly in almost any part of the body.[7] Common sites obstructed by sickled cells include the abdomen, chest, bones, and joints. Many areas may be affected simultaneously. Infarctions caused by sluggish blood flow may cause chronic damage to the liver, spleen, heart, kidneys, retina, and other organs (Fig. 13-10). *Acute chest syndrome* is an atypical pneumonia resulting from pulmonary infarction.[8–10] It is the second leading cause of hospitalization in persons with sickle cell disease and is characterized by pulmonary infiltrates, shortness of breath, fever, chest pain, and cough. The syndrome can cause chronic respiratory insufficiency and is a leading cause of death in sickle cell disease. Children may experience growth retardation and susceptibility to osteomyelitis. Painful bone crises may be caused by marrow infarcts of the bones of the hands and feet, resulting in swelling of those extremities. Another major complication is stroke. Approximately 25% of persons with sickle cell disease have neurologic complications, including stroke, related to vessel occlusion.[10]

In addition to these crises, persons with sickle cell disease are prone to infections. Because of the spleen's sluggish blood flow and low oxygen tension, hemoglobin in red cells traversing the spleen becomes deoxygenated, causing ischemia. Splenic injury begins in early childhood, characterized by intense congestion, and is usually asymptomatic. The congestion causes functional asplenia and predisposes the person to life-threatening infections by encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Klebsiella* species. Neonates and small children have not had

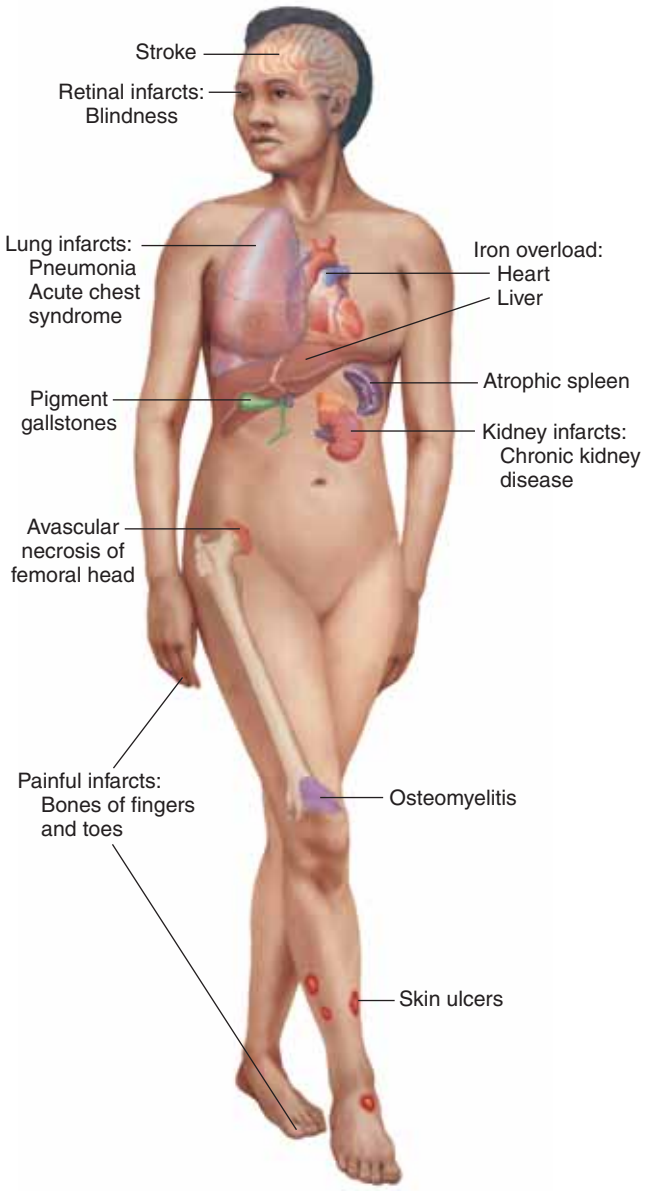


FIGURE 13-10. Clinical manifestations of sickle cell disease.

time to create antibodies to these organisms and rely on the spleen for their removal. In the absence of specific antibody to the polysaccharide capsular antigens of these organisms, splenic activity is essential for removing these organisms when they enter the blood.

Diagnosis and Treatment. The signs and symptoms of sickle cell disease make their appearance during infancy. Neonatal diagnosis of sickle cell disease is made on the basis of clinical findings and hemoglobin solubility results, which are confirmed by hemoglobin electrophoresis. Prenatal diagnosis is done by the analysis of fetal DNA obtained by amniocentesis.[7]

In the United States, screening programs have been implemented to detect newborns with sickle cell disease and other hemoglobinopathies. Cord blood or heel-stick samples are subjected to electrophoresis to separate the

HbF from the small amount of HbA and HbS. Other hemoglobins may also be detected and quantified by further laboratory evaluation. Many states mandate screening of all newborns, regardless of ethnic origin.

The clinical course of persons with sickle cell disease is highly variable. As a result of improvements in supportive care, an increasing number of persons are surviving into adulthood and producing offspring. Of particular importance is the early prophylactic treatment with penicillin to prevent pneumococcal infection. Treatment should begin as early as 2 months of age and continued until at least 5 years of age.[11] Maintaining full immunization, including *H. influenzae* vaccine and hepatitis B vaccine, is recommended. The National Institutes of Health Committee on Management of Sickle Cell Disease also recommends administration of the 7-valent pneumococcal vaccine beginning at 2 to 6 months of age[11] (see Chapter 25). The 7-valent vaccine should be followed by immunization with the 23-valent pneumococcal vaccine at 24 months of age or later.

Hydroxyurea, an inhibitor of DNA synthesis, has been shown to reduce pain crises and prevent the complications of sickle cell disease. The drug produces an increase in red cell levels of HbF by decreasing the terminal differentiation of erythroid stem cells into HbS; acts as an anti-inflammatory agent by inhibiting the production of white blood cells; and is oxidized by heme groups to produce nitric oxide, a potent vasodilator and inhibitor of platelet aggregation.[5] Although the drug halves pain episodes and pulmonary complications, approximately 40% of persons do not respond.[12] Other therapies under investigation include drugs that affect globin gene expression; prevent hemoglobin polymerization, membrane damage, and cell dehydration; or inhibit sickle cell adhesion to endothelial cells.[12] Bone marrow or stem cell transplantation has the potential for cure in symptomatic children but carries the risk of graft-versus-host disease. Progress in gene therapy to treat sickle cell disease has been slow but promising, and may be a future option.

The Thalassemias

The thalassemias are a heterogeneous group of inherited disorders caused by mutations that decrease the rate of α- or β-globin chains. β-Thalassemias are caused by deficient synthesis of the β chain and α-thalassemias by deficient synthesis of the α chain.[5,6] The defect is inherited as a mendelian trait, and a person may be heterozygous for the trait and have a mild form of the disease or be homozygous and have the severe form of the disease. Like sickle cell disease, the thalassemias occur with a high degree of frequency in certain populations. The β-thalassemias, sometimes called *Cooley anemia* or *Mediterranean anemia,* are most common in the Mediterranean populations of southern Italy and Greece, whereas the α-thalassemias are more common among Asians. Both α- and β-thalassemias are common in Africans and African Americans.

Two factors contribute to the anemia that occurs in thalassemia: a deficiency in hemoglobin due to the decreased synthesis of the affected chain, coupled with excess production of the unaffected chain. The reduced hemoglobin synthesis results in a hypochromic, microcytic anemia, whereas the accumulation of the unaffected chain interferes with normal red cell maturation and contributes to membrane changes that lead to hemolysis and anemia.

The β-Thalassemias. The β-thalassemias result from a point mutation in the β-globin gene that directs β-chain synthesis.[13] Sequencing of the β-thalassemia genes has revealed more than 100 different mutations, the majority of which consist of single-base changes. The presence of one normal gene in heterozygous persons (thalassemia minor) usually results in sufficient normal hemoglobin synthesis to prevent severe anemia. Persons who are homozygous for the trait (thalassemia major) have severe, transfusion-dependent anemia that is evident at 6 to 9 months of age when the hemoglobin switches from HbF to HbA. If transfusion therapy is not started early in life, severe growth retardation occurs in children with the disorder.

Two conditions contribute to the pathogenesis of the anemia in β-thalassemias: inadequate HbA formation due to reduced β-globin chain synthesis and red cell hemolysis resulting from an unbalanced rate of β-globin and α-globin synthesis. The excess α-globin chains form insoluble aggregates, called *Heinz bodies*, that precipitate within red cells and produce membrane damage that is severe enough to cause extravascular hemolysis. Erythroblasts in the bone marrow undergo a similar fate, which in severe β-thalassemia results in destruction of the majority of erythroid precursors before their maturation into red cells. In addition to anemia, persons with moderate to severe forms of the disease suffer from coagulation abnormalities. Thrombotic events (stroke and pulmonary embolism) appear to be related to altered platelet function, endothelial activation, and an imbalance of procoagulant and anticoagulant factors.[13]

In severe β-thalassemia, marked anemia produced by ineffective hematopoiesis and hemolysis leads to increased erythropoietin secretion and hyperplasia in the bone marrow and sites of extramedullary hematopoiesis. The expanding mass of erythropoietic marrow invades the bony cortex, impairs bone growth, and produces other bone abnormalities. There is thinning of the cortical bone, with new bone formation evident on the maxilla and frontal bones of the face (i.e., chipmunk facies). The long bones, ribs, and vertebrae may become vulnerable to fracture because of osteoporosis or osteopenia, which contributes to increased morbidity in older persons. Enlargement of the spleen (splenomegaly) and liver (hepatomegaly) result from extramedullary hematopoiesis and increased red cell destruction. Ineffective hematopoiesis also stimulates an inappropriate increase in absorption of dietary iron. Excess iron stores, which accumulate from increased dietary absorption and repeated transfusions, are deposited in the myocardium, liver, and endocrine organs and induce organ damage. Cardiac, hepatic, and endocrine diseases are common causes of morbidity and mortality from iron overload. Disorders of the pituitary, thyroid, and adrenal glands and the pancreas result in significant morbidity and require hormone replacement therapy.[13]

Regular blood transfusions improve growth and development and prevent most of the complications, and iron chelation therapy can reduce the iron overload and extend life expectancy.[13] Stem cell transplantation is a potential cure for low-risk patients, particularly in younger persons with no complications of the disease or its treatment, and has excellent results.[13] In the future, stem cell gene replacement may provide a cure for many with the disease.

The α-Thalassemias. The α-thalassemias are caused by a gene deletion that results in defective α-chain synthesis. Synthesis of the α-globin chains of hemoglobin is controlled by two pairs or four genes; hence, α-thalassemia shows great variation in severity related to the number of gene deletions. Silent carriers who have a deletion of a single α-globin gene are asymptomatic, whereas those with deletion of two genes have the α-thalassemia trait and exhibit mild hemolytic anemia. Deletion of three of the four α-chain genes leads to unstable aggregates of α chains called *hemoglobin H* (HbH). This disorder is the most important clinical form and is common in Asians. The β chains are more soluble than the α chains, and their accumulation is less toxic to the red cells, so that senescent rather than precursor red cells are affected. Most persons with HbH have moderately severe hemolytic anemia but do not usually require transfusions.[14] The most severe form of α-thalassemia occurs in infants in whom all four α-globin genes are deleted. Such a defect results in a hemoglobin molecule (Hb Bart) that is formed exclusively from the chains of HbF. Hb Bart, which has an extremely high oxygen affinity, cannot release oxygen in the tissues. This disorder usually results in death in utero or shortly after birth.[14]

Inherited Enzyme Defects

The red cell is vulnerable to injury by endogenous and exogenous oxidants, which are normally inactivated by the glucose-containing tripeptide *glutathione*, one of the body's principal means of preventing oxidative damage. Abnormalities of glutathione metabolism resulting from impaired enzyme function reduces the ability of red cells to protect against oxidative stress. The most common inherited enzyme defect that results in hemolytic anemia is a deficiency of glucose-6-phosphatase (G6PD). The gene that determines this enzyme is located on the X chromosome, and the defect is expressed only in males and homozygous females. There are several hundred variants of this gene, but only the $G6PD^{--}$ variant that is found in 10% to 15% of American blacks and the G6PD Mediterranean variant are known to cause most of the clinically significant hemolytic anemia.[5,6]

G6PD deficiency makes red cells more vulnerable to oxidants and causes direct oxidation of hemoglobin to methemoglobin, which cannot transport oxygen, and denaturing of the hemoglobin molecule to form Heinz bodies, which are precipitated in the red blood cell. Hemolysis usually occurs as the damaged red blood cells move through the narrow vessels of the spleen, causing hemoglobinemia, hemoglobinuria, and jaundice. The hemolysis is short-lived, occurring 2 to 3 days after the triggering event. In African Americans, the defect is mildly expressed and is not associated with chronic hemolytic anemia unless triggered by oxidant drugs, acidosis, or infection. In affected persons, the hemolysis can be triggered by exposure to oxidant drugs such as the antimalarial drug primaquine, quinine, the sulfonamides, and nitrofurantoin. Severe G6PD deficiency (as in Mediterranean variants) may produce a chronic hemolytic anemia. The disorder can be diagnosed through the use of a G6PD assay or screening test. No treatment is necessary except to avoid known oxidant drugs.

Acquired Hemolytic Anemias

Several acquired factors exogenous to the red blood cell produce hemolysis by direct membrane destruction or antibody-mediated lysis. Various drugs, chemicals, toxins, venoms, and infections such as malaria destroy red cell membranes. Hemolysis can also be caused by mechanical factors such as prosthetic heart valves, vasculitis, and severe burns. Obstructions in the microcirculation, as in disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and renal disease, may traumatize the red cells by producing turbulence and changing pressure gradients.

Although commonly referred to as autoantibody anemias, the currently preferred designation is immunohemolytic anemia, since they may be initiated by an ingested drug. The antibodies that cause hemolysis are of two types: warm-reacting antibodies of the immunoglobulin G (IgG) class, which are maximally active at 37°C, and cold-reacting antibodies of the IgM type, which are optimally active at about 4°C.

In the warm-reacting antibody type, the most common form of immunohemolytic anemia, the antibodies react with antigens on the red cell membrane, causing destructive changes that lead to spherocytosis, with subsequent phagocytic destruction in the spleen or reticuloendothelial system. The antibodies lack specificity for the ABO antigens but may react with the Rh antigens. The hemolytic reactions usually has a rapid onset and may be severe and life-threatening. There are varied causes for this anemia: approximately 50% are idiopathic, and 50% are related to predisposing conditions such as lymphoid neoplasms, autoimmune disorders (particularly systemic lupus erythematosus), and exposure to drugs such as penicillin and the cephalosporins.[5,6] Some drugs, of which the antihypertensive drug α-methyldopa is the prototype, induce the production of antibodies against red cells antigens, particularly Rh antigens. About 10% of persons taking α-methyldopa develop antibodies, and about 10% develop clinically significant hemolysis.[5]

In the cold-reacting agglutinin type of hemolytic anemia, which is less common than the warm-reacting type, IgM antibodies bind red cells and cause agglutination and activate complement. Cold agglutinin antibodies sometimes appear transiently following certain infections (e.g., Epstein-Barr, influenza), in which case the condition is relatively benign. The condition may also develop as a chronic complication of B-cell neoplasms and as an

idiopathic condition. Symptoms are variable and occur in parts of the body, such as the ears, fingers, and toes, where the temperature may fall below 30°C. Vascular obstruction caused by agglutinated red cells results in pallor, cyanosis, and Raynaud phenomenon in parts of the body exposed to cold temperatures.

The diagnosis of immunohemolytic anemia requires use of the Coombs test to detect the presence of antibody or complement on the surface of red blood cells. The *direct Coombs test* uses antibodies specific for human immunoglobulins or complement to detect antibodies on red blood cells. It is positive in cases of autoimmune hemolytic anemia, Rh disease of the newborn, transfusion reactions, and drug-induced hemolysis. The *indirect Coombs test* uses commercially available red cells with known antigens to characterize the antigen target and temperature dependence of responsible antigen.

Anemias of Deficient Red Cell Production

Anemia may result from the decreased production of erythrocytes by the bone marrow. This category includes anemias caused by a deficiency of substances that are needed for hematopoiesis, particularly iron, vitamin B_{12}, and folic acid. Other disorders that suppress erythropoiesis include those associated with bone marrow failure or replacement of the bone marrow by tumor cells or inflammatory cells.

Iron-Deficiency Anemia

Iron deficiency is a common worldwide cause of anemia affecting persons of all ages. The anemia results from dietary deficiency, loss of iron through bleeding, or increased demands. Because iron is a component of heme, a deficiency leads to decreased hemoglobin synthesis and consequent impairment of oxygen delivery.

Body iron is used repeatedly. When red cells become senescent and are broken down, their iron is released and reused in the production of new red cells. Despite this efficiency, small amounts of iron are lost in the feces and need to be replaced by dietary uptake. Iron balance is maintained by the absorption of 0.5 to 1.5 mg daily to replace the 1 mg lost in the feces. The average Western diet supplies about 20 mg.[6] The absorbed iron is more than sufficient to supply the needs of most individuals, but may be barely adequate in toddlers, adolescents, and women of child-bearing age.

The usual reason for iron deficiency in adults in the Western world is chronic blood loss because iron cannot be recycled to the pool. In men and postmenopausal women, blood loss may occur from gastrointestinal bleeding because of peptic ulcer, intestinal polyps, hemorrhoids, or cancer. Excessive aspirin intake may cause undetected gastrointestinal bleeding. In women, menstruation may account for an average of 1.5 mg of iron lost per day, causing a deficiency.[15] Although cessation of menstruation removes a major source of iron loss in the pregnant woman, iron requirements increase at this time, and deficiency is common. The expansion of the mother's blood volume requires approximately 500 mg of additional iron, and the growing fetus requires approximately 360 mg during pregnancy. In the postnatal period, lactation requires approximately 1 mg of iron daily.[15]

A child's growth places extra demands on the body. Blood volume increases, with a greater need for iron. Iron requirements are proportionally higher in infancy (3 to 24 months) than at any other age, although they are also increased in childhood and adolescence. In infancy, the two main causes of iron-deficiency anemia are low iron levels at birth because of maternal deficiency and a diet consisting mainly of cow's milk, which is low in absorbable iron. Adolescents are also susceptible to iron deficiency because of high requirements due to growth spurts, dietary deficiencies, and menstrual loss.[16]

Iron-deficiency anemia is characterized by low hemoglobin and hematocrit, decreased iron stores, and low serum iron and ferritin levels. The red cells are decreased in number and are microcytic and hypochromic (see Fig. 13-8). Poikilocytosis (irregular shape) and anisocytosis (irregular size) are also present. Laboratory values indicate reduced MCHC and MCV. Membrane changes may predispose to hemolysis, causing further loss of red cells.

The manifestations of iron-deficiency anemia are related to impaired oxygen transport and lack of hemoglobin. Depending on the severity of the anemia, pallor, easy fatigability, dyspnea, and tachycardia may occur. Epithelial atrophy is common and results in waxy pallor, brittle hair and nails, sometimes a spoon-shaped deformity of the fingernails, smooth tongue, sores in the corners of the mouth, and sometimes dysphagia and decreased acid secretion. A poorly understood symptom occasionally seen is pica, the bizarre, compulsive eating of ice, dirt, or other abnormal substances. Iron deficiency in infants may also result in long-term manifestations such as poor cognitive, motor, and emotional function that may be related to effects on brain development or neurotransmitter function.[17]

Prevention of iron deficiency is a primary concern in infants and children. Avoidance of cow's milk, iron supplementation at 4 to 6 months of age in breast-fed infants, and use of iron-fortified formulas and cereals are recommended for infants younger than 1 year of age.[18] In the second year, a diet rich in iron-containing foods and use of iron-fortified vitamins will help prevent iron deficiency. The treatment of iron-deficiency anemia in children and adults is directed toward controlling chronic blood loss, increasing dietary intake of iron, and administering supplemental iron. Ferrous sulfate, which is the usual oral replacement therapy, replenishes iron stores in several months. Parenteral iron therapy may be used when oral forms are not tolerated or are ineffective. Caution is required because of the possibility of severe hypersensitivity reactions.

Megaloblastic Anemias

Megaloblastic anemias are caused by impaired DNA synthesis that results in enlarged red cells (MCV >100 fL) due to impaired maturation and division.[19] There are two principal causes of megaloblastic anemia: vitamin B_{12} and folic acid deficiencies. Because megaloblastic anemias develop slowly, there are often few symptoms until the anemia is far advanced.

Vitamin B_{12}–Deficiency Anemia. Vitamin B_{12}, also known as *cobalamin*, serves as a cofactor for two important reactions in humans. It is essential for DNA synthesis and nuclear maturation, which in turn leads to normal red cell maturation and division.[5,20] Vitamin B_{12} is also involved in a reaction that prevents abnormal fatty acids from being incorporated into neuronal lipids. This abnormality may predispose to myelin breakdown and produce some of the neurologic complications of vitamin B_{12} deficiency.[5]

Vitamin B_{12} is found in all foods of animal origin. Dietary deficiency is rare and usually found only in strict vegetarians who avoid all dairy products as well as meat and fish. Vitamin B_{12} is absorbed by a unique process. After release from the animal protein, it is bound to intrinsic factor, a protein secreted by the gastric parietal cells (Fig. 13-11). The vitamin B_{12}–intrinsic factor complex protects vitamin B_{12} from digestion by intestinal enzymes. The complex travels to the ileum, where it binds to membrane receptors on the epithelial cells. Vitamin B_{12} is then separated from intrinsic factor and transported across the membrane into the circulation. There it is bound to its carrier protein, transcobalamin II, which transports vitamin B_{12} to its storage and tissue sites.

An important cause of vitamin B_{12} deficiency is pernicious anemia, resulting from an atrophic gastritis (see Chapter 29). Pernicious anemia is believed to result from immunologically mediated, possibly autoimmune, destruction of the gastric mucosa. The resultant chronic atrophic gastritis is marked by loss of parietal cells and production of antibodies that interfere with binding of vitamin B_{12} to intrinsic factor. Other causes of vitamin B_{12} deficiency anemia include gastrectomy, ileal resection, inflammation or neoplasms in the terminal ileum, and malabsorption syndromes in which vitamin B_{12} and other B-vitamin compounds are poorly absorbed.

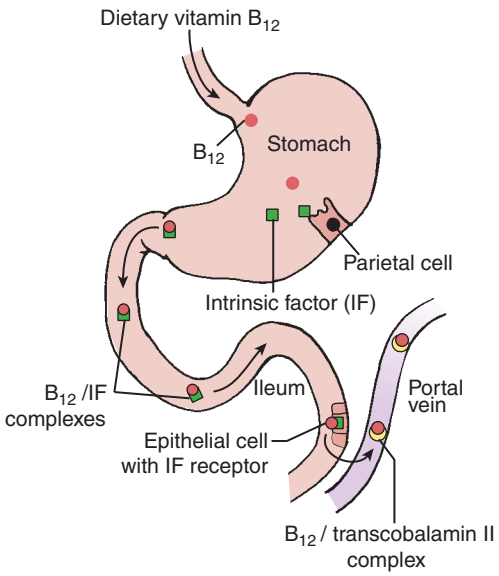


FIGURE 13-11. Absorption of vitamin B_{12}.

The hallmark of vitamin B_{12} deficiency is megaloblastic anemia. When vitamin B_{12} is deficient, the red cells that are produced are abnormally large because of excess cytoplasmic growth and structural proteins (see Fig. 13-8). The cells have immature nuclei and show evidence of cellular destruction. They have flimsy membranes and are oval rather than biconcave. These oddly shaped cells have a short life span that can be measured in weeks rather than months. The loss of red cells results in a moderate to severe anemia and mild jaundice. The MCV is elevated, and the MCHC is normal. As with other anemias, there is pallor, easy fatigability, and in severe cases dyspnea. The megaloblastic state also produces changes in mucosal cells, leading to glossitis (sore tongue), as well as other vague gastrointestinal disturbances such as anorexia and diarrhea. Vitamin B_{12} deficiency also leads to a complex neurologic syndrome caused by deranged methylation of myelin protein. Demyelination of the dorsal and lateral columns of the spinal cord causes symmetric paresthesias of the feet and fingers, loss of vibratory and position sense, and eventual spastic ataxia. In more advanced cases, cerebral function may be altered. In some cases, dementia and other neuropsychiatric changes may precede hematologic changes.

Diagnosis of vitamin B_{12} deficiency is made by finding an abnormally low serum vitamin B_{12} level. The diagnosis of pernicious anemia is usually made by the detection of parietal cell and intrinsic factor antibodies.[19] Lifelong treatment consisting of intramuscular injections or high oral doses of vitamin B_{12} reverses the anemia and prevents the neurologic changes.

Folic Acid–Deficiency Anemia. Folic acid is also required for DNA synthesis and red cell maturation, and its deficiency produces the same type of megaloblastic red cell changes that occur in vitamin B_{12}–deficiency anemia (i.e., increased MCV and normal MCHC).

Folic acid is readily absorbed from the intestine. It is found in vegetables (particularly the green leafy types), fruits, cereals, and meats. Much of the vitamin, however, is lost in cooking. The most common causes of folic acid deficiency are malnutrition or dietary lack, especially in the elderly or in association with alcoholism. Total body stores of folic acid amount to 2000 to 5000 μg, and 50 μg is required in the daily diet.[6] A dietary deficiency may result in anemia in a few months. Malabsorption of folic acid may be due to syndromes such as celiac disease or other intestinal disorders. Some drugs used to treat seizure disorders (e.g., primidone, phenytoin, phenobarbital) and triamterene, a diuretic, predispose to a deficiency by interfering with folic acid absorption. In neoplastic disease, tumor cells compete for folate, and deficiency is common. Methotrexate, a folic acid analog used in the treatment of cancer, impairs the action of folic acid by blocking its conversion to the active form. Because pregnancy increases the need for folic acid 5- to 10-fold, a deficiency commonly occurs. Poor dietary habits, anorexia, and nausea are other reasons for folic acid deficiency during pregnancy. Studies also show an association between folate deficiency and neural tube defects (see Chapter 6).[19]

The features of folic acid deficiency are similar to those of vitamin B_{12} deficiency, with megaloblastic anemia and symptoms referable to changes in the mucosal surface of the gastrointestinal tract. However, there are none of the neurologic abnormalities associated with B_{12} deficiency.

Aplastic Anemia

Aplastic anemia describes a disorder of pluripotential bone marrow stem cells that results in a reduction of all three hematopoietic cell lines—red blood cells, white blood cells, and platelets.[21,22] Pure red cell aplasia, in which only the red cells are affected, rarely occurs. Anemia results from the failure of the marrow to replace senescent red cells that are destroyed and leave the circulation, although the cells that remain are of normal size and color. At the same time, because the leukocytes, particularly the neutrophils, and the thrombocytes have a short life span, a deficiency of these cells usually is apparent before the anemia becomes severe.

The onset of aplastic anemia may be insidious, or it may strike with suddenness and great severity. It can occur at any age. The initial presenting symptoms include weakness, fatigability, and pallor caused by anemia. Petechiae (i.e., small, punctate skin hemorrhages) and ecchymoses (i.e., bruises) often occur on the skin, and bleeding from the nose, gums, vagina, or gastrointestinal tract may occur because of decreased platelet levels. The decrease in the number of neutrophils increases susceptibility to infection.

Among the causes of aplastic anemia are exposure to high doses of radiation, chemicals, and toxins that suppress hematopoiesis directly or through immune mechanisms. Chemotherapy and irradiation commonly result in bone marrow depression, which causes anemia, thrombocytopenia, and neutropenia. Identified toxic agents include benzene, the antibiotic chloramphenicol, and the alkylating agents and antimetabolites used in the treatment of cancer (see Chapter 7). Aplastic anemia caused by exposure to chemical agents may be an idiosyncratic reaction because it affects only certain susceptible persons. It typically occurs weeks after a drug is initiated. Such reactions often are severe and sometimes irreversible and fatal. It can also develop in the course of many infections and has been reported most often as a complication of viral hepatitis, mononucleosis, and other viral illnesses, including acquired immunodeficiency syndrome (AIDS). In two thirds of cases, the cause is unknown, a condition referred to as *idiopathic aplastic anemia*. The mechanisms underlying the pathogenesis of aplastic anemia are unknown. It is suggested that exposure to the chemicals, infectious agents, and other insults generates a cellular immune response resulting in production of cytokines by activated T cells. These cytokines (e.g., interferon, tumor necrosis factor [TNF]) then suppress hematopoietic stem cell growth and development.[5]

Therapy for aplastic anemia in the young and severely affected includes stem cell replacement by bone marrow or peripheral blood transplantation. Histocompatible donors supply the stem cells to replace the patient's destroyed marrow cells. Graft-versus-host disease, rejection, and infection are major risks of the procedure, yet 75% or more survive.[22] For those who are not transplantation candidates, immunosuppressive therapy with lymphocyte immune globulin (i.e., antithymocyte globulin) prevents suppression of proliferating stem cells, producing remission in up to 50% of patients.[21,22] Persons with aplastic anemia should avoid the offending agents and be treated with antibiotics for infection. Red cell transfusions to correct the anemia and platelets and corticosteroid therapy to minimize bleeding may also be required.

Anemia of Chronic Disease

Anemia often occurs as a complication of chronic infections, inflammation, and cancer. The most common causes of chronic disease anemias are acute and chronic infections, including AIDS and osteomyelitis; cancers; autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease; and chronic kidney disease.[23] It is theorized that the short red cell life span, deficient red cell production, a blunted response to erythropoietin, and low serum iron are caused by actions of cytokines and cells of the reticuloendothelial system. Microorganisms, tumor cells, and autoimmune dysregulation lead to T-cell activation and production of cytokines (e.g., interleukin-1, interferon, and TNF) that suppress the erythropoietin response, inhibit erythroid precursors, and cause changes in iron homeostasis.[23] The mild anemia is normocytic and normochromic with low reticulocyte counts.

Chronic renal failure almost always results in anemia, primarily because of a deficiency of erythropoietin. Unidentified uremic toxins and retained nitrogen also interfere with the actions of erythropoietin and with red cell production and survival. Hemolysis and blood loss associated with hemodialysis and bleeding tendencies also contribute to the anemia of renal failure. Therapy for these anemias includes treatment for the underlying disease, short-term erythropoietin therapy, iron supplementation, and blood transfusions.[23]

In summary, anemia is a condition of an abnormally low number of circulating red blood cells or hemoglobin level, or both. It is not a disease, but a manifestation of a disease process or alteration in body function. The manifestations of anemia are those associated with impaired oxygen transport; alterations in red blood cell number, hemoglobin content, and cell structure; and signs and symptoms of the underlying process causing the anemia.

Anemia can result from excessive blood loss, red cell destruction due to hemolysis, or deficient hemoglobin or red cell production. Blood loss anemia can be acute or chronic. With bleeding, iron and other components of the erythrocyte are lost from the body. Hemolytic anemia is characterized by the premature destruction of red cells, with retention in the body of iron and the other products of red cell destruction. Hemolytic anemia can be caused by defects in the red cell membrane,

hemoglobinopathies (sickle cell disease or thalassemia), or inherited enzyme defects (G6PD deficiency). Acquired forms of hemolytic anemia are caused by agents extrinsic to the red blood cell, such as drugs, bacterial and other toxins, antibodies, and physical trauma.

Anemias that result from the diminished red cell production include anemias that are caused by a deficiency of the substances that are needed for erythropoiesis and bone marrow suppression or failure. Iron-deficiency anemia, which is characterized by decreased hemoglobin synthesis, can result from dietary deficiency, loss of iron through bleeding, or increased demands for red cell production. Vitamin B_{12} and folic acid deficiencies impair red cell production by interfering with DNA synthesis. Aplastic anemia is caused by bone marrow suppression and usually results in a reduction of white blood cells and platelets, as well as red blood cells. Chronic diseases such as inflammatory disorders (rheumatoid arthritis), cancers, and renal failure cause anemia through the production of inflammatory cytokines that interfere with erythropoietin production or response.

Polycythemia

Polycythemia represents an abnormally high total red blood cell count with a hematocrit greater than 50%. It is categorized as *relative* or *absolute*. In *relative* polycythemia, the hematocrit rises because of a loss of plasma volume without a corresponding decrease in red cells. This may occur with water deprivation, excess use of diuretics, or gastrointestinal losses. Relative polycythemia is corrected by increasing the vascular fluid volume. *Absolute* polycythemia is a rise in hematocrit due to an increase in total red cell mass and is classified as primary or secondary.

Primary Polycythemia

Primary polycythemia, or *polycythemia vera*, is a neoplastic disease of the pluripotent cells of the bone marrow characterized by an absolute increase in total red blood cell mass accompanied by elevated white cell and platelet counts. It most commonly is seen in men with a median age of 62 years, but may occur at any age.[24,25] In polycythemia vera, the manifestations are variable and are related to an increase in the red cell count, hemoglobin level, and hematocrit with increased blood volume and viscosity. Additional early findings include splenomegaly and depletion of iron stores.[25] Viscosity rises exponentially with the hematocrit and interferes with cardiac output and blood flow. Hypertension is common and there may be complaints of headache, dizziness, inability to concentrate, and some difficulty with hearing and vision because of decreased cerebral blood flow. Venous stasis gives rise to a plethoric appearance or dusky redness, even cyanosis, particularly of the lips, fingernails, and mucous membranes. Because of the increased concentration of blood cells, the person may experience itching and pain in the fingers or toes, and the hypermetabolism may induce night sweats and weight loss. Thromboembolism and hemorrhage, due to platelet abnormalities, are common complications that can be prevented by phlebotomy to reduce the hematocrit to less than 42% in women and less than 45% in men.[25] The goal of treatment in primary polycythemia is to reduce blood viscosity. This can be done by withdrawing blood by periodic phlebotomy to reduce red cell volume. Low-dose aspirin may control the high platelet counts, and suppression of bone marrow function with chemotherapy (hydroxyurea) controls the elevated white cell count.[25]

Secondary Polycythemia

Secondary polycythemia results from a physiologic increase in the level of erythropoietin, commonly as a compensatory response to hypoxia. Conditions causing hypoxia include living at high altitudes, chronic heart and lung disease, and smoking. The resultant release of erythropoietin by the kidney causes the increased formation of red blood cells in the bone marrow. Neoplasms that secrete erythropoietin may also cause a secondary polycythemia. Kidney disease such as hydronephrosis or renal cysts may obstruct blood flow, cause hypoxia, and lead to an increase in erythropoietin. Treatment of secondary polycythemia focuses on relieving hypoxia. For example, continuous low-flow oxygen therapy can be used to correct the severe hypoxia that occurs in some persons with chronic obstructive pulmonary disease. This form of treatment is thought to relieve the pulmonary hypertension and polycythemia and to delay the onset of cor pulmonale.

In summary, polycythemia describes a condition in which the red blood cell mass is increased. It can present as a relative, primary, or secondary disorder. Relative polycythemia results from a loss of vascular fluid and is corrected by replacing the fluid. Primary polycythemia, or polycythemia vera, is a proliferative disease of the bone marrow with an absolute increase in total red blood cell mass accompanied by elevated white cell and platelet counts. Secondary polycythemia results from increased erythropoietin levels caused by hypoxic conditions such as chronic heart and lung disease. Many of the manifestations of polycythemia are related to increased blood volume and viscosity that lead to hypertension and stagnation of blood flow.

Age-Related Changes in Red Blood Cells

Red Cell Changes in the Neonate

At birth, changes in the red blood cell indices reflect the transition to extrauterine life and the need to transport oxygen from the lungs (Table 13-2). Hemoglobin

TABLE 13-2 Red Cell Values for Term Infants

Age	RBC × 10^6/μL Mean ± SD	Hb (g/dL) Mean ± SD	Hct (%) Mean ± SD	MCV (fL) Mean ± SD
Days				
1	5.14 ± 0.7	19.3 ± 2.2	61 ± 7.4	119 ± 9.4
4	5.00 ± 0.6	18.6 ± 2.1	57 ± 8.1	114 ± 7.5
7	4.86 ± 0.6	17.9 ± 2.5	56 ± 9.4	118 ± 11.2
Weeks				
1–2	4.80 ± 0.8	17.3 ± 2.3	54 ± 8.3	112 ± 19.0
3–4	4.00 ± 0.6	14.2 ± 2.1	43 ± 5.7	105 ± 7.5
8–9	3.40 ± 0.5	10.7 ± 0.9	31 ± 2.5	93 ± 12.0
11–12	3.70 ± 0.3	11.3 ± 0.9	33 ± 3.3	88 ± 7.9

Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; RBC, red blood cell count.

Adapted from Matoth Y., Zaizor R., Varsano I. (1971). Postnatal changes in some red cell parameters. *Acta Paediatrica Scandinavica* 60, 317.

concentrations at birth are high, reflecting the high synthetic activity in utero to provide adequate oxygen delivery. Toward the end of the first postnatal week, hemoglobin concentration begins to decline, gradually falling to a minimum value at approximately age 2 months. The red cell count, hematocrit, and MCV likewise fall. The factors responsible for the decline include reduced red cell production and plasma dilution caused by increased blood volume with growth. Neonatal red cells also have a shorter life span of 50 to 70 days, and are thought to be more fragile than those of older persons. During the early neonatal period, there is also a switch from HbF to HbA. The amount of HbF in term infants averages about 70% of the total hemoglobin and declines to trace amounts by 6 to 12 months of age.[26] The switch to HbA provides greater unloading of oxygen to the tissues because HbA has a lower affinity for oxygen compared with HbF. Infants who are small for gestational age or born to diabetic or smoking mothers or who experienced hypoxia in utero have higher total hemoglobin levels, higher HbF levels, and a delayed switch to HbA.

A physiologic anemia of the newborn develops at approximately 2 months of age. It seldom produces symptoms and cannot be altered by nutritional supplements. Anemia of prematurity, an exaggerated physiologic response in infants with low birth weight, is thought to result from a poor erythropoietin response. A contributing factor is the frequent blood sampling often required in these infants. The hemoglobin level rapidly declines after birth to a low of 7 to 10 g/dL at approximately 6 weeks of age. Signs and symptoms include apnea, poor weight gain, pallor, decreased activity, and tachycardia. In infants born before 33 weeks' gestation or those with hematocrits below 33%, the clinical features are more evident.

Anemia at birth, characterized by pallor, congestive heart failure, or shock, usually is caused by hemolytic disease of the newborn. Bleeding from the umbilical cord, internal hemorrhage, congenital hemolytic disease, or frequent blood sampling are other possible causes of anemia. The severity of symptoms and presence of coexisting disease may warrant red cell transfusion.

Hyperbilirubinemia in the Neonate

Hyperbilirubinemia, an increased level of serum bilirubin, is a common cause of jaundice in the neonate. A benign, self-limited condition, it most often is related to the developmental state of the neonate. Rarely, cases of hyperbilirubinemia are pathologic and may lead to kernicterus and serious brain damage.

In the first week of life, approximately 60% of term and 80% of preterm neonates are jaundiced.[26] This physiologic jaundice appears in term infants on the second or third day of life. Ordinarily, the indirect bilirubin in umbilical cord blood is 1 to 3 mg/dL and increases by no more than 5 mg/dL in 24 hours, giving rise to jaundice. The levels peak at 5 to 6 mg/dL between days 2 and 4 and decrease to less than 2 mg/dL by days 5 to 7.[26] The increase in bilirubin is related to the increased red cell breakdown and the inability of the immature liver to conjugate bilirubin. Premature infants exhibit a slower rise and longer duration of serum bilirubin levels, perhaps because of poor hepatic uptake and reduced albumin binding of bilirubin. Peak bilirubin levels of 8 to 12 mg/dL appear on days 5 to 7. Most neonatal jaundice resolves within 1 week and is untreated.

Many factors can contribute to elevated bilirubin levels in the neonate, including breast-feeding, hemolytic disease of the newborn, hypoxia, infections, and acidosis. Bowel or biliary obstruction and liver disease are less common causes. Associated risk factors include prematurity, Asian ancestry, and maternal diabetes. Breast milk jaundice occurs in approximately 2% of breast-fed infants.[27] These neonates accumulate significant levels of unconjugated bilirubin 7 days after birth, with maximum levels of 10 to 30 mg/dL reached in the third week of life. It is thought that the breast milk contains fatty acids that inhibit bilirubin conjugation in the neonatal liver. A factor in breast milk is also thought to increase the absorption of bilirubin in the duodenum. This type of jaundice

disappears if breast-feeding is discontinued. Nursing can be resumed in 3 to 4 days without any hyperbilirubinemia ensuing.

Hyperbilirubinemia places the neonate at risk for the development of a neurologic syndrome called *kernicterus*. This condition is caused by the accumulation of unconjugated bilirubin in brain cells. Unconjugated bilirubin is lipid soluble, crosses the permeable blood-brain barrier of the neonate, and is deposited in cells of the basal ganglia, causing brain damage. Asphyxia and hyperosmolality may also contribute by damaging the blood-brain barrier and allowing bilirubin to cross and enter the cells. The level of unconjugated bilirubin and the duration of exposure that will be toxic to the infant are unknown. The less mature infant, however, is at greater risk for kernicterus.[27] The manifestations of kernicterus may appear 2 to 5 days after birth in term infants or by day 7 in premature infants. Lethargy, poor feeding, and short-term behavioral changes may be evident in mildly affected infants. Severe manifestations include rigidity, tremors, ataxia, and hearing loss. Extreme cases cause seizures and death. Most survivors are seriously damaged and by 3 years of age exhibit involuntary muscle spasm, seizures, mental retardation, and deafness.

Hyperbilirubinemia in the neonate is treated with phototherapy or exchange transfusion. Phototherapy is more commonly used to treat jaundiced infants and reduce the risk of kernicterus. Exposure to fluorescent light in the blue range of the visible spectrum (420- to 470-nm wavelength) reduces bilirubin levels. Bilirubin in the skin absorbs the light energy and is converted to a structural isomer that is more water soluble and can be excreted in the stool and urine. Effective treatment depends on the area of skin exposed and the infant's ability to metabolize and excrete bilirubin. Frequent monitoring of bilirubin levels, body temperature, and hydration is critical to the infant's care. Exchange transfusion is considered when signs of kernicterus are evident or hyperbilirubinemia is sustained or rising and unresponsive to phototherapy.

Hemolytic Disease of the Newborn

Erythroblastosis fetalis, or hemolytic disease of the newborn, occurs in Rh-positive infants of Rh-negative mothers who have been sensitized. The mother can produce anti-Rh antibodies from pregnancies in which the fetus is Rh positive or from blood transfusions of Rh-positive blood. The Rh-negative mother usually becomes sensitized during the first few days after delivery, when fetal Rh-positive red cells from the placental site are released into the maternal circulation. Because the antibodies take several weeks to develop, the first Rh-positive infant of an Rh-negative mother usually is not affected. Infants with Rh-negative blood have no antigens on their red cells to react with the maternal antibodies and are not affected.

After an Rh-negative mother has been sensitized, the Rh antibodies from her blood are transferred to subsequent infants through the placental circulation. These antibodies react with the red cell antigens of the Rh-positive fetus, causing agglutination and hemolysis. This leads to severe anemia with compensatory hyperplasia and enlargement of the blood-forming organs, including the spleen and liver, in the fetus. Liver function may be impaired, with decreased production of albumin causing massive edema, called *hydrops fetalis*. If blood levels of unconjugated bilirubin are abnormally high because of red cell hemolysis, there is a danger of kernicterus developing in the infant, resulting in severe brain damage or death.

Several advances have served significantly to decrease the threat to infants born to Rh-negative mothers: prevention of sensitization, antenatal identification of the at-risk fetus, and intrauterine transfusion to the affected fetus. The injection of Rh immune globulin (i.e., γ-globulin containing Rh antibody) prevents sensitization in Rh-negative mothers who have given birth to Rh-positive infants if administered at 28 weeks' gestation and within 72 hours of delivery, abortion, genetic amniocentesis, or fetal-maternal bleeding. After sensitization has developed, the immune globulin is of no value. Fetal Rh phenotyping can now be performed to identify at-risk fetuses in the first trimester using fetal blood or amniotic cells.[28] Hemolysis in these fetuses can be treated by intrauterine transfusions of red cells through the umbilical cord. Exchange transfusions are administered after birth by removing and replacing the infant's blood volume with type O Rh-negative blood. The exchange transfusion removes most of the hemolyzed red cells and some of the total bilirubin, treating the anemia and hyperbilirubinemia.

Red Cell Changes in the Elderly

Anemia is an increasingly common health problem in the elderly, affecting approximately one fourth of 80-year-olds in the community and half of the chronically ill elderly.[29] Its prevalence is known to increase with age, with the highest prevalence in men aged 85 years and older. Undiagnosed and untreated anemia can have severe consequences and is associated with increased risk of mortality, cardiovascular disease, lower functional ability, self-care deficits, cognitive disorders, and reduced bone density that increases the risk for fractures with falls.[29]

Hemoglobin levels decline after middle age. In studies of men older than 60 years of age, mean hemoglobin levels ranged from 15.3 to 12.4 g/dL, with the lowest levels found in the oldest persons. The decline is less in women, with mean levels ranging from 13.8 to 11.7 mg/dL.[30] In most asymptomatic elderly persons, lower hemoglobin levels result from iron deficiency and anemia of chronic disease.

As with other body systems, the capacity for red cell production changes with aging. The location of bone cells involved in red cell production shifts toward the axial skeleton, and the number of progenitor cells declines from approximately 50% at age 65 to approximately 30% at age 75 years.[30] Despite these changes, the elderly are usually able to maintain hemoglobin and hematocrit levels within a range similar to that of younger adults.[31] However, during a stress situation such as bleeding, the red blood cells of the elderly are not replaced as promptly as those of their younger counterparts. This inability to replace red

blood cells closely correlates with the increased prevalence of anemia in the elderly.

Although the age-associated decline in the hematopoietic reserve in the elderly is not completely understood, several factors seem to play a role, including a reduction in hematopoietic progenitors, reduced production of hematopoietic growth factors, and inhibition of erythropoietin or its interaction with its receptors.[29,32] Inflammatory cytokines, which have been found to increase with age, may mediate this reduced sensitivity to erythropoietin.

The diagnosis of anemia in the elderly requires a complete physical examination, a complete blood count, and studies to rule out comorbid conditions such as malignancy, gastrointestinal conditions that cause bleeding, and pernicious anemia. The complete blood count should include a peripheral blood smear and a reticulocyte count and index. If the reticulocyte index is appropriately increased for the level of anemia, then blood loss or red cell destruction should be suspected. If the reticulocyte index is inappropriately low, then decreased red cell production is indicated.[32]

The treatment of anemia in the elderly should focus on the underlying cause and correction of the red cell deficit. An important aspect of anemia of chronic disease is the inability to use and mobilize iron effectively.[29] Orally administered iron is poorly used in older adults, despite normal iron absorption.[30] Although erythropoietin remains the treatment of choice for anemias associated with cancer and renal disease, its potential use in treating anemias associated with aging remains to be established.

In summary, hemoglobin concentrations at birth are high, reflecting the in utero need for oxygen delivery; toward the end of the first postnatal week, these levels begin to decline, gradually falling to a minimum value at approximately 2 months of age. During the early neonatal period, there is a shift from fetal to adult hemoglobin. Many infants have physiologic jaundice because of hyperbilirubinemia during the first week of life, probably related to increased red cell breakdown and the inability of the infant's liver to conjugate bilirubin. The term *kernicterus* describes elevated levels of lipid-soluble, unconjugated bilirubin, which can be toxic to brain cells. Depending on severity, it is treated with phototherapy or exchange transfusions (or both). Hemolytic disease of the newborn occurs in Rh-positive infants of Rh-negative mothers who have been sensitized. It involves hemolysis of infant red cells in response to maternal Rh antibodies that have crossed the placenta. Administration of Rh immune globulin to the mother within 72 hours of delivery of an Rh-positive infant, abortion, or amniocentesis prevents sensitization.

Anemia is an increasingly common health problem in the elderly, affecting approximately 25% of persons aged 80 years and older. As with many other types of tissue cells, the replacement capacity for red cells decreases with aging. Although most elderly persons are able to maintain their hemoglobin and hematocrit levels within a normal range, they are unable to replace their red cells as promptly as their younger counterparts during a stress situation such as bleeding. This inability to replace red blood cells closely correlates with the increased prevalence of anemia in the elderly, which is usually the result of bleeding, infection, malignancy, or chronic disease.

REVIEW EXERCISES

1. A 29-year-old woman complains of generalized fatigue. Her physical examination reveals a heart rate of 115 beats/minute, blood pressure of 115/75, and respiratory rate of 28 breaths/minute. Her skin and nail beds are pale. Her laboratory results include red blood cell count $3.0 \times 10^6/\mu L$, hematocrit 30%, hemoglobin 9 g/dL, and a decrease in serum ferritin levels.

- **A.** What disorder do you suspect this woman has?
- **B.** What additional data would be helpful in determining the etiology of her condition?
- **C.** Which of her signs reflect the body's attempt to compensate for the disorder?
- **D.** What is the significance of the low ferritin level, and how could it be used to make decisions related to her treatment?

2. A 65-year-old woman is being seen in the clinic because of numbness in her lower legs and feet and difficulty walking. She has no other complaints. She takes a blood pressure pill, two calcium pills, and a multivitamin pill daily. Her laboratory results include red blood cell count $3.0 \times 10^6/\mu L$, hematocrit 20%, hemoglobin 9 g/dL, and a markedly elevated MVC.

- **A.** What type of anemia does she have?
- **B.** What is the reason for her neurologic symptoms?
- **C.** What type of treatment would be appropriate?

3. A 12-year-old boy with sickle cell disease presents in the emergency department with severe chest pain. His mother reports that he was doing well until he came down with a respiratory tract infection. She also states he insisted on playing basketball with the other boys in the neighborhood even though he wasn't feeling well.

- **A.** What is the most likely cause of pain in this boy?
- **B.** Infections and aerobic-type exercise that increase the levels of deoxygenated hemoglobin produce sickling in persons who are homozygous for the sickle cell gene and have sickle cell disease, but not in persons who are heterozygous and have sickle cell trait. Explain.
- **C.** People with sickle disease experience anemia but not iron deficiency. Explain.

REFERENCES

1. English E. (2003). Blood components, immunity, and hemostasis. In Rhoades R.A., Tanner R.A. (Eds.), *Medical physiology* (2nd ed., pp. 191–197). Philadelphia: Lippincott Williams & Wilkins.
2. Ross M.H., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 247–253). Philadelphia: Lippincott Williams & Wilkins.
3. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 419–438, 862–864). Philadelphia: W.B. Saunders.
4. Fisher J.W. (2003). Erythropoietin: Physiology and pharmacology update. *Experimental Biology and Medicine* 228, 1–14.
5. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., 639–675). Philadelphia: Saunders Elsevier.
6. Schwarting R., McKenzie S., Rubin R. (2008). Hematopathology. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 861–880). Philadelphia: Lippincott Williams & Wilkins.
7. Chiang E.Y., Frenette P.S. (2005). Sickle cell vaso-occlusion. *Hematology and Oncology Clinics of North America* 19, 771–784.
8. Ballas S.K. (2001). Sickle cell disease. *Seminars in Hematology* 38, 307–314.
9. Gladwin M.T., Vichinsky E. (2008). Pulmonary complications of sickle cell disease. *New England Journal of Medicine* 359(21), 2254–2265.
10. Stuart M.J., Nagel R.L. (2004). Sickle-cell disease. *Lancet* 364, 1343–1360.
11. National Institutes of Health. (2002). *The management of sickle cell disease.* NIH publication no. 02-2117. [Online] Available: http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf. Accessed February 10, 2009.
12. Vichinsky E. (2002). New therapies in sickle cell disease. *Lancet* 360, 629–631.
13. Rund D., Rachmilewitz E. (2005). β-Thalassemia. *New England Journal of Medicine* 353, 1135–1146.
14. Lo L., Singer S.T. (2002). Thalassemia: Current approach to an old disease. *Pediatric Clinics of North America* 49, 1165–1191.
15. Brittenham G.M. (2000). Disorders of iron metabolism: Iron deficiency and overload. In Hoffman R., Benz E.J., Shattil S.J., et al. (Eds.), *Hematology: Basic principles and practice* (3rd ed., pp. 405, 413). New York: Churchill Livingstone.
16. Glader B. (2004). Anemia of inadequate production. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 1606–1607). Philadelphia: Elsevier Saunders.
17. Lozoff B., Beard J., Connor J., et al. (2006). Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutritional Reviews* 64, S34–S43.
18. Kazal L.A. (2002). Prevention of iron deficiency in infants and toddlers. *American Family Physician* 66, 1217–1224.
19. Aslinia F., Mazza J.J., Yale S.H. (2006). Megaloblastic anemia and other causes of macrocytosis. *Clinical Medicine and Research* 3, 236–241.
20. Oh R., Brown D.L. (2003). Vitamin B_{12} deficiency. *American Family Physician* 67, 979–986.
21. Young N.S. (2002). Acquired aplastic anemia. *Annals of Internal Medicine* 136, 534–546.
22. Young N.S., Calada R.T., Scheinberg P. (2006). Current concepts in the pathophysiology and treatment of aplastic anemia. *Blood* 108, 2509–2519.
23. Weiss G., Goodnough L.T. (2005). Anemia of chronic disease. *New England Journal of Medicine* 352, 1011–1023.
24. Stuart B.J., Viera A.J. (2004). Polycythemia vera. *American Family Physician* 69, 2139–2144.
25. Tefferi A., Spivak J.L. (2005). Polycythemia vera: Scientific advances and current practice. *Seminars in Hematology* 42, 206–220.
26. Ohls R.K., Christensen R.D. (2007). Development of the hematopoietic system. In Kliegman R.M., Behrman R.E., Jenson H.B., et al. (Eds.), *Nelson Textbook of Pediatrics* (18th ed., pp. 1997–2005). Philadelphia: Elsevier Saunders.
27. Piazzo A.J., Stoll B.J. (2007). Jaundice and hyperbilirubinemia in the newborn. In Kliegman R.M., Behrman R.E., Jenson H.B., et al. (Eds.), *Nelson Textbook of Pediatrics* (18th ed., pp. 756–766). Philadelphia: Elsevier Saunders.
28. Kramer K., Cohen H.J. (2000). Antenatal diagnosis of hematologic disorders. In Hoffman R., Benz E.J., Shattil S.J., et al. (Eds.), *Hematology: Basic principles and practice* (3rd ed., p. 2495). New York: Churchill Livingstone.
29. Eisenstaedt R., Pennix B.W., Woodman R.C. (2006). Anemia in the elderly: Current understanding and emerging concepts. *Blood Review* 20, 213–226.
30. Balducci L. (2003). Epidemiology of anemia in the elderly: Information on diagnostic evaluation. *Journal of the American Geriatrics Society* 51(Suppl 3), S2–S9.
31. Rothstein G. (2003). Disordered hematopoiesis and myelodysplasia in the elderly. *Journal of the American Geriatrics Society* 51(Suppl 3), S22–S26.
32. Lipschitz D. (2003). Medical and functional consequences of anemia in the elderly. *Journal of the American Geriatrics Society* 51(Suppl 3), S10–S13.

UNIT 4

Infection and Immunity

Infectious Diseases
- *Terminology*
- *Agents of Infectious Disease*
  - Prions
  - Viruses
  - Bacteria
  - Rickettsiaceae, Anaplasmataceae, Chlamydiaceae, and Coxiella
  - Fungi
  - Parasites

Epidemiology of Infectious Diseases
- *Mechanisms of Transmission*
  - Portal of Entry
  - Source
- *Mechanisms of Disease Production*
  - Virulence Factors
- *Symptomatology*
- *Site of Infection*
- *Disease Course*

Diagnosis and Treatment
- *Techniques for Diagnosing Infectious Agents*
  - Culture
  - Serology
  - DNA and RNA Sequencing
- *Treatment*
  - Antimicrobial Agents
  - Surgical Interventions

New and Emerging Infectious Diseases
- *Global Infectious Diseases*
- *Agents of Bioterrorism*

Chapter 14

Mechanisms of Infectious Disease

All living creatures share two basic objectives in life: survival and reproduction. This doctrine applies equally to all members of the living world, including bacteria, viruses, fungi, and protozoa. To satisfy these goals, organisms must extract from the environment essential nutrients for growth and proliferation; for countless microscopic organisms, that environment includes the human body. Normally, the contact between humans and microorganisms is incidental and, in certain situations, may actually benefit both organisms. Under extraordinary circumstances, however, the invasion of the human body by microorganisms can produce harmful and potentially lethal consequences. The consequences of these invasions are collectively called *infectious diseases*.

Infectious Diseases

Terminology

All scientific disciplines evolve with a distinct vocabulary, and the study of infectious diseases is no exception. The most appropriate way to approach this subject is with a brief discussion of the terminology used to characterize interactions between humans and microbes.

Any organism capable of supporting the nutritional and physical growth requirements of another is called a *host*. Throughout this chapter, the term *host* most often refers to humans supporting the growth of microorganisms. Occasionally, *infection* and *colonization* are used

interchangeably. However, the term *infection* describes the presence and multiplication within another living organism, with subsequent injury to the host, whereas *colonization* describes the act of establishing a presence, a step required in the multifaceted process of infection.

One common misconception should be dispelled from the start: not all interactions between microorganisms and humans are detrimental. The internal and external exposed surfaces of the human body are normally and harmlessly inhabited by a multitude of bacteria, collectively referred to as the normal *microflora*. Although the colonizing bacteria acquire nutritional needs and shelter, the host is not adversely affected by the relationship. An interaction such as this is called *commensalism*, and the colonizing microorganisms are sometimes referred to as *commensal flora*. The term *mutualism* is applied to an interaction in which the microorganism and the host both derive benefits from the interaction. For example, certain inhabitants of the human intestinal tract extract nutrients from the host and secrete essential vitamin byproducts of metabolism (e.g., vitamin K) that are absorbed and used by the host. A *parasitic relationship* is one in which only the infecting organism benefits from the relationship and the host either gains nothing from the relationship or sustains injury from the interaction. If the host sustains injury or pathologic damage in response to a parasitic infection, the process is called an *infectious disease*.

The severity of an infectious disease can range from mild to life-threatening, depending on many variables, including the health of the host at the time of infection and the *virulence* (disease-producing potential) of the microorganism. A select group of microorganisms called *pathogens* are so virulent that they are rarely found in the absence of disease. Fortunately, there are few human pathogens in the microbial world. Most microorganisms are harmless *saprophytes*, free-living organisms obtaining their growth from dead or decaying organic material in the environment. All microorganisms, even saprophytes and members of the normal flora, can be *opportunistic pathogens*, capable of producing an infectious disease when the health and immunity of the host have been severely weakened by illness, malnutrition, or medical therapy.

Agents of Infectious Disease

- The agents of infectious disease represent a diversity of microorganisms that are usually not visible to the human eye.
- Microorganisms can be separated into eukaryotes (fungi and parasites), organisms containing a membrane-bound nucleus, and prokaryotes (bacteria), organisms in which the nucleus is not separated.
- Eukaryotes and prokaryotes are organisms because they contain all the enzymes and biologic equipment necessary for replication and exploiting metabolic energy.
- Viruses, which are the smallest pathogens, have no organized cellular structure, but consist of a protein coat surrounding a nucleic acid core of DNA or RNA. Unlike eukaryotes and prokaryotes, viruses are incapable of replication outside of a living cell.
- Parasites (protozoa, helminths, and arthropods) are members of the animal kingdom that infect or colonize other animals, which then transmit them to humans or in some cases directly infect the human host.

Agents of Infectious Disease

The agents of infectious disease include prions, viruses, bacteria, *Rickettsiaceae* and *Chlamydiaceae*, fungi, and parasites. A summary of the salient characteristics of these human microorganisms is provided in Table 14-1.

TABLE 14-1 Comparison of Characteristics of Human Microbial Pathogens

Organism	Defined Nucleus	Genomic Material	Size*	Intracellular or Extracellular	Motility
Prions	No	Unknown	55 kDa	E	–
Viruses	No	DNA or RNA	0.02–0.3	I	–
Bacteria	No	DNA	0.5–15	I/E	±
Mycoplasmas	No	DNA	0.2–0.3	E	–
Spirochetes	No	DNA	6–15	E	+
Rickettsiaceae	No	DNA	0.2–2	I	–
Chlamydiaceae	No	DNA	0.3–1	I	–
Yeasts	Yes	DNA	2–60	I/E	–
Molds	Yes	DNA	2–15 (hyphal width)	E	–
Protozoans	Yes	DNA	1–60	I/E	+
Helminths	Yes	DNA	2 mm to >1 m	E	+

*Micrometers unless indicated.

Prions

Can a protein alone cause a transmissible infectious disease? Until recently, microbiologists assumed that all infectious agents must possess a genetic master plan (a genome of either ribonucleic acid [RNA] or deoxyribonucleic acid [DNA]) that codes for the production of the essential proteins and enzymes necessary for survival and reproduction. Prions, protein particles that lack any kind of a demonstrable genome, appear to be an exception to this rule. A number of prion-associated diseases have been identified, including Creutzfeldt-Jakob disease in humans, chronic wasting disease in deer and elk, and bovine spongiform encephalopathy (BSE or mad cow disease) in cattle. The various prion-associated diseases produce very similar pathologic processes and symptoms in the hosts and are collectively called *transmissible neurodegenerative diseases*. All are characterized by a slowly progressive, noninflammatory neuronal degeneration, leading to loss of coordination (ataxia), dementia, and death over a period ranging from months to years. In fact, recent studies indicate that prion proteins (called PrP^{SC}) are actually altered or mutated forms of a normal host protein called PrP^{C}. Differences in the posttranslational structure cause the two proteins to behave differently. The PrP^{SC} is resistant to the action of proteases (enzymes that degrade excess or deformed proteins) and aggregates in the cytoplasm of affected neurons as amyloid fibrils. The normal PrP^{C} is protease sensitive and appears on the cell surface.

Prion diseases present significant problems to the medical community because their method of replication is not clearly understood. Based on current models, it is believed that PrP^{SC} binds to the normal PrP^{C} on the cell surface, causing it to be processed into PrP^{SC}, which is released from the cell and then aggregates into amyloid-like plaques in the brain. The cell then replenishes the PrP^{C} and the cycle continues. As PrP^{SC} accumulates, it spreads within the axons of the nerve cells, causing progressively greater damage of host neurons and the eventual incapacitation of the host. In addition, because prions lack reproductive and metabolic functions, the currently available antimicrobial agents are useless against them.

Viruses

Viruses are the smallest obligate intracellular pathogens. They have no organized cellular structures but instead consist of a protein coat, or capsid, surrounding a nucleic acid core, or genome, of RNA or DNA—never both (Fig. 14-1). Some viruses are enclosed within a lipoprotein envelope derived from the cytoplasmic membrane of the parasitized host cell. Enveloped viruses include members of the herpesvirus group and paramyxoviruses, such as influenza and poxviruses. Certain enveloped viruses are continuously shed from the infected cell surface, enveloped in buds pinched from the cell membrane.

The viruses of humans and animals have been categorized somewhat arbitrarily according to various characteristics. These include the type of viral genome (single-stranded or double-stranded DNA or RNA), physical characteristics (e.g., size, presence or absence of a membrane envelope), the mechanism of replication

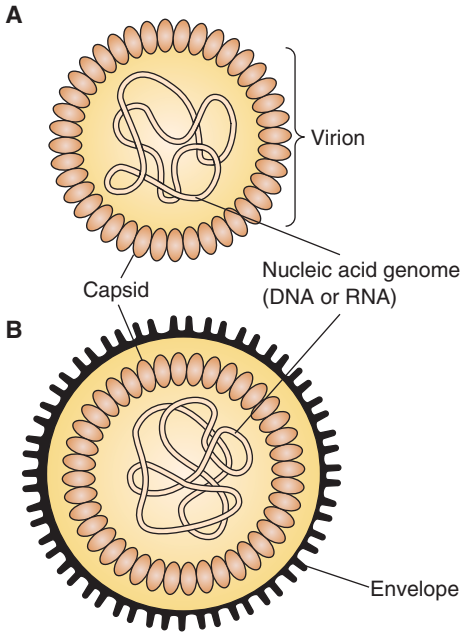


FIGURE 14-1. **(A)** The basic structure of a virus includes a protein coat surrounding an inner core of nucleic acid (DNA or RNA). **(B)** Some viruses may also be enclosed in a lipoprotein outer envelope.

(e.g., retroviruses), the mode of transmission (e.g., arthropod-borne viruses, enteroviruses), target tissue, and the type of disease produced (e.g., hepatitis A, B, C, D, and E viruses), to name just a few.

Viruses are incapable of replication outside of a living cell. They must penetrate a susceptible living cell and use the biosynthetic machinery of the cell to produce viral progeny. The process of viral replication is shown in Figure 14-2. Not every viral agent causes lysis and death of the host cell during the course of replication. Some viruses enter the host cell and insert their genome into the host cell chromosome, where it remains in a latent, nonreplicating state for long periods without causing disease. Under the appropriate stimulation, the virus undergoes active replication and produces symptoms of disease months to years later. Members of the herpesvirus group and adenovirus are the best examples of latent viruses. Herpesviruses include the viral agents of chickenpox and zoster (varicella-zoster), cold sores (herpes simplex virus [HSV] type 1), genital herpes (HSV type 2), infectious mononucleosis (Epstein-Barr virus), and Kaposi sarcoma (herpesvirus 8). The resumption of the latent viral replication may produce symptoms of primary disease (e.g., genital herpes) or cause an entirely different symptomatology (e.g., shingles instead of chickenpox).

A family of viruses that has gained a great deal of attention in the media recently are the Orthomyxoviridae or influenza viruses. Most of the recent attention has focused on the 2009 H1N1, or swine influenza virus that causes human infection and acute respiratory illness. This virus emerged on April 17, 2009, as a triple reassortment of human, avian, and swine influenza viruses. By combining three types of influenza viruses, a novel strain emerged that was not recognized by most of our

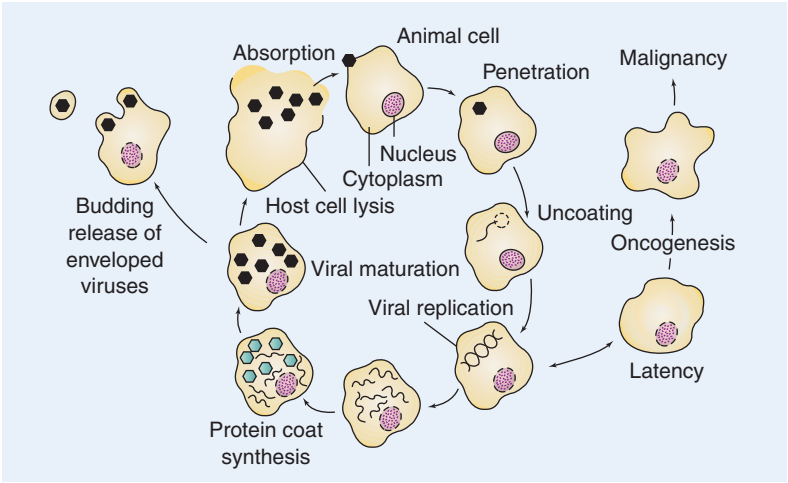


FIGURE 14-2. Schematic representation of the many possible consequences of viral infection of host cells, including cell lysis (poliovirus), continuous release of budding viral particles, or latency (herpesviruses) and oncogenesis (papovaviruses).

immune systems. This reassortment allowed the virus to spread throughout the world in less than 1 year, resulting in the first pandemic since 1968.

Since the early 1980s, members of the retrovirus group have received considerable attention after identification of the human immunodeficiency viruses (HIV) as the causative agent of acquired immunodeficiency syndrome (AIDS). The retroviruses have a unique mechanism of replication. After entry into the host cell, the viral RNA genome is first translated into DNA by a viral enzyme called *reverse transcriptase* (see Chapter 16). The viral DNA copy is then integrated into the host chromosome where it exists in a latent state, similar to the herpesviruses. Reactivation and replication require a reversal of the entire process. Some retroviruses lyse the host cell during the process of replication. In the case of HIV, the infected cells regulate the immunologic defense system of the host and their lysis leads to a permanent suppression of the immune response.

In addition to causing infectious diseases, certain viruses also have the ability to transform normal host cells into malignant cells during the replication cycle. This group of viruses is referred to as *oncogenic* and includes certain retroviruses and DNA viruses, such as the Epstein-Barr virus, hepatitis B virus, and human papillomavirus (see Chapter 7).

Bacteria

Bacteria are autonomously replicating unicellular organisms known as *prokaryotes* because they lack an organized nucleus. Compared with nucleated eukaryotic cells (see Chapter 1), the bacterial cell is small and structurally primitive (Fig. 14-3). Similar to eukaryotic cells, but unlike viruses, bacteria contain both DNA and RNA, although their genome consists of only a single chromosome of DNA. Many bacteria transiently harbor smaller extrachromosomal pieces of circular DNA called *plasmids*. Occasionally, plasmids contain genetic information that increases the virulence or antibiotic resistance of the organism.

The prokaryotic cell is organized into an internal compartment called the *cytoplasm*, which contains the reproductive and metabolic machinery of the cell. The cytoplasm is surrounded by a flexible lipid membrane, called the *cytoplasmic membrane*. This in turn is enclosed within a rigid cell wall. The structure and synthesis of the cell wall determine the microscopic shape of the bacterium (e.g., spherical [cocci], helical [spirilla], or elongate [bacilli], Fig. 14-4). Most bacteria produce a cell wall composed of a distinctive polymer known as *peptidoglycan*. This polymer is produced only by prokaryotes and is therefore an attractive target for antibacterial therapy. Several bacteria synthesize an extracellular capsule composed of protein or carbohydrate. The capsule protects the organism from environmental hazards such as the immunologic defenses of the host.

FIGURE 14-3. Electron micrograph of the rod-shaped, gram-positive bacterium *Listeria monocytogene*s showing the simple prokaryotic cell structure including the cytoplasm, the cytoplasmic membrane, and the rigid cell wall. (Public Images Library, Centers for Disease Control and Prevention. Courtesy Balasubr Swaminathan, Peggy Hayes.)

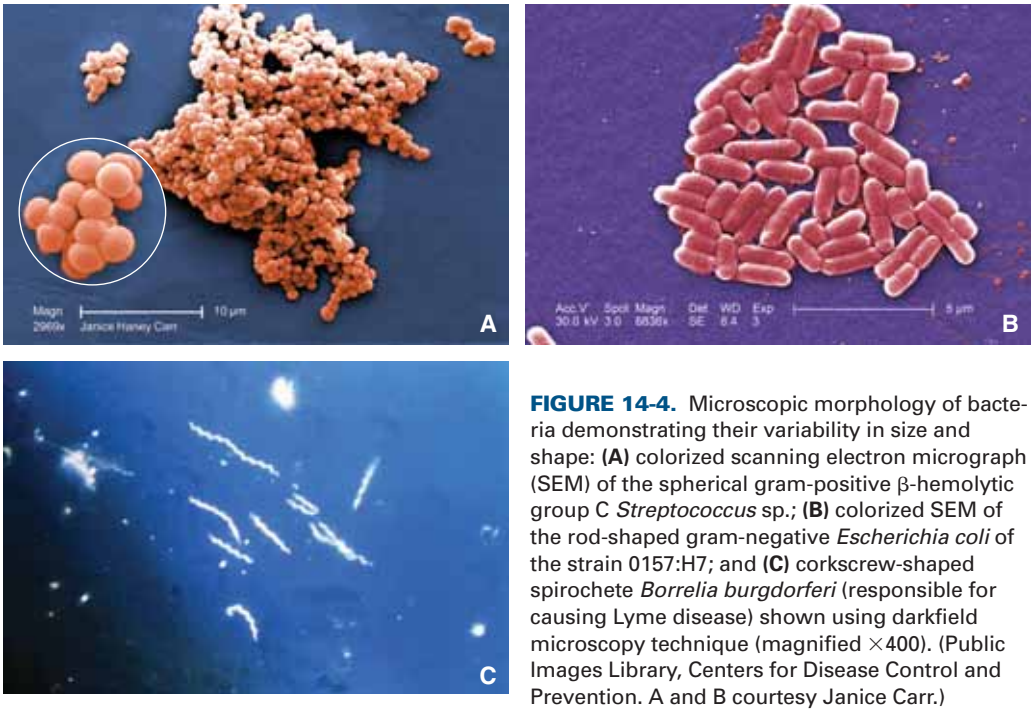


FIGURE 14-4. Microscopic morphology of bacteria demonstrating their variability in size and shape: **(A)** colorized scanning electron micrograph (SEM) of the spherical gram-positive β-hemolytic group C *Streptococcus* sp.; **(B)** colorized SEM of the rod-shaped gram-negative *Escherichia coli* of the strain 0157:H7; and **(C)** corkscrew-shaped spirochete *Borrelia burgdorferi* (responsible for causing Lyme disease) shown using darkfield microscopy technique (magnified ×400). (Public Images Library, Centers for Disease Control and Prevention. A and B courtesy Janice Carr.)

Certain bacteria are motile as the result of external whiplike appendages called *flagella*. The flagella rotate like a propeller, transporting the organism through a liquid environment. Bacteria can also produce hairlike structures projecting from the cell surface called *pili* or *fimbriae,* which enable the organism to adhere to surfaces such as mucous membranes or other bacteria.

Most prokaryotes reproduce asexually by simple cellular division. The manner in which an organism divides can influence the microscopic morphology. For instance, when the cocci divide in chains, they are called *streptococci;* in pairs, *diplococci*; and in clusters, *staphylococci* (Fig. 14-5). The growth rate of bacteria varies significantly among different species and depends greatly on physical growth conditions and the availability of nutrients. In the laboratory, a single bacterium placed in a suitable growth environment, such as an agar plate, reproduces to the extent that it forms a visible colony composed of millions of bacteria within a few hours.

In nature, however, bacteria rarely exist as single cells floating in an aqueous environment. Rather, bacteria prefer to stick to and colonize environmental surfaces,

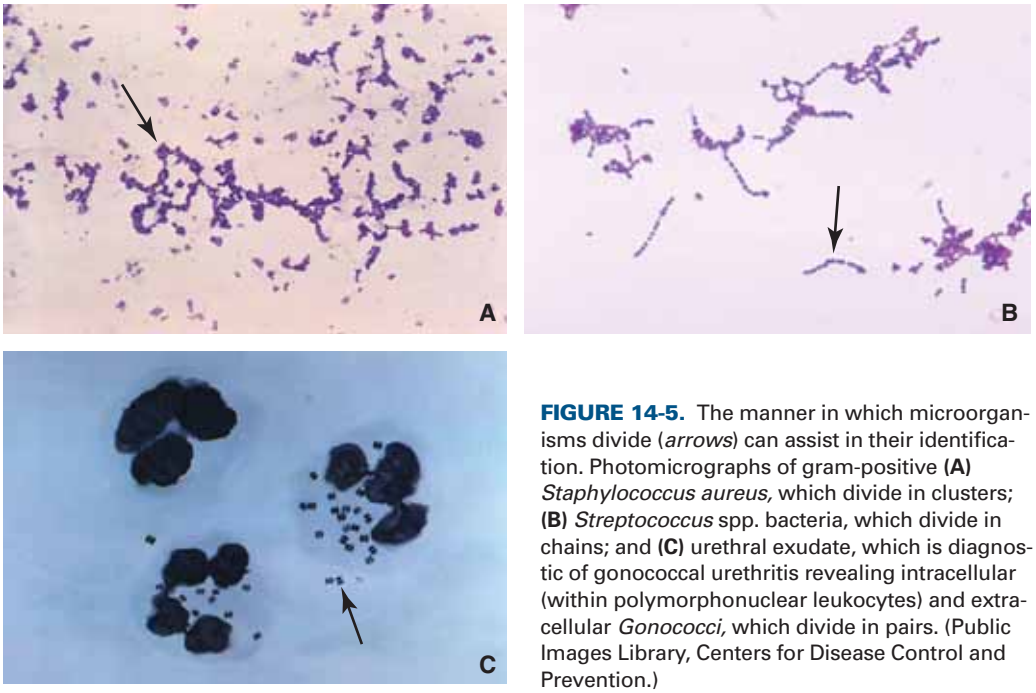


FIGURE 14-5. The manner in which microorganisms divide (*arrows*) can assist in their identification. Photomicrographs of gram-positive **(A)** *Staphylococcus aureus,* which divide in clusters; **(B)** *Streptococcus* spp. bacteria, which divide in chains; and **(C)** urethral exudate, which is diagnostic of gonococcal urethritis revealing intracellular (within polymorphonuclear leukocytes) and extracellular *Gonococci,* which divide in pairs. (Public Images Library, Centers for Disease Control and Prevention.)

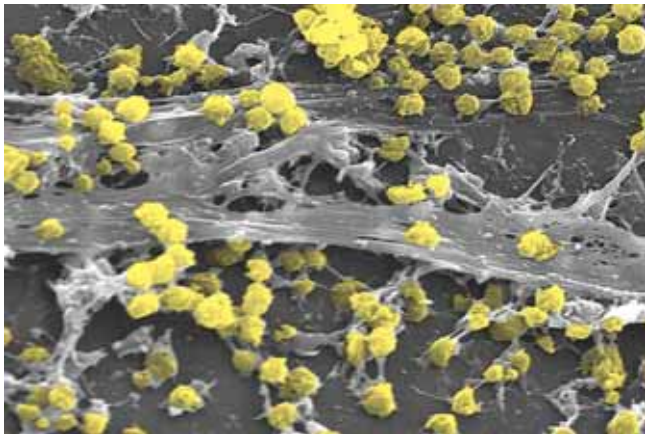


FIGURE 14-6. Electron micrograph depicting large numbers of *Staphylococcus aureus* bacteria, which were found on the luminal surface of an indwelling catheter. Of importance are the sticky-looking substances woven between the round cocci bacteria, which were composed of polysaccharides and are known as *biofilm*. This biofilm has been found to protect the bacteria that secrete the substance from attacks by antimicrobial agents such as antibiotics (magnified ×2363). (Public Images Library, Centers for Disease Control and Prevention. Courtesy Janice Carr.)

producing structured communities called *biofilms* (Fig. 14-6). The organization and structure of biofilms permit access to available nutrients and elimination of metabolic waste. Within the biofilm, individual organisms use chemical signaling as a form of primitive intercellular communication to represent the state of the environment. These signals inform members of the community when sufficient nutrients are available for proliferation or when environmental conditions warrant dormancy or evacuation. Examples of biofilms abound in nature and are found on surfaces of aquatic environments and on humans. One has only to disassemble a clogged sink drain to see a perfect example of a bacterial biofilm.

The physical appearance of a colony of bacteria grown on an agar plate can be quite distinctive for different species. Some produce pigments that give colonies a unique color. Some bacteria produce highly resistant spores when faced with an unfavorable environment. The spores can exist in a quiescent state almost indefinitely until suitable growth conditions are encountered, at which time the spores germinate and the organism resumes normal metabolism and replication.

Bacteria are extremely adaptable life forms. They are found not just in humans and other hosts, but in almost every environmental extreme on earth. However, each individual bacterial species has a well-defined set of growth parameters, including nutrition, temperature, light, humidity, and atmosphere. Bacteria with extremely strict growth requirements are called *fastidious*. For example, *Neisseria gonorrhoeae,* the bacterium that causes gonorrhea, cannot live for extended periods outside the human body. Some bacteria require oxygen for growth and metabolism and are called *aerobes;* others cannot survive in an oxygen-containing environment and are called *anaerobes*. An organism capable of adapting its metabolism to aerobic or anaerobic conditions is called *facultatively anaerobic*. It is of interest to note that the vast majority of bacterial species found in humans and in the surrounding environment have not been cultivated on artificial media.

In the laboratory, bacteria are generally classified according to the microscopic appearance and staining properties of the cell. The Gram stain, originally developed in 1884 by the Danish bacteriologist Christian Gram, is still the most widely used staining procedure. Bacteria are designated as *gram-positive* organisms if they are stained purple by a primary basic dye (usually crystal violet); those that are not stained by the crystal violet but are counterstained red by a second dye (safranin) are called *gram-negative* organisms. Staining characteristics and microscopic morphology are used in combination to describe bacteria. For example, *Streptococcus pyogenes,* the agent of scarlet fever and rheumatic fever, is a gram-positive streptococcal organism that is spherical, grows in chains, and stains purple by Gram stain. *Legionella pneumophila,* the bacterium responsible for Legionnaire disease, is a gram-negative rod.

Another means of classifying bacteria according to microscopic staining properties is the *acid-fast stain*. Because of their unique cell membrane fatty acid content and composition, certain bacteria are resistant to the decolorization of a primary stain (either carbol fuchsin or a combination of auramine and rhodamine) when treated with a solution of acid alcohol. These organisms are termed *acid-fast* and include a number of significant human pathogens, most notably *Mycobacterium tuberculosis* (the cause of tuberculosis) and other mycobacteria.

For purposes of taxonomy (i.e., identification and classification), each member of the bacterial kingdom is categorized into a small group of biochemically and genetically related organisms called the *genus,* and further subdivided into distinct individuals within the genus called *species*. The genus and species assignment of the organism is reflected in its name (e.g., *Staphylococcus* [genus] *aureus* [species]).

Spirochetes. The spirochetes are an eccentric category of bacteria that are mentioned separately because of their unusual cellular morphology and distinctive mechanism of motility. Technically, the spirochetes are gram-negative rods but are unique in that the cell's shape is helical and the length of the organism is many times its width (Fig. 14-7). A series of filaments are wound about the cell wall and extend the entire length of the cell. These filaments propel the organism through an aqueous environment in a corkscrew motion.

Spirochetes are composed of four genera: *Leptospira, Borrelia, Treponema,* and *Brachyspira*. Each genus has saprophytic pathogenic strains. The pathogenic leptospires infect a wide variety of wild and domestic animals. Infected animals shed the organisms into the environment through the urinary tract. Transmission to humans occurs by contact with infected animals or urine-contaminated surroundings. Leptospires gain access to the host directly through mucous membranes or breaks in the skin and can produce a severe and potentially fatal illness called *Weil syndrome*. In contrast, the borreliae are transmitted from infected animals to humans through the bite of an arthropod vector such as lice or ticks. Included in the genus *Borrelia* are the agents of

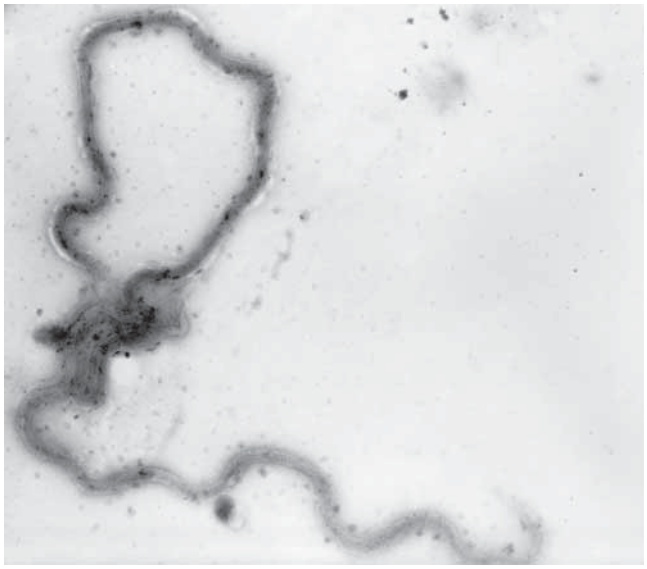


FIGURE 14-7. A photomicrograph of a *Treponema pallidum* bacterium that causes syphilis. This microscopic bacterium (spirochete) is a wormlike spiral-shaped microorganism that wiggles vigorously when viewed under the microscope. (Public Images Library, Centers for Disease Control and Prevention.)

relapsing fever (*Borrelia recurrentis*) and Lyme disease (*Borrelia burgdorferi*). Pathogenic *Treponema* species require no intermediates and are spread from person to person by direct contact. The most important member of the genus is *Treponema pallidum,* the causative agent of syphilis.

Mycoplasmas. The mycoplasmas are unicellular prokaryotes capable of independent replication. These organisms are less than one-third the size of bacteria and contain a small DNA genome approximately one-half the size of the bacterial chromosome. The cell is composed of cytoplasm surrounded by a membrane, but, unlike bacteria, the mycoplasmas do not produce a rigid peptidoglycan cell wall. As a consequence, the microscopic appearance of the cell is highly variable, ranging from coccoid forms to filaments, and the mycoplasmas are resistant to cell wall–inhibiting antibiotics such as penicillins and cephalosporins.

The mycoplasmas affecting humans are divided into three genera: *Mycoplasma, Ureaplasma,* and *Acholeplasma.* The first two require cholesterol from the environment to produce the cell membrane; the acholeplasmas do not. In the human host, mycoplasmas are commensals. However, a number of species are capable of producing serious diseases, including pneumonia (*Mycoplasma pneumoniae*), genital infections (*Mycoplasma hominis* and *Ureaplasma urealyticum*), and maternally transmitted respiratory infections to infants with low birth weight (*U. urealyticum*).

Rickettsiaceae, Anaplasmataceae, Chlamydiaceae, and Coxiella

This interesting group of organisms combines the characteristics of viral and bacterial agents to produce disease in humans. All are obligate intracellular pathogens, like the viruses, but produce a rigid peptidoglycan cell wall, reproduce asexually by cellular division, and contain RNA and DNA, similar to the bacteria.

The *Rickettsiaceae* depend on the host cell for essential vitamins and nutrients, but the *Chlamydiaceae* appear to scavenge intermediates of energy metabolism such as adenosine triphosphate (ATP). The *Rickettsiaceae* infect but do not produce disease in the cells of certain arthropods such as fleas, ticks, and lice. The organisms are accidentally transmitted to humans through the bite of the arthropod (i.e., the vector) and produce a number of potentially lethal diseases, including Rocky Mountain spotted fever and epidemic typhus.

The *Chlamydiaceae* are slightly smaller than the *Rickettsiaceae* but are structurally similar and are transmitted directly between susceptible vertebrates without an intermediate arthropod host. Transmission and replication of *Chlamydiaceae* occur through a defined life cycle. The infectious form, called an *elementary body,* attaches to and enters the host cell, where it transforms into a larger *reticulate body*. This undergoes active replication into multiple elementary bodies, which are then shed into the extracellular environment to initiate another infectious cycle. Chlamydial diseases of humans include sexually transmitted genital infections (*Chlamydophila trachomatis;* see Chapter 41); ocular infections and pneumonia of newborns (*C. trachomatis*); upper and lower respiratory tract infections in children, adolescents, and young adults (*Chlamydophila pneumoniae*); and respiratory disease acquired from infected birds (*Chlamydophila psittaci*).

Organisms within the family *Anaplasmataceae* (including the reorganized genera *Ehrlichia, Anaplasma, Neorickettsia,* and *Wolbachia*) are also obligate intracellular organisms that resemble the *Rickettsiaceae* in structure and produce a variety of veterinary and human diseases, some of which have a tick vector. These organisms target host mononuclear and polymorphonuclear white blood cells for infection and, similar to the *Chlamydiaceae*, multiply in the cytoplasm of infected leukocytes within vacuoles called *morulae*. Unlike the *Chlamydiaceae*, however, the *Anaplasmataceae* do not have a defined life cycle and are independent of the host cell for energy production. The most common infections caused by *Anaplasmataceae* are human monocytic and granulocytic ehrlichiosis. Human monocytic ehrlichiosis is a disease caused by *Ehrlichia chaffeensis* that can easily be confused with Rocky Mountain spotted fever. Clinical disease severity ranges from mild to life-threatening. Manifestations include generalized malaise, anorexia and nausea, fever, and headache. Decreases in white blood cells (leukopenia) and platelets (thrombocytopenia) often occur. Severe sequelae include severe respiratory failure, encephalopathy, and acute renal failure. The disease is usually more severe in the elderly and persons with compromised immune function (e.g., HIV/AIDS). Human granulocytic ehrlichiosis is also transmitted by ticks. The symptoms are similar to those seen with human monocytic ehrlichiosis.

The genus *Coxiella* contains only one species, *Coxiella burnetii.* Like its rickettsial counterparts, it is a gram-negative intracellular organism that infects a variety of

animals, including cattle, sheep, and goats. In humans, *Coxiella* infection produces a disease called *Q fever,* characterized by a nonspecific febrile illness often accompanied by headache, chills, arthralgias, and mild pneumonia. The organism produces a highly resistant sporelike stage that is transmitted to humans when contaminated animal tissue is aerosolized (e.g., during meat processing) or by ingestion of contaminated milk.

Fungi

The fungi are free-living, eukaryotic saprophytes found in every habitat on earth. Some are members of the normal human microflora. Fortunately, few fungi are capable of causing diseases in humans, and most of these are incidental, self-limited infections of skin and subcutaneous tissue. Serious fungal infections are rare and usually initiated through puncture wounds or inhalation. Despite their normally harmless nature, fungi can cause life-threatening opportunistic diseases when host defense capabilities have been disabled.

The fungi can be separated into two groups, yeasts and molds, based on rudimentary differences in their morphology (Fig. 14-8). The yeasts are single-celled organisms, approximately the size of red blood cells that reproduce by a budding process. The buds separate from the parent cell and mature into identical daughter cells. Molds produce long, hollow, branching filaments called *hyphae*. Some molds produce cross-walls, which segregate the hyphae into compartments, and others do not. A limited number of fungi are capable of growing as yeasts at one temperature and as molds at another. These organisms are called *dimorphic fungi* and include a number of human pathogens such as the agents of blastomycosis (*Blastomyces dermatitidis*), histoplasmosis (*Histoplasma capsulatum*), and coccidioidomycosis (*Coccidioides immitis*).

The appearance of a fungal colony tends to reflect its cellular composition. Colonies of yeast are generally smooth with a waxy or creamy texture. Molds tend to produce cottony or powdery colonies composed of mats of hyphae collectively called a *mycelium*. The mycelium can penetrate the growth surface or project above the colony like the roots and branches of a tree. Yeasts and molds produce a rigid cell wall layer that is chemically unrelated to the peptidoglycan of bacteria and is therefore not susceptible to the effects of penicillin-like antibiotics.

Most fungi are capable of sexual or asexual reproduction. The former process involves the fusion of zygotes with the production of a recombinant zygospore. Asexual reproduction involves the formation of highly resistant spores called *conidia* or *sporangiospores,* which are borne by specialized structures that arise from the hyphae. Molds are identified in the laboratory by the characteristic microscopic appearance of the asexual fruiting structures and spores.

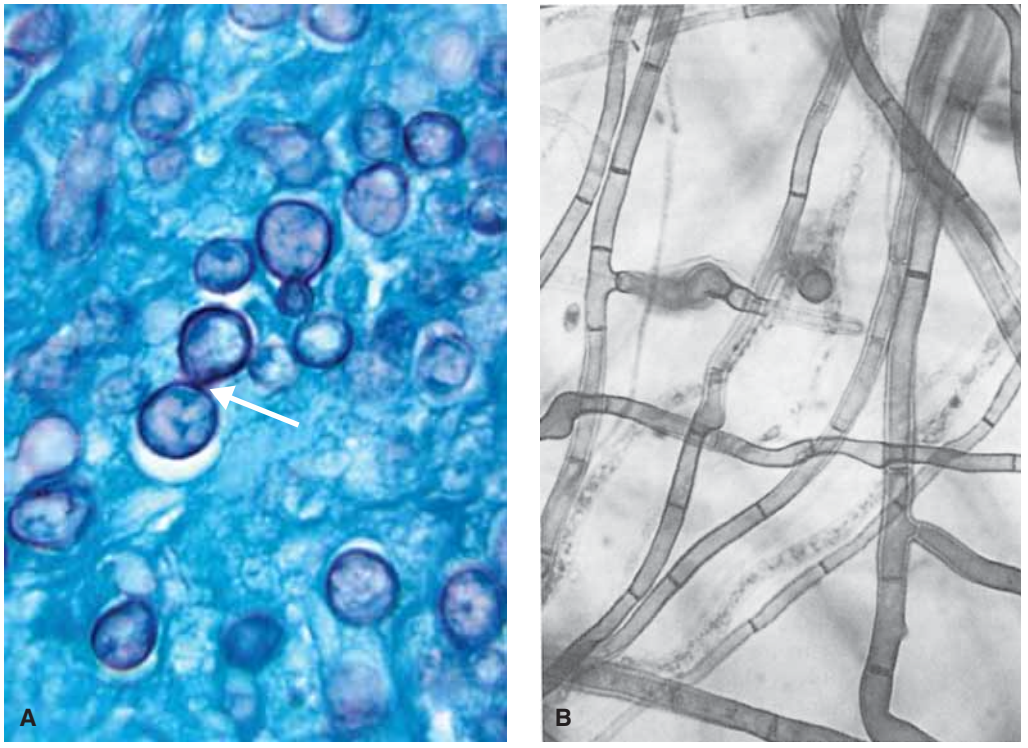


FIGURE 14-8. The microscopic morphology of fungal pathogens in humans. **(A)** Histopathologic changes seen in histoplasmosis due to *Histoplasma capsulatum var. duboisii.* Note the presence of typical yeast cells, some of which are undergoing replication by budding (*arrow*). **(B)** The molds produce long branched and unbranched filaments called *hyphae.* (A from Public Images Library, Centers for Disease Control and Prevention.)

Like the bacterial pathogens of humans, fungi can produce disease in the human host only if they can grow at the temperature of the infected body site. For example, a number of fungal pathogens called *dermatophytes* are incapable of growing at core body temperature (37°C), and the infection is limited to the cooler cutaneous surfaces. Diseases caused by these organisms, including ringworm, athlete's foot, and jock itch, are collectively called *superficial mycoses*. Systemic mycoses are serious fungal infections of deep tissues and, by definition, are caused by organisms capable of growth at 37°C. Yeasts such as *Candida albicans* are commensal flora of the skin, mucous membranes, and gastrointestinal tract and are capable of growth at a wider range of temperatures. Intact immune mechanisms and competition for nutrients provided by the bacterial flora normally keep colonizing fungi in check. Alterations in either of these components by disease states or antibiotic therapy can upset the balance, permitting fungal overgrowth and setting the stage for opportunistic infections.

Parasites

In a strict sense, any organism that derives benefits from its biologic relationship with another organism is a parasite. In the study of clinical microbiology, however, the term *parasite* has evolved to designate members of the animal kingdom that infect and cause disease in other animals and includes protozoa, helminths, and arthropods.

The protozoa are unicellular animals with a complete complement of eukaryotic cellular machinery, including a well-defined nucleus and organelles. Reproduction may be sexual or asexual, and life cycles may be simple or complicated, with several maturation stages requiring more than one host for completion. Most are saprophytes, but a few have adapted to the accommodations of the human environment and produce a variety of diseases, including malaria, amebic dysentery, and giardiasis. Protozoan infections can be passed directly from host to host such as through sexual contact, indirectly through contaminated water or food, or by way of an arthropod vector. Direct or indirect transmission results from the ingestion of highly resistant cysts or spores that are shed in the feces of an infected host. When the cysts reach the intestine, they mature into vegetative forms called *trophozoites,* which are capable of asexual reproduction or cyst formation. Most trophozoites are motile by means of flagella, cilia, or ameboid motion.

The helminths are a collection of wormlike parasites that include the nematodes or roundworms, cestodes or tapeworms, and trematodes or flukes. The helminths reproduce sexually within the definitive host, and some require an intermediate host for the development and maturation of offspring. Humans can serve as the definitive or intermediate host and, in certain diseases such as trichinosis, as both. Transmission of helminth diseases occurs primarily through the ingestion of fertilized eggs (ova) or the penetration of infectious larval stages through the skin—directly or with the aid of an arthropod vector. Helminth infections can involve many organ systems and sites, including the liver and lung, urinary and intestinal tracts, circulatory and central nervous systems, and muscle. Although most helminth diseases have been eradicated from the United States, they are still a major health concern of developing nations.

The parasitic arthropods of humans and animals include the vectors of infectious diseases (e.g., ticks, mosquitoes, biting flies) and the ectoparasites. The ectoparasites infest external body surfaces and cause localized tissue damage or inflammation secondary to the bite or burrowing action of the arthropod. The most prominent human ectoparasites are mites (scabies), chiggers, lice (head, body, and pubic), and fleas. Transmission of ectoparasites occurs directly by contact with immature or mature forms of the arthropod or its eggs found on the infested host or the host's clothing, bedding, or grooming articles such as combs and brushes. Many of the ectoparasites are vectors of other infectious diseases, including endemic typhus and bubonic plague (fleas) and epidemic typhus (lice).

In summary, throughout life, humans are continuously and harmlessly exposed to and colonized by a multitude of microscopic organisms. This relationship is kept in check by the intact defense mechanisms of the host (e.g., mucosal and cutaneous barriers, normal immune function) and the innocuous nature of most environmental microorganisms. Those factors that weaken the host's resistance or increase the virulence of colonizing microorganisms can disturb the equilibrium of the relationship and cause disease. The degree to which the balance is shifted in favor of the microorganism determines the severity of illness.

There is an extreme diversity of prokaryotic and eukaryotic microorganisms capable of causing infectious diseases in humans. With the advent of immunosuppressive medical therapy and immunosuppressive diseases such as AIDS, the number and type of potential microbic pathogens, the so-called opportunistic pathogens, have increased dramatically. However, most infectious illnesses in humans continue to be caused by only a small fraction of the organisms that comprise the microscopic world.

Epidemiology of Infectious Diseases

Epidemiology, in the context of this chapter, is the study of factors, events, and circumstances that influence the transmission of infectious diseases among humans. The ultimate goal of the epidemiologist is to devise strategies that interrupt or eliminate the spread of an infectious agent. To accomplish this, infectious diseases must be classified according to incidence, portal of entry and source, symptoms, disease course, site of infection, and

virulence factors so that potential outbreaks may be predicted and averted or appropriately treated.

Mechanisms of Transmission

The outcomes of infections depend on the ability of microbes to breach host barriers and colonize and damage host tissues. Host barriers to infection prevent the microbes from entering the body and assist innate and adaptive immune defenses in eliminating the agent (see Chapter 15).

Portal of Entry

Microbes can enter the host by direct contact, ingestion, and inhalation. The portal of entry does not dictate the site of infection. Ingested pathogens may penetrate the intestinal mucosa, disseminate through the circulatory system, and cause diseases in other organs such as the lung or liver. Whatever the mechanisms of entry, the transmission of infectious agents is directly related to the number of infectious agents absorbed by the host.

Penetration. Any disruption in the integrity of the body's surface barrier—skin or mucous membranes—is a potential site for invasion of microorganisms. The break may be the result of an accidental injury causing abrasions, burns, or penetrating wounds; medical procedures such as surgery or catheterization; or a primary infectious process that produces surface lesions such as chickenpox or impetigo. Direct inoculation from intravenous drug use or an animal or arthropod bite also can occur.

Direct Contact. Some pathogens are transmitted directly from infected tissue or secretions to exposed, intact mucous membranes. This is especially true of certain sexually transmitted infections (STIs) such as gonorrhea, syphilis, chlamydia, and genital herpes, for which exposure of uninfected membranes to pathogens occurs during intimate contact (see Chapter 41).

The transmission of STIs is not limited to sexual contact. *Vertical transmission* of these agents, from mother to child, can occur across the placenta or during birth when the mucous membranes of the child come in contact with infected vaginal secretions of the mother. When an infectious disease is transmitted from mother to child during gestation or birth, it is classified as a *congenital infection.* The most frequently observed congenital infections include toxoplasmosis (caused by the parasite *Toxoplasma gondii*), syphilis, rubella, cytomegalovirus infection, and herpes simplex virus infections (the so-called TORCH infections, discussed in Chapter 6); varicella-zoster (chickenpox); parvovirus B19; group B streptococci (*Streptococcus agalactiae*); and HIV. Of these, cytomegalovirus is by far the most common cause of congenital infection in the United States, affecting nearly 1% of all newborns. However, with more than 6000 HIV-infected women giving birth each year in the United States and Canada, and with a 13% to 30% chance of vertical transmission, HIV is rapidly gaining in stature as a congenitally transmitted infection (see Chapter 16).

Ingestion. The entry of pathogenic microorganisms or their toxic products through the oral cavity and gastrointestinal tract represents one of the more efficient means of disease transmission in humans. Many bacterial, viral, and parasitic infections, including cholera, typhoid fever, dysentery (amebic and bacillary), food poisoning, traveler's diarrhea, cryptosporidiosis, and hepatitis A, are initiated through the ingestion of contaminated food and water. This mechanism of transmission necessitates that an infectious agent survive the low pH and enzyme activity of gastric secretions and the peristaltic action of the intestines in numbers sufficient to establish infection, deemed an infectious dose. Ingested pathogens also must compete successfully with the normal bacterial flora of the bowel for nutritional needs. Persons with reduced gastric acidity because of disease or medication are more susceptible to infection by this route because the number of ingested microorganisms surviving the gastric environment is greater. Ingestion has also been postulated as a means of transmission of HIV infection from mother to child through breast-feeding.

Inhalation. The respiratory tract of healthy persons is equipped with a multitiered defense system to prevent potential pathogens from entering the lungs. The surface of the respiratory tree is lined with a layer of mucus that is continuously swept up and away from the lungs and toward the mouth by the beating motion of ciliated epithelial cells. Humidification of inspired air increases the size of aerosolized particles, which are effectively filtered by the mucous membranes of the upper respiratory tract. Coughing also aids in the removal of particulate matter from the lower respiratory tract. Respiratory secretions contain antibodies and enzymes capable of inactivating infectious agents. Particulate matter and microorganisms that ultimately reach the lung are cleared by phagocytic cells.

Despite this impressive array of protective mechanisms, a number of pathogens can invade the human body through the respiratory tract, including agents of bacterial pneumonia (*Streptococcus pneumoniae, L. pneumophila*), meningitis (*Neisseria meningitidis, Haemophilus influenzae*), and tuberculosis, as well as the viruses responsible for measles, mumps, chickenpox, influenza, and the common cold. Defective pulmonary function or mucociliary clearance caused by noninfectious processes such as cystic fibrosis, emphysema, or smoking can increase the risk of inhalation-acquired diseases.

Source

The source of an infectious disease refers to the location, host, object, or substance from which the infectious agent was acquired: essentially the "who, what, where, and when" of disease transmission. The source may be endogenous (acquired from the host's own microbial flora, as would be the case in an opportunistic infection) or exogenous (acquired from sources in the external environment, such as the water, food, soil, or air). The source of the infectious agent can also be another human being, as from mother to child during gestation (congenital

infections); an inanimate object; an animal; or a biting arthropod. Inanimate objects that carry an infectious agent are known as *fomites*. For example, rhinoviruses and many other nonenveloped viruses can be spread by contact with contaminated fomites such as handkerchiefs and toys. Zoonoses are a category of infectious diseases passed from other animal species to humans. Examples of zoonoses include cat-scratch disease, rabies, and visceral or cutaneous larval migrans. The spread of infectious diseases such as Lyme disease through biting arthropod vectors has already been mentioned.

Source can denote a place. For instance, infections that develop in patients while they are hospitalized are called *nosocomial,* and those that are acquired outside of health care facilities are called *community acquired*. The source may also pertain to the body substance that is the most likely vehicle for transmission, such as feces, blood, body fluids, respiratory secretions, and urine. Infections can be transmitted from person to person through shared inanimate objects (fomites) contaminated with infected body fluids. An example of this mechanism of transmission would include the spread of the HIV and hepatitis B virus through the use of shared syringes by intravenous drug users. Infection can also be spread through a complex combination of source, portal of entry, and vector. The well-publicized 1993 outbreak of hantavirus pulmonary syndrome in the southwestern United States is a prime example. This viral illness was transmitted to humans by inhalation of dust contaminated with saliva, feces, and urine of infected rodents.

Mechanisms of Disease Production

Infectious agents establish infection and damage tissues by entering host cells and directly causing their death; inducing host responses that, although directed against the invader, cause additional tissue damage; and through the generation of virulence factors that enhance their ability to cause disease.

Virulence Factors

Virulence factors are substances or products generated by infectious agents that enhance their ability to cause disease. Although a large number of microbial products fit this description, they can be grouped generally into four categories: toxins, adhesion factors, evasive factors, and invasive factors (Table 14-2).

Toxins. Toxins are substances that alter or destroy the normal function of the host or host's cells. Toxin production is a trait chiefly monopolized by bacterial pathogens, although certain fungal and protozoan pathogens also elaborate substances toxic to humans. Bacterial toxins have a diverse spectrum of activity and exert their effects on a wide variety of host target cells. For classification purposes, however, the bacterial toxins can be divided into two main types: *endotoxins* and *exotoxins*.

Bacterial endotoxins are a lipopolysaccharide (LPS) found in the cell wall of gram-negative bacteria. Free LPS attaches to a circulating LPS-binding protein, and the complex then binds to specific leukocyte receptors that participate in activation of the innate immune system (see Chapter 15). The host response to LPS can be both beneficial and harmful. At low levels, LPS induces many important cytokines, as well as expression of costimulatory molecules, resulting in leukocyte recruitment and enhancement of T-lymphocyte activation. However, at high levels, LPS can precipitate septic shock, disseminated intravascular coagulation, and acute respiratory distress syndrome.

Exotoxins are proteins released from the bacterial cell during growth. Bacterial exotoxins enzymatically inactivate or modify key cellular constituents, leading to cell death or dysfunction. Diphtheria toxin, for example, inhibits cellular protein synthesis; botulism toxin decreases the release of neurotransmitter from cholinergic neurons, causing flaccid paralysis; tetanus toxin decreases the release of neurotransmitter from inhibitory neurons, producing spastic paralysis; and cholera toxin

TABLE 14-2 Examples of Virulence Factors Produced by Pathogenic Microorganisms

Factor	Category	Organism	Effect on Host
Cholera toxin	Exotoxin	*Vibrio cholerae* (bacterium)	Secretory diarrhea
Diphtheria toxin	Exotoxin	*Corynebacterium diphtheriae* (bacterium)	Inhibits protein synthesis
Lipopolysaccharide	Endotoxin	Many gram-negative bacteria	Fever, hypotension, shock
Toxic shock toxin	Enterotoxin	*Staphylococcus aureus* (bacterium)	Rash, diarrhea, vomiting, hepatitis
Hemagglutinin	Adherence	Influenza virus	Establishment of infection
Pili	Adherence	*Neisseria gonorrhoeae* (bacterium)	Establishment of infection
Leukocidin	Evasive	*S. aureus*	Kills phagocytes
IgA protease	Evasive	*Haemophilus influenzae* (bacterium)	Inactivates antibody
Capsule	Evasive	*Cryptococcus neoformans* (yeast)	Prevents phagocytosis
Collagenase	Invasive	*Pseudomonas aeruginosa* (bacterium)	Penetration of tissue
Protease	Invasive	*Aspergillus* (mold)	Penetration of tissue
Phospholipase	Invasive	*Clostridium perfringens* (bacterium)	Penetration of tissue
Botulinum toxin	Exotoxin	*Clostridium botulinum* (bacterium)	Neuroparalysis, inhibits acetylcholine release
Pneumolysin	Exotoxin	*Streptococcus pneumoniae* (bacterium)	Inhibition of respiratory ciliated and phagocytic cell function

induces fluid secretion into the lumen of the intestine, causing diarrhea. Bacterial exotoxins that produce vomiting and diarrhea are sometimes referred to as *enterotoxins*. There has been resurgent interest in streptococcal pyrogenic exotoxin A (SPEA), an exotoxin produced by certain strains of group A, β-hemolytic streptococci (*S. pyogenes*) that causes a life-threatening toxic shock–like syndrome. The syndrome, sometimes called *Henson disease* because it was this infection that caused the death of the famous puppeteer Jim Henson, is typified by invasion of the skin and soft tissues, acute respiratory distress syndrome, and renal failure. Other enterotoxins that have gained notoriety include the Shiga toxins produced by *Escherichia coli* O157:H7 (see Chapter 29). The ingestion of undercooked hamburger meat or unpasteurized fruit juices contaminated with this organism produces hemorrhagic colitis and a sometimes fatal illness called *hemolytic uremic syndrome* (HUS), characterized by vascular endothelial damage, acute renal failure, and thrombocytopenia. HUS occurs primarily in infants and young children who have not developed antibodies to the Shiga toxins.

Adhesion Factors. No interaction between microorganisms and humans can progress to infection or disease if the pathogen is unable to attach to and colonize the host. The process of microbial attachment may be site specific (e.g., mucous membranes, skin surfaces), cell specific (e.g., T lymphocytes, respiratory epithelium, intestinal epithelium), or nonspecific (e.g., moist areas, charged surfaces). In any of these cases, adhesion requires a positive interaction between the surfaces of host cells and the infectious agent.

The site to which microorganisms adhere is called a *receptor,* and the reciprocal molecule or substance that binds to the receptor is called a *ligand*. Receptors may be proteins, carbohydrates, lipids, or complex molecules composed of all three. Similarly, ligands may be simple or complex molecules and, in some cases, highly specific structures. Ligands that bind to specific carbohydrates are called *lectins*. After initial attachment, a number of bacterial agents become embedded in a gelatinous matrix of polysaccharides called a *slime* or *mucous layer.* The slime layer serves two purposes: it anchors the agent firmly to host tissue surfaces and it protects the agent from the immunologic defenses of the host.

Many viral agents, including influenza, mumps, measles, and adenovirus, produce filamentous appendages or spikes called *hemagglutinins* that recognize carbohydrate receptors on the surfaces of specific cells in the upper respiratory tract of the host.

Evasive Factors. A number of factors produced by microorganisms enhance virulence by evading various components of the host's immune system. Extracellular polysaccharides, including capsules, slime, and mucous layers, discourage engulfment and killing of pathogens by the host's phagocytic white blood cells (i.e., neutrophils and macrophages). Encapsulated organisms such as *S. agalactiae, S. pneumoniae, N. meningitidis,* and *H. influenzae* type b (before the vaccine) are a cause of significant morbidity and mortality in neonates and children who lack protective anticapsular antibodies. Certain bacterial, fungal, and parasitic pathogens avoid phagocytosis by excreting leukocidin C toxins, which cause specific and lethal damage to the cell membrane of host neutrophils and macrophages. Other pathogens, such as the bacterial agents of salmonellosis, listeriosis, and Legionnaire disease, are adapted to survive and reproduce within phagocytic white blood cells after ingestion, avoiding or neutralizing the usually lethal products contained within the lysosomes of the cell. *H. pylori,* the infectious cause of gastritis and gastric ulcers, produces a urease enzyme on its outer cell wall. The urease converts gastric urea into ammonia, thus neutralizing the acidic environment of the stomach and allowing the organism to survive in this hostile environment.

Other unique strategies used by pathogenic microbes to evade immunologic surveillance have evolved solely to avoid recognition by host antibodies. Strains of *S. aureus* produce a surface protein (protein A) that immobilizes immunoglobulin G (IgG), holding the antigen-binding region harmlessly away from the organisms. This pathogen also secretes a unique enzyme called *coagulase*. Coagulase converts soluble human coagulation factors into a solid clot, which envelops and protects the organism from phagocytic host cells and antibodies. *H. influenzae* and *N. gonorrhoeae* secrete enzymes that cleave and inactivate secretory IgA, neutralizing the primary defense of the respiratory and genital tracts at the site of infection. *Borrelia* species, including the agents of Lyme disease and relapsing fever, alter surface antigens during the disease course to avoid immunologic detection.

Invasive Factors. Invasive factors are products produced by infectious agents that facilitate the penetration of anatomic barriers and host tissue. Most invasive factors are enzymes capable of destroying cellular membranes (e.g., phospholipases), connective tissue (e.g., elastases, collagenases), intercellular matrices (e.g., hyaluronidase), and structural protein complexes (e.g., proteases). It is the combined effects of invasive factors, toxins, and antimicrobial and inflammatory substances released by host cells to counter infection that mediate the tissue damage and pathophysiology of infectious diseases.

Symptomatology

The term *symptomatology* refers to the collection of signs and symptoms expressed by the host during the disease course. This is also known as the *clinical picture* or *disease presentation,* and can be characteristic of any given infectious agent. In terms of pathophysiology, symptoms are the outward expression of the struggle between invading organisms and the retaliatory inflammatory and immune responses of the host. The symptoms of an infectious disease may be specific and reflect the site of infection (e.g., diarrhea, rash, convulsions, hemorrhage, and pneumonia). Conversely, symptoms such as fever, myalgia, headache, and lethargy are relatively nonspecific and can be shared by a number of diverse infectious diseases. The symptoms of a diseased host can be obvious, as in

the case of chickenpox or measles. Other, covert symptoms, such as an increased white blood cell count, may require laboratory testing to detect. Accurate recognition and documentation of symptomatology can aid in the diagnosis of an infectious disease.

Site of Infection

Inflammation of an anatomic location is usually designated by adding the suffix *-itis* to the name of the involved tissue (e.g., bronchitis, infection of the bronchi and bronchioles; encephalitis, brain infection; carditis, infection of the heart). These are general terms, however, and they apply equally to inflammation from infectious and noninfectious causes. The suffix *-emia* is used to designate the presence of a substance in the blood (e.g., *bacteremia, viremia,* and *fungemia* describe the presence of these infectious agents in the bloodstream). The term *sepsis,* or *septicemia,* refers to the presence of microbial toxins in the blood.

The site of an infectious disease is determined ultimately by the type of pathogen, the portal of entry, and the competence of the host's immunologic defense system. Many pathogenic microorganisms are restricted in their capacity to invade the human body. *M. pneumoniae,* influenza viruses, and *L. pneumophila* rarely cause disease outside the respiratory tract; infections caused by *N. gonorrhoeae* are generally confined to the genitourinary tract; and shigellosis and giardiasis seldom extend beyond the gastrointestinal tract. These are considered localized infectious diseases. The bacterium *Helicobacter pylori* is an extreme example of a site-specific pathogen. *H. pylori* is a significant cause of gastric ulcers but has not been implicated in disease processes elsewhere in the human body. Bacteria such as *N. meningitidis,* a prominent pathogen of children and young adults; *Salmonella typhi,* the cause of typhoid fever; and *B. burgdorferi,* the agent of Lyme disease, tend to disseminate from the primary site of infection to involve other locations and organ systems. These are examples of systemic pathogens disseminated throughout the body by the circulatory system.

An *abscess* is a localized pocket of infection composed of devitalized tissue, microorganisms, and the host's phagocytic white blood cells: in essence, a stalemate in the infectious process. In this case, the dissemination of the pathogen has been contained by the host, but white cell function within the toxic environment of the abscess is hampered, and the elimination of microorganisms is retarded. Abscesses usually must be surgically drained to effect a complete cure. Similarly, infections of biomedical implants such as catheters, artificial heart valves, and prosthetic bone implants are seldom cured by the host's immune response and antimicrobial therapy. The infecting organism colonizes the surface of the implant, producing a dense matrix of cells, host proteins, and capsular material—a biofilm—necessitating the removal of the device.

Disease Course

The course of any infectious disease can be divided into several distinguishable stages after the point when the potential pathogen enters the host. These stages are the incubation period, the prodromal stage, the acute stage, the convalescent stage, and the resolution stage (Fig. 14-9). The stages are based on the progression and intensity of the host's symptoms over time. The duration of each phase and the pattern of the overall illness can be specific for different pathogens, thereby aiding in the diagnosis of an infectious disease.

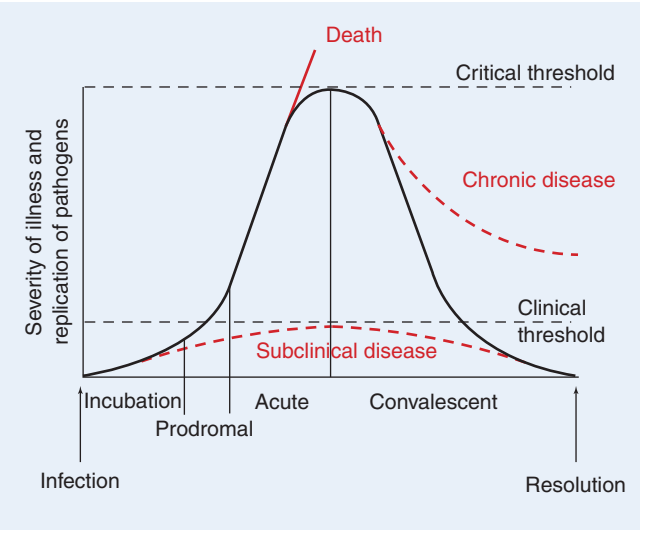


FIGURE 14-9. Stages of a primary infectious disease as they appear in relation to the severity of symptoms and numbers of infectious agents. The clinical threshold corresponds with the initial expression of recognizable symptoms, whereas the critical threshold represents the peak of disease intensity.

The incubation period is the phase during which the pathogen begins active replication without producing recognizable symptoms in the host. The incubation period may be short, as in the case of salmonellosis (6 to 24 hours), or prolonged, such as that of hepatitis B (50 to 180 days) or HIV (months to years). The duration of the incubation period can be influenced by additional factors, including the general health of the host, the portal of entry, and the infectious dose of the pathogen.

The hallmark of the *prodromal stage* is the initial appearance of symptoms in the host, although the clinical presentation during this time may be only a vague sense of malaise. The host may experience mild fever, myalgia, headache, and fatigue. These are constitutional changes shared by a great number of disease processes. The duration of the prodromal stage can vary considerably from host to host.

The *acute stage* is the period during which the host experiences the maximum impact of the infectious process corresponding to rapid proliferation and dissemination of the pathogen. During this phase, toxic byproducts of microbial metabolism, cell lysis, and the immune response mounted by the host combine to produce tissue damage and inflammation. The symptoms of the host are pronounced and more specific than in the prodromal stage, usually typifying the pathogen and sites of involvement.

The *convalescent period* is characterized by the containment of infection, progressive elimination of the

pathogen, repair of damaged tissue, and resolution of associated symptoms. Similar to the incubation period, the time required for complete convalescence may be days, weeks, or months, depending on the type of pathogen and the voracity of the host's immune response. The *resolution* is the total elimination of a pathogen from the body without residual signs or symptoms of disease.

Several notable exceptions to the classic presentation of an infectious process have been recognized. Chronic infectious diseases have a markedly protracted and sometimes irregular course. The host may experience symptoms of the infectious process continuously or sporadically for months or years without a convalescent phase. In contrast, *subclinical* or *subacute illness* progresses from infection to resolution without clinically apparent symptoms. A disease is called *insidious* if the prodromal phase is protracted; a fulminant illness is characterized by abrupt onset of symptoms with little or no prodrome. Fatal infections are variants of the typical disease course.

In summary, epidemiology is the study of factors, events, and circumstances that influence the transmission of disease. The outcomes of infections depend on the ability of microbes to breach host barriers and colonize and damage host tissues. Microbes can enter the host by direct contact, ingestion, and inhalation. The source of infection may be endogenous (acquired from the host's own microbial flora, as would be the case in an opportunistic infection) or exogenous (acquired from sources in the external environment, such as the water, food, soil, or air). It can also be another human being, as from mother to child during gestation (congenital infections); an inanimate object; an animal; or a biting arthropod.

The site of an infectious disease is determined ultimately by the type of pathogen, the portal of entry, and the competence of the host's immunologic defense system. It may be localized to the site of entry, disseminate from the primary site of infection to involve other locations and organ systems, or travel through the circulatory system to produce disseminated infection. Virulence factors, which are substances or products generated by infectious agents that enhance their ability to cause disease, include toxins (endotoxins and exotoxins), adhesion factors, evasive factors, and invasive factors. The natural history of an infectious disease includes its incubation period, as well as its prodromal, acute, convalescent, and resolution stages.

Diagnosis and Treatment

Techniques for Diagnosing Infectious Agents

The diagnosis of an infectious disease requires two criteria: the recovery of a probable pathogen or evidence of its presence from the infected sites of a diseased host and accurate documentation of clinical signs and symptoms (symptomatology) compatible with an infectious process. In the laboratory, the diagnosis of an infectious agent is accomplished using three basic techniques: culture, serology, or the detection of characteristic antigens, genomic sequences, or metabolites produced by the pathogen.

Culture

Culture refers to the propagation of a microorganism outside of the body, usually on or in artificial growth media such as agar plates or broth (Fig. 14-10). The specimen from the host is inoculated into broth or onto the surface of an agar plate, and the culture is placed in a controlled environment such as an incubator until the growth of microorganisms becomes detectable. In the case of a bacterial pathogen, identification is based on microscopic appearance and Gram stain reaction, shape, texture, and color (i.e., morphology) of the colonies, and by a panel of biochemical reactions that fingerprint salient biochemical characteristics of the organism. Certain bacteria such as *Mycobacterium leprae,* the agent of leprosy, and *T. pallidum,* the syphilis spirochete, do not grow on artificial media and require additional methods of identification. Fungi and mycoplasmas are cultured in much the same way as bacteria, but with more reliance on microscopic and colonial morphology for identification.

Chlamydiaceae, Rickettsiaceae, and all human viruses are obligate intracellular pathogens. As a result, the propagation of these agents in the laboratory requires the inoculation of eukaryotic cells grown in culture (cell cultures). A cell culture consists of a flask containing a single layer, or monolayer, of eukaryotic cells covering the bottom and overlaid with broth containing essential nutrients and growth factors. When a virus infects and replicates within cultured eukaryotic cells, it produces pathologic changes in the appearance of the cell called the *cytopathic effect* (CPE). The CPE can be detected microscopically, and the pattern and extent of cellular destruction is often characteristic of a particular virus.

Although culture media have been developed for the growth of certain human-infecting protozoa and helminths in the laboratory, the diagnosis of parasitic infectious diseases has traditionally relied on microscopic or, in the case of worms, visible identification of organisms, cysts, or ova directly from infected patient specimens.

Serology

Serology—literally, "the study of serum"—is an indirect means of identifying infectious agents by measuring serum antibodies in the diseased host. A tentative diagnosis can be made if the antibody level, also called *antibody titer,* against a specific pathogen rises during the acute phase of the disease and falls during convalescence. Serologic identification of an infectious agent is not as accurate as culture, but it may be a useful adjunct, especially for the diagnosis of diseases caused by pathogens such as the hepatitis B virus that cannot be cultured. The measurement of antibody titers has another advantage in that specific antibody types such as IgM and IgG are

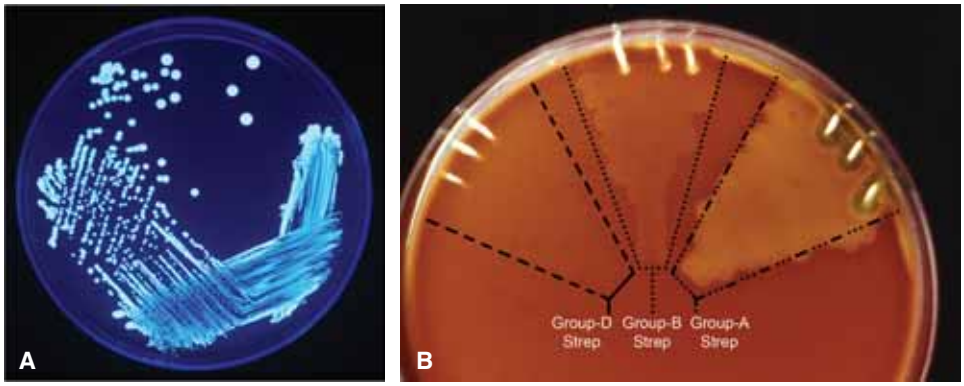


FIGURE 14-10. Use of agar culture for propagation and identification of microorganisms. **(A)** Photograph showing numerous *Legionella* species colonies that have been cultivated on an agar culture plate and illuminated using ultraviolet light. **(B)** Quantitative differences in hemolytic reactivity seen in trypticase soy agar culture plate containing 5% sheep's blood growing group D *Streptococci* (left wedge), group B *Streptococci* (middle wedge), and group A *Streptococci* (right wedge) bacteria. The plate was grown under normal atmospheric conditions, at 35°C, for a period of 18 hours. It is important to note that the group B *Streptococci* (GBS) in the center wedge produced a hemolytic reaction that is less than the reaction produced by group A *Streptococci* (GAS) in the right wedge of bacterial growth. Hemolysis, which results from destruction of red blood cells, is one of the traits used to help identify the bacteria. (Public Images Library, Centers for Disease Control and Prevention. A courtesy James Gathway; B courtesy Richard Gacklam.)

produced by the host during different phases of an infectious process. IgM-specific antibodies generally rise and fall during the acute phase of the disease, whereas the synthesis of the IgG class of antibodies increases during the acute phase and remains elevated until or beyond resolution. Measurements of class-specific antibodies are also useful in the diagnosis of congenital infections. IgM antibodies do not cross the placenta, but certain IgG antibodies are transferred passively from mother to child during the final trimester of gestation. Consequently, an elevated level of pathogen-specific IgM antibodies in the serum of a neonate must have originated from the child and therefore indicates congenital infection. A similarly increased IgG titer in the neonate does not differentiate congenital from maternal infection.

The technology of *direct antigen detection* has evolved rapidly over the past decade and in the process has revolutionized the diagnosis of certain infectious diseases. Antigen detection incorporates features of culture and serology but reduces to a fraction the time required for diagnosis. In principle, this method relies on purified antibodies to detect antigens of infectious agents in specimens obtained from the diseased host. The source of antibodies used for antigen detection can be animals immunized against a particular pathogen or *hybridomas*. Hybridomas are created by fusing normal antibody-producing spleen cells from an immunized animal with malignant myeloma cells; the resulting hybrid synthesizes large quantities of antibody. An antibody produced by a hybridoma is called a *monoclonal antibody* and is highly specific for a single antigen and a single pathogen. Regardless of the source, the antibodies are labeled with a substance that allows microscopic or overt detection when bound to the pathogen or its products. In general, the three types of labels used for this purpose are fluorescent dyes, enzymes, and particles such as latex beads. Fluorescent antibodies allow visualization of an infectious agent with the aid of fluorescence microscopy. Depending on the type of fluorescent dye used, the organism may appear bright green or orange against a black background, making detection extremely easy. Enzyme-labeled antibodies function in a similar manner. The enzyme is capable of converting a colorless compound into a colored substance, thereby permitting detection of antibody bound to an infectious agent without the use of a fluorescent microscope. Particles coated with antibodies clump together, or agglutinate, when the appropriate antigen is present in a specimen. Particle agglutination is especially useful when examining infected body fluids such as urine, serum, or spinal fluid.

DNA and RNA Sequencing

Methods for identifying infectious agents through the detection of DNA or RNA sequences unique to a single agent have recently seen rapid development and increased use. Several techniques have been devised to accomplish this goal, each having different degrees of sensitivity regarding the number of organisms that need to be present in a specimen for detection. The first of these methods is called *DNA probe hybridization*. Small fragments of DNA are cut from the genome of a specific pathogen and labeled with compounds (photo-emitting chemicals or antigens) that allow detection. The labeled DNA probes are added to specimens from an infected host. If the pathogen is present, the probe attaches to the complementary strand of DNA on the genome of the infectious agent, permitting rapid diagnosis. The use of

labeled probes has allowed visualization of particular agents within and around individual cells in histologic sections of tissue.

A second and more sensitive method of DNA detection is called the *polymerase chain reaction* (PCR; Fig. 14-11). This method incorporates two unique reagents: a specific pair of oligonucleotides (usually less than 25 nucleotides long) called *primers* and a heat-stable DNA polymerase. To perform the assay, the primers are added to the specimen containing the suspect pathogen, and the sample is heated to melt the DNA in the specimen and then allowed to cool. The primers locate and bind only to the complementary target DNA of the pathogen in question. The heat-stable polymerase begins to replicate the DNA from the point at which the primers attached, similar to two trains approaching one another on separate but converging tracks. After the initial cycle, DNA polymerization ceases at the point where the primers were located, producing a strand of DNA with a distinct size, depending on the distance separating the two primers. The specimen is heated again, and the process starts anew. After many cycles of heating, cooling, and polymerization, a large number of uniformly sized DNA fragments are produced only if the specific pathogen (or its DNA) is present in the specimen. The polymerized DNA fragments are separated by electrophoresis and visualized with a dye or identified by hybridization with a specific probe.

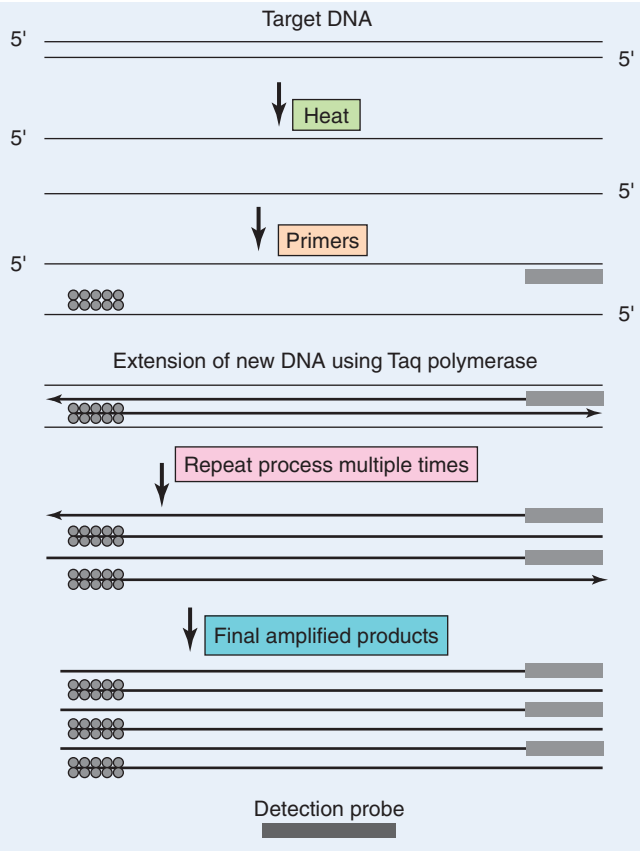


FIGURE 14-11. Polymerase chain reaction. The target DNA is first melted using heat (generally around 94°C) to separate the strands of DNA. Primers that recognize specific sequences in the target DNA are allowed to bind as the reaction cools. Using a unique, thermostable DNA polymerase called Taq and an abundance of deoxynucleoside triphosphates, new DNA strands are amplified from the point of the primer attachment. The process is repeated many times (called *cycles*) until millions of copies of DNA are produced, all of which have the same length defined by the distance (in base pairs) between the primer binding sites. These copies are then detected by electrophoresis and staining or through the use of labeled DNA probes that, similar to the primers, recognize a specific sequence located in the amplified section of DNA.

A modification of PCR, known as real-time PCR, continues to revolutionize medical diagnostics. Real-time PCR uses the same principles as PCR, but includes a fluorescence-labeled probe that specifically binds a target DNA sequence between the oligonucleotide primers. As the DNA is replicated by the DNA polymerase, the level of fluorescence in the reaction is measured. If fluorescence increases beyond a minimum threshold, the PCR is considered positive and indicates the presence of the target DNA in a specimen.

Several variations of molecular gene detection techniques in addition to PCR have been developed and incorporated into diagnostic kits for use in the clinical laboratory, including ligase chain reaction (LCR), transcription-mediated amplification (TMA), strand displacement amplification, branched-chain DNA signal amplification (bDNA), hybrid capture assays, and DNA sequencing.

Many of the newer gene detection technologies have been adapted for quantitation of the target DNA or RNA in serum specimens of patients infected with viruses such as HIV and hepatitis C. If the therapy is effective, viral replication is suppressed and the viral load (level of viral genome) in the peripheral blood is reduced. Conversely, if mutations in the viral genome lead to resistant strains or if the antiviral therapy is ineffective, viral replication continues and the patient's viral load rises, indicating a need to change the therapeutic approach.

Molecular biology has revolutionized medical diagnostics. Using techniques such as PCR, laboratories now can detect as little as one virus or bacterium in a single specimen, allowing for the diagnosis of infections caused by microorganisms that are impossible or difficult to grow in culture. These methods have increased sensitivity while decreasing the time required to identify the etiologic agent of infectious disease. For example, using standard viral culture, it can take days to weeks to grow a virus and correlate the CPE with the virus. Using molecular biologic techniques, laboratories are able to complete the same work in a few hours.

Treatment

The goal of treatment for an infectious disease is complete removal of the pathogen from the host and the restoration of normal physiologic function to damaged tissues. Most infectious diseases of humans are self-limiting in that they require little or no medical therapy for a complete cure. When an infectious process gains the upper hand and

therapeutic intervention is essential, the choice of treatment may be medicinal through the use of antimicrobial agents or surgical by removing infected tissues. The decision about which therapeutic modality or combination of therapies to use is based on the extent, urgency, and location of the disease process; the pathogen; and the availability of effective antimicrobial agents.

Antimicrobial Agents

Antibacterial Agents. Antibacterial agents are generally called *antibiotics*. Most antibiotics are actually produced by other microorganisms, primarily bacteria and fungi, as by-products of metabolism, and usually are effective only against other prokaryotic organisms. An antibiotic is considered *bactericidal* if it causes irreversible and lethal damage to the bacterial pathogen and *bacteriostatic* if its inhibitory effects on bacterial growth are reversed when the agent is eliminated. Antibiotics can be classified into families of compounds with related chemical structure and activity.

Not all antibiotics are effective against all pathogenic bacteria. Some agents are effective only against gram-negative bacteria, and others are specific for gram-positive organisms (e.g., vancomycin). The so-called broad-spectrum antibiotics, such as the newer cephalosporins, are active against a wide variety of gram-positive and gram-negative bacteria. Members of the *Mycobacterium* genus, including *M. tuberculosis,* are extremely resistant to the effects of the major classes of antibiotics and require an entirely different spectrum of agents for therapy. The four basic mechanisms of the antibiotic action are interference with a specific step in bacterial cell wall synthesis (e.g., penicillins, cephalosporins), inhibition of bacterial protein synthesis (e.g., aminoglycosides, tetracyclines), interruption of nucleic acid synthesis (e.g., fluoroquinolones, nalidixic acid), and interference with normal metabolism (e.g., sulfonamides, trimethoprim).

Of great concern is the increasing prevalence of bacteria resistant to the effects of antibiotics. The ways in which bacteria acquire resistance to antibiotics are becoming as numerous as the types of antibiotics. Bacterial resistance mechanisms include the production of enzymes that inactivate antibiotics, such as β-lactamases; genetic mutations that alter antibiotic binding sites; alternative metabolic pathways that bypass antibiotic activity; and changes in the filtration qualities of the bacterial cell wall that prevent access of antibiotics to the target site in the organism. It is the continuous search for a "better mousetrap" that makes anti-infective therapy such a fascinating aspect of infectious diseases.

Antiviral Agents. Until recently, few effective antiviral agents were available for treating human infections. The reason for this is host toxicity; viral replication requires the use of eukaryotic host cell enzymes, and the drugs that effectively interrupt viral replication are likely to interfere with host cell reproduction as well. However, in response to the AIDS epidemic, there has been massive, albeit delayed, development of antiretroviral agents. Almost all antiviral compounds are synthetic and, with few exceptions, the primary target of antiviral compounds is viral RNA or DNA synthesis. Agents such as acyclovir mimic the nucleoside building blocks of RNA and DNA. During active viral replication, the nucleoside analogs inhibit the viral DNA polymerase, preventing duplication of the viral genome and spread of infectious viral progeny to other susceptible host cells. Similar to the specificity of antibiotics, antiviral agents may be active against RNA viruses only, DNA viruses only, or occasionally both. Other nucleoside analogs such as zidovudine and nonnucleoside inhibitors were developed specifically for the treatment of AIDS by targeting the HIV-specific enzyme, reverse transcriptase, for inhibition. This key enzyme is essential for viral replication and has no counterpart in the infected eukaryotic host cells. Another class of antiviral agents developed solely for the treatment of HIV infections are the *protease inhibitors*. These drugs inhibit an HIV-specific enzyme that is necessary for late maturation events in the virus life cycle.

Antifungal Agents. The target site of the two most important families of antifungal agents is the cytoplasmic membranes of yeasts or molds. Fungal membranes differ from human cell membranes in that they contain the sterol ergosterol instead of cholesterol. The polyene family of antifungal compounds (e.g., amphotericin B, nystatin) preferentially binds to ergosterol and forms holes in the cytoplasmic membrane, causing leakage of the fungal cell contents and, eventually, lysis of the cell. The imidazole class of drugs (e.g., fluconazole, itraconazole) inhibits the synthesis of ergosterol, thereby damaging the integrity of the fungal cytoplasmic membrane. Both types of drugs bind to a certain extent to the cholesterol component of host cell membranes and elicit a variety of toxic side effects in treated patients.

Surgical Interventions

Before the discovery of antimicrobial agents, surgical removal of infected tissues, organs, or limbs was occasionally the only option available to prevent the demise of the infected host. Today, medicinal therapy with antibiotics and other anti-infective agents is an effective solution for most infectious diseases. However, surgical intervention is still an important option for cases in which the pathogen is resistant to available treatments. Surgical interventions may be used to hasten the recovery process by providing access to an infected site by antimicrobial agents (drainage of an abscess), cleaning the site (débridement), or removing infected organs or tissue (e.g., appendectomy). In some situations, surgery may be the only means of effecting a complete cure, as in the case of endocarditis resulting in an infected heart valve, in which the diseased valve must be replaced with a mechanical or biologic valve to restore normal function. In other situations, surgical containment of a rapidly progressing infectious process such as gas gangrene may be the only means of saving a person's life.

In summary, the diagnosis of infectious disease relies on the recovery of the probable pathogen or evidence of its presence from infected sites in the host and accurate documentation of signs and symptoms compatible with an infectious process. In the laboratory, the diagnosis of an infectious agent is accomplished through the use of culture, serology, and DNA/RNA sequencing techniques. The goal for treatment of infectious disease is complete removal of the infectious agent from the host and restoration of normal physiologic function to damaged tissues. Treatment methods include the use of antimicrobial agents and, when necessary, surgical interventions that provide access to an infected site by antimicrobial agents (drainage of an abscess), clean the site (débridement), or remove infected organs or tissue (e.g., appendectomy).

New and Emerging Infectious Diseases

In recent years, the terms *emerging* (i.e., newly recognized) and *reemerging* (i.e., previously recognized) *infectious diseases* have entered the vocabulary of medical science. These infections also include deliberately emerging infections that are the result of bioterrorism.

Global Infectious Diseases

Aided by a global market and the ease of international travel, the end of the 20th century and the first years of the 21st century have witnessed the importation of a host of novel infectious diseases. Unexpected pathogens in the 1990s, such as the outbreak of the West Nile virus (WNV) in the New York City area, have become important reminders of emerging infections. In fact, WNV has become almost synonymous with mosquito-borne illness. This outbreak, which led to seven deaths (primarily in the elderly), marked the first time that WNV had been recognized in the Western Hemisphere since its discovery in Uganda nearly 60 years earlier. Because WNV is a mosquito-borne disease and is transmitted to a number of susceptible avian (e.g., blue jays, crows, and hawks) and equine hosts, the potential for rapid and sustained spread of the disease across the United States was appreciated early. By the fall of 2002, a national surveillance network had detected WNV activity in 2289 counties from 44 states, including Los Angeles County, and had identified more than 3000 human cases. The disease ranges in intensity from a nonspecific febrile illness to fulminant meningoencephalitis. Efforts to prevent further spread of the disease are currently centered on surveillance of WNV-associated illness in birds, humans, and other mammals, as well as mosquito control.

In 2002, severe acute respiratory syndrome (SARS) emerged as a global threat. The first inkling of the impending threat was when the Chinese Ministry of Health reported 305 cases of a mysterious and virulent respiratory tract illness that had appeared in Guangdong province in southern China in a 4-month period of time. In a very short time, patients with compatible symptoms were recognized in Hong Kong and Vietnam. The World Health Organization (WHO) promptly issued a global alert and started international surveillance for patients with typical symptomatology who had a history of travel to the endemic region. As of June 2003, more than 8000 cases of SARS from 29 countries and 809 deaths were reported to the WHO. In a remarkable feat of molecular technology, the etiology of SARS was quickly determined to be a novel coronavirus, possibly of mammalian or avian origin, and its entire genome was sequenced by the end of May 2003.

Toronto became the site of North America's largest outbreak of SARS, where the infection was first recognized in a woman who returned from Hong Kong in February 2003. Transmission to other persons resulted subsequently in an outbreak among 257 persons in several Greater Toronto hospitals, after which the number of recognized cases declined substantially as the result of public health measures that included strict infection control measures. A second wave of SARS cases among patients, visitors, and health care workers occurred at a Toronto hospital 4 weeks after SARS transmission, probably due to relaxation of strict SARS control measures.

The worldwide movement of animals for commercial trade represents a substantial risk for translocation of zoonotic infections. In 2003, monkeypox, one of the orthopoxvirus family viruses, was introduced into the United States when a shipment of African Gambian giant rats was sold to dealers, one of whom housed the rats with prairie dogs intended for the pet market. The prairie dogs subsequently became ill and transmitted the infection to 71 humans, including prairie dog owners and veterinary staff caring for the animals.

These three scenarios highlight the rapidity with which novel or exotic diseases can be introduced into nonindigenous regions of the world and to a susceptible population. Although great strides in molecular microbiology have allowed for the rapid identification of new or rare microorganisms, the potential devastation in terms of human life and economic loss is great, underscoring the need to maintain resources for public health surveillance and intervention.

Agents of Bioterrorism

In October of 2001, less than 1 month after the tragedy of September 11, the world became instantly acquainted with the term *bioterrorism*. By the end of November of that year, 22 cases of human anthrax had been identified, resulting in five deaths, and all cases were associated with exposure to four intentionally contaminated envelopes delivered through the U.S. Postal Service. Although the possibility of such an attack had been discussed in a workshop hosted by the Centers for Disease Control and Prevention (CDC) 3 years earlier, the reality of the 2001 outbreak brought a new sense of awareness concerning the use of microorganisms as weapons.

Anthrax is an ancient disease caused by the cutaneous inoculation, inhalation, or ingestion of the spores of *Bacillus anthracis,* a gram-positive bacillus. Anthrax is more commonly known as a disease of herbivores that can be transmitted to humans through contact with infected secretions, soil, or animal products. It is a rare disease in the United States, and so the sudden increase in cases over a short time was a chilling indication that the spread of the organism had been intentional. Fortunately, the number of deaths was limited thanks to prompt recognition of cases by physicians and public health personnel and rapid institution of antimicrobial prophylaxis to exposed individuals.

To prepare for the possibility of bioterrorist attacks, the CDC along with other federal, state, and local agencies has created the laboratory response network (LRN). The LRN is a four-tiered structure consisting of laboratories with ever-increasing expertise, responsibility, and biocontainment facilities that allow for the rapid and coordinated detection and identification of bioterrorism events under safe working conditions.

Potential agents of bioterrorism have been categorized into three levels (A, B, C) based on risk of use, transmissibility, invasiveness, and mortality rate. The agents placed in the highest bioterrorism threat level include *B. anthracis, Yersinia pestis* (the cause of bubonic plague), *Francisella tularensis* (the cause of tularemia), variola major virus (the cause of smallpox), and several hemorrhagic fever viruses (Ebola, Marburg, Lassa, and Junin). The toxin of the anaerobic gram-positive organism *Clostridium botulinum,* which causes the neuromuscular paralysis termed *botulism,* is also listed as a category A agent. Interestingly, purified *C. botulinum* toxins A and B are finding increasing use under the trade names Botox, Myobloc, and Neurobloc for various medicinal and cosmetic purposes. The category B agents include agents of food-borne and water-borne diseases (*Salmonella, Shigella, Vibrio cholerae, E. coli* O157:H7), agents of zoonotic infections (*Brucella* species, *C. burnetii, Burkholderia mallei*), viral encephalitides (Venezuelan, Western, and Eastern equine encephalitis viruses), and toxins from *S. aureus, Clostridium perfringens,* and *Ricinus communis* (the castor bean). Category C agents are defined as emerging pathogens and potential risks for the future, even though many of these organisms are causes of ancient diseases. Category C agents include *M. tuberculosis,* Nipah virus, hantavirus, tick-borne and yellow fever viruses, and the only protozoan of the group, *Cryptosporidium parvum.*

In summary, the challenges associated with maintaining health throughout a global community are becoming increasingly apparent. Aided by a global market and the ease of international travel, the past decade has witnessed the importation and emergence of a host of novel infectious diseases. There is also the potential threat of the deliberate use of microorganisms as weapons of bioterrorism.

REVIEW EXERCISES

1. Newborn infants who have not yet developed intestinal flora are routinely given an intramuscular injection of vitamin K to prevent bleeding due to a deficiency in vitamin K–dependent coagulation factors.

A. Use the concept of mutualism to explain why this is done.

2. Persons with human granulocytic ehrlichiosis may be coinfected with Lyme disease.

A. Explain.

3. Persons with chronic lung disease are often taught to contact their health care provider when they notice a change in the color of their sputum (i.e., from white or clear to yellow or green tinged) because it might be a sign of a bacterial infection.

A. Explain.

4. Microorganisms are capable of causing infection only if they can grow at the temperature of the infected body site.

A. Using this concept, explain the different sites of fungal infections due to the dermatophyte fungal species that cause tinea pedis (athlete's foot) and *Candida albicans,* which causes infections of the mouth (thrush) and female genitalia (vulvovaginitis).

5. The threat of global infections, such as SARS, continues to grow.

A. What would you propose to be one of the most important functions of health care professionals in terms of controlling the spread of such infections?

BIBLIOGRAPHY

Centers for Disease Control and Prevention. (1999). Outbreak of West Nile-like viral encephalitis—New York, 1999. *Morbidity and Mortality Weekly Report* 48, 845–849.

Centers for Disease Control and Prevention. (2002). Provisional surveillance summary of the West Nile virus epidemic—United States, January–November 2002. *Morbidity and Mortality Weekly Report* 51, 1129–1133.

Centers for Disease Control and Prevention. (2003). Multistate outbreak of monkeypox—Illinois, Indiana, and Wisconsin, 2003. *Morbidity and Mortality Weekly Report* 52, 537–540.

Centers for Disease Control and Prevention. (2003). Update: Severe acute respiratory syndrome—Toronto, Canada, 2003. *Morbidity and Mortality Weekly Report* 52, 547–550.

Centers for Disease Control and Prevention. (2003). Update: Severe acute respiratory syndrome—worldwide and United States, 2003. *Morbidity and Mortality Weekly Report* 52, 664–665.

Centers for Disease Control and Prevention. (2006). Ongoing multistate outbreak of *Escherichia coli* serotype O157:H7 infections

associated with consumption of fresh spinach—United States, September 2006. *Morbidity and Mortality Weekly Report* 55(Dispatch), 1–2.

Drusano G.L. (2004). Antimicrobial pharmacodynamics: Critical interactions of "bug and drug." *Nature Reviews Microbiology* 2, 289–300.

Dumler J.S., Bakken J.S. (1995). Ehrlichial diseases in humans: Emerging tick-borne infections. *Clinical Infectious Diseases* 20, 1102–1110.

Dunne W.M. Jr. (2002). Bacterial adhesion: Seen any good biofilms lately? *Clinical Microbiology Review* 15, 155–166.

Hsueh P.R., Yang P.C. (2005). Severe acute respiratory syndrome epidemic in Taiwan, 2003. *Journal of Microbiology, Immunology and Infection* 38, 82–88.

Jernigan D.M., Raghunathan P.L., Bell B.P., et al. (2002). Investigation of bioterrorism-related anthrax, United States, 2001: Epidemiologic findings. *Emerging Infectious Diseases* 8, 1019–1028.

Lampiris H.W., Maddix D.S. (2007). Clinical use of antimicrobial agents. In Katzung B.G. (Ed.), *Basic and clinical pharmacology* (10th ed., pp. 867–877). New York: McGraw-Hill.

Marano N., Arquin P.M., Pappaloanou M. (2007). Impact of globalization and animal trade in infection disease ecology. *Emerging Infectious Diseases* 13(12), 1807–1808.

McFee R.B. (2007). Global infections—Avian influenza and other significant emerging pathogens—an overview. *Disease of the Month* 53, 343–347.

Morens D.M., Folkers G.K., Fauci A.S. (2004). The challenge of emerging and re-emerging diseases. *Nature* 430(6996), 242–249.

O'Brien K.K., Higdon M.L., Halverson J.J. (2003). Recognition and management of bioterrorism infections. *American Family Physician* 67, 1927–1934.

Peiris J.S.M., Lai S.T., Poon L.L.M., et al. (2003). Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 361, 1319–1325.

Prince A.S. (2002). Biofilms, antimicrobial resistance, and airway infection. *New England Journal of Medicine* 347, 1110–1111.

Ryan E.T., Wilson M.E., Kain K.C. (2002). Illness after international travel. *New England Journal of Medicine* 347, 505–516.

Stone J.H., Dierberg K., Aram G., et al. (2004). Human monocytic ehrlichiosis. *Journal of the American Medical Association* 292, 2263–2270.

Tang Y.-W., Persing D.H. (2003). Molecular detection and identification of microorganisms. In Murray P.R., Baron E.J., Pfaller M.A., et al. (Eds.), *Manual of clinical microbiology* (7th ed., pp. 215–244). Washington, DC: American Society for Microbiology.

Tyler K.L. (2000). Prions and prion diseases of the central nervous system (neurodegenerative diseases). In Mandell G.L., Bennett J.E., Dolin R. (Eds.), *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (5th ed., pp. 1971–1985). Philadelphia: Churchill Livingstone.

Writing Committee of the WHO consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza (2010). Clinical aspects of pandemic 2009 Influenza A (H1N1) Infection. *New England Journal of Medicine* 362 (18), 1708–1719.

Introduction to the Immune System
Innate and Adaptive Immunity
Cells of the Immune System
Myeloid Lineage Phagocytic Cells
Lymphoid Lineage Lymphocytes and Natural Killer Cells
Tissues of the Immune System
Central Lymphoid Tissues
Peripheral Lymphoid Tissues
Cytokines That Mediate and Regulate Immunity
General Properties of Cytokines
Chemokines
Colony-Stimulating Factors
Innate Immunity
Epithelial Barriers
Cells of Innate Immunity
Pathogen Recognition
Pattern Recognition
Toll-Like Receptors
Soluble Mediators of Innate Immunity
Opsonins
Inflammatory Cytokines
The Complement System
Role of Innate Immunity in Stimulating Adaptive Immunity
Adaptive Immunity
Antigens
Cells of Adaptive Immunity
Antigen-Presenting Cells
Lymphocytes
Major Histocompatibility Complex Molecules
B Lymphocytes and Humoral Immunity
Immunoglobulins
Humoral Immunity
T Lymphocytes and Cell-Mediated Immunity
Helper T Cells
Cytotoxic T Cells
Regulatory T Cells
Cell-Mediated Immunity
Active Versus Passive Immunity
Regulation of the Immune Response
Developmental Aspects of the Immune System
Transfer of Immunity from Mother to Infant
Immune Response in the Elderly

Chapter 15

Innate and Adaptive Immunity

The immune system has evolved to defend against bacteria, viruses, and other foreign substances. Through recognition of molecular patterns, the immune system can distinguish itself from foreign substances and can discriminate potentially harmful from nonharmful agents. It also defends against abnormal cells and molecules that periodically develop. Although the immune response normally is protective, it also can produce undesirable effects such as when the response is excessive, as in allergies, or when it recognizes self-tissue as foreign, as in autoimmune disease. This chapter is divided into three parts: (1) introduction to the immune system, (2) innate immunity, and (3) adaptive immunity.

Introduction to the Immune System

The term *immunity* has come to mean the protection from disease and, more specifically, infectious disease. The collective, coordinated response of the cells and molecules of the immune system is called the *immune response*. Although the relationship between microbes and infectious diseases dates far back in history, it has only been within the last 30 to 40 years that an understanding of the cellular and biochemical mechanisms involved in the immune response has begun to emerge. Advances in cell culture techniques, immunochemistry, recombinant deoxyribonucleic acid (DNA) technology, and the creation of genetically altered animals, such as "transgenic" and "knockout" mice, have transformed immunology from a largely descriptive science to one of immune phenomena that can be explained in structural and biochemical terms.

Innate and Adaptive Immunity

There are two host defenses that cooperate to protect the body—the early, rapid responses of innate immunity and the very effective, but later responses of adaptive immunity. As the first line of defense, *innate* (also called *natural* or *native*) *immunity* consists of the physical, chemical, molecular, and cellular defenses that are in place before

infection and can function immediately as an effective barrier to microbes. *Adaptive* (also called *specific* or *acquired*) *immunity* is the second major immune defense, responding less rapidly than innate immunity but more effectively. Adaptive immunity uses focused recognition of each unique type of foreign agent followed in days by an amplified and effective response.

The major components of innate immunity are the skin and mucous membranes, phagocytic leukocytes (mainly neutrophils and macrophages), specialized lymphocytes (i.e., natural killer cells), and several plasma proteins, including the proteins of the complement system (Fig. 15-1). The innate immune system is able to distinguish self from nonself and is able to recognize and react against classes of microbial agents. The response of the innate immune system is rapid, usually within minutes to hours, and prevents the establishment of infection and deeper tissue penetration of microorganisms. The effector responses used by the innate immune system to eliminate the microbes are very similar for different classes of microorganisms. Although most innate responses are very effective in controlling and destroying the invading agent, pathogenic microbes have evolved several approaches to evade innate defenses. The microorganisms not controlled by innate immunity are usually controlled by the more specific approaches of adaptive immunity.

The adaptive immune system consists of lymphocytes and their products, including antibodies (Fig. 15-1). Whereas the cells of the innate immune system recognize structures shared by classes of microorganisms, the cells of the adaptive immune system (i.e., lymphocytes) are capable of recognizing a vast array of substances produced by microorganisms as well as noninfectious substances and developing a specific immune response that differs with each substance. Substances that elicit adaptive immune responses are called *antigens*. A memory of the substance is also developed so that a repeat exposure to the same microbe or agent produces a quicker and more vigorous response. There are two types of adaptive immune responses: humoral and cell-mediated immunity. *Humoral immunity* is mediated by molecules called *antibodies* that are produced by cells called *B lymphocytes*. Antibodies are secreted into the circulation and mucosal fluid, where they neutralize or eliminate extracellular microbes and microbial toxins. One of the important functions of humoral immunity is to stop microbes that

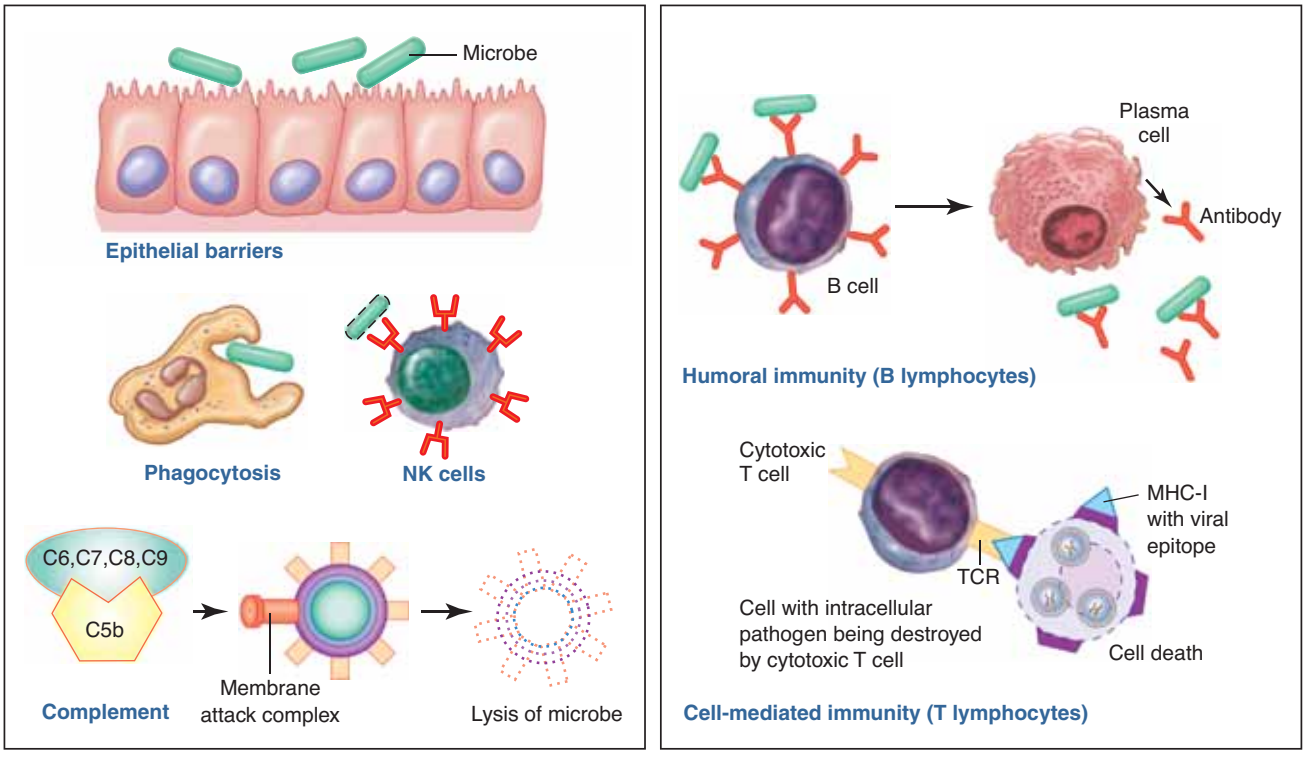


FIGURE 15-1. Mechanisms of innate and adaptive immunity. **(A)** The major effectors of the innate immune system include the immediately available epithelial barriers, phagocytic leukocytes, natural killer (NK) cell, and complement system. These effectors are in place before an encounter with an infectious agent and provide rapid protection against infection. **(B)** Adaptive immunity develops later than innate immunity, is acquired through previous experience with a foreign agent, and is mediated by T and B lymphocytes and their products. Humoral immunity is provided by B lymphocytes that differentiate into antibody-producing plasma cells that interact with and protect against microbes that are present in the blood or on mucosal surfaces. Cell-mediated immunity is provided by T cytotoxic cells that destroy cells infected with intracellular pathogens.

are present on mucosal surfaces and in the blood from gaining access to and colonizing body tissues. *Cell-mediated immunity,* which defends against intracellular microbes such as viruses, is provided by cells called *T lymphocytes*. Some T lymphocytes activate phagocytes to destroy microbes that have been engulfed, whereas others kill any type of host cell that is harboring microbes.

Recent studies have shown that essential, cooperative interactions exist between innate and adaptive immunity. Innate immunity communicates to lymphocytes involved in adaptive immunity the characteristics of the pathogen and information about its intracellular or extracellular location. The innate immune response also stimulates and influences the nature of adaptive immune responses. At the effector stage of immunity, the adaptive immune response amplifies and increases its efficiency by recruitment and activation of additional phagocytes and molecules of the innate immune system. Both innate and adaptive immunity destroy the invading agent by using the effector responses of phagocytosis and the complement system. Thus, immunity is truly an interactive, cooperative effort.

Cells of the Immune System

The cells of the immune system consist of phagocytic leukocytes, lymphocytes, and antigen-presenting cells. The key cells of innate immunity include phagocytic white blood cells or leukocytes (neutrophils and macrophages) and NK cells. Adaptive immune responses depend on lymphocytes, which provide lifelong immunity after exposure to disease-producing microbes or environmental agents. Dendritic cells and macrophages function as antigen-presenting cells for adaptive immunity.

All of the cellular elements of the blood, including the red blood cells, platelets, and white blood cells, derive from the hematopoietic stem cells in the bone marrow (see Chapter 11). As these stem cells differentiate, they give rise to cells with more limited developmental potential including the immediate progenitors of the two main categories of white blood cells, the myeloid and lymphoid lineages. The common myeloid progenitor is the precursor of most of the phagocytic cells of the innate immune system, and the lymphoid lineage consists of the lymphocytes of the adaptive immune system and natural killer cells of innate immunity. The general properties of these cells are presented in this section, whereas their specific functions in relation to innate or adaptive immunity are discussed in those sections of the chapter.

Myeloid Lineage Phagocytic Cells

The common myeloid progenitor is the precursor of the monocytes/macrophages, granulocytes, and dendritic cells of the innate immune system. These three cell types make up the phagocytic cells of the immune system.

Monocytes/Macrophages. Macrophages are part of the monocytic phagocyte system. They are resident in almost all tissues and are the mature form of monocytes, which circulate in the blood and continually migrate into tissues, where they differentiate into macrophages. Macrophages are relatively long-lived cells and perform several different functions during the innate immune response and subsequent adaptive immune response. One is to engulf and kill invading microorganisms. In this phagocytic role they are an important first-line defense in innate immunity, and they dispose of pathogens and infected cells targeted for disposal by an adaptive immune response. As phagocytic cells, macrophages also function as antigen-presenting cells of the adaptive immune response.

In addition to phagocytosis, macrophages function to orchestrate immune responses: they help induce inflammation, and they secrete signaling proteins that activate other immune cells and recruit them into an immune response. In addition to their specialized role in the immune system, macrophages act as general scavenger cells in the body, clearing dead cells and cell debris.

Granulocytes. The granulocytes are so called because they have densely staining granules in the cytoplasm. There are three types of granulocytes—neutrophils, eosinophils, and basophils—which are distinguished by the staining properties of their granules. Compared to the macrophages, they are relatively short-lived, surviving only a few days, and produced in increased numbers during an immune response. Neutrophils, which are named for their neutral-staining granules, are the most numerous of the granulocytes and the most important cell in innate immunity. They take up a variety of microorganisms by phagocytosis and efficiently destroy them using degradative enzymes and other antimicrobial substances stored in their cytoplasmic granules. The protective functions of the basophils and eosinophils are less well understood. They are thought to be an important defense against parasites, which are too large to be ingested by macrophages and neutrophils. They are also involved in allergic reactions, in which their effects are damaging and not protective (see Chapter 16).

Dendritic Cells. The dendritic cells are the third class of phagocytic cells of the immune system. They have long fingerlike processes, which give them their name. Most dendritic cells are found as immature cells under epithelial tissue and in most organs, where they are poised to capture foreign agents and transport them to peripheral lymphoid organs. Once activated, they undergo a complex maturation process as they migrate to the regional lymph nodes. These cells function as key antigen-presenting cells that initiate adaptive immune responses by processing and presenting molecules of foreign antigens to the lymphocytes. Thus, the dendritic cell functions as an important intermediary between innate and adaptive immunity. Dendritic cells, like macrophages, also release several communication molecules that direct the nature of adaptive immune responses.

Lymphoid Lineage Lymphocytes and Natural Killer Cells

The common lymphoid progenitor in the bone marrow gives rise to antigen-specific lymphocytes of the adaptive

immune system and also to a type of lymphocyte called the *natural killer (NK) cell* that responds to infection but not to specific antigens, and is thus considered part of the innate immune system. Lymphocytes are the only cells that produce specific receptors for antigen and thus are the key mediators of adaptive immunity. There are two types of lymphocytes: B and T lymphocytes. A *naive lymphocyte* is a mature B or T lymphocyte that has not previously encountered antigen or is not the progeny of an antigen-stimulated mature lymphocyte.

B lymphocytes (B cells) are the only cells capable of producing antibodies; therefore, they are the cells that mediate humoral immunity. B cells use membrane-bound antibodies to recognize a wide variety of proteins, polysaccharides, lipids, and small chemicals. These antigens may be expressed on microbial surfaces or they may be in soluble forms (toxins). B cells differentiate in response to antigen and other signals into cells that produce antibody. The secreted antibodies enter the circulation and mucosal fluids and bind to microbes before they have a chance to colonize body tissues.

The other class of lymphocytes, the *T lymphocytes* (T cells), are responsible for cell-mediated immunity. The antigen receptors of most T lymphocytes only recognize peptide fragments of protein antigens that are bound to specialized peptide display molecules called *major histocompatibility complex (MHC) molecules* on the surface of specialized cells called *antigen-presenting cells*. Among T lymphocytes are a subset of T cells called *helper T cells* that help B lymphocytes produce antibodies and help phagocytic cells destroy ingested pathogens, and another subset called *cytotoxic T cells* that kill or lyse intracellular microbes.

Although all lymphocytes are morphologically similar, they vary in terms of lineage, cell membrane molecules and receptors, function, and response to antigen. These cells are often distinguished by surface proteins that can be identified using monoclonal antibodies. The standard nomenclature for these proteins is the CD (clusters of differentiation) numeric designation (CD4, CD8), which is used to delineate surface proteins that define a particular cell type or stage of cell differentiation and are recognized by a "cluster" or group of antibodies.

The classification of lymphocytes and other immune cells by CD antigen expression is now widely used in clinical medicine and experimental immunology. In human immunodeficiency virus (HIV) infection, for example, a decline or rise in the $CD4^+$ helper T-cell count is used to follow the progression of the disease and response to treatment. Further investigation of the CD molecules has shown that they are not merely phenotypic markers of cell type but are themselves involved in a variety of lymphocyte functions, including promotion of cell-to-cell adhesion and transduction of signals that lead to lymphocyte activation.

Natural Killer Cells. NK cells are part of the innate immune system and may be the first line of defense against viral infections. They also have the ability to recognize and kill tumor cells, abnormal body cells, and cells infected with *intracellular pathogens*, such as viruses and intracellular bacteria.

Tissues of the Immune System

The cells of the immune system are present in large numbers in the central and peripheral lymphoid organs. These organs and tissues are widely distributed in the body and provide different, but often overlapping, functions (Fig. 15-2). The central lymphoid organs, the bone marrow and the thymus, provide the environment for immune cell production and maturation. The lymph nodes, spleen, tonsils, appendix, Peyer patches in the intestine, and mucosa-associated lymphoid tissues in the respiratory, gastrointestinal, and reproductive systems comprise the peripheral lymphoid tissues and organs. These tissues function to concentrate antigen, aid processing of antigen, and promote cellular interactions necessary for development of adaptive immune responses. The lymphoid organs are connected by networks of lymph channels, blood vessels, and capillaries. The immune cells continuously circulate through the various tissues and organs to seek out and destroy foreign material.

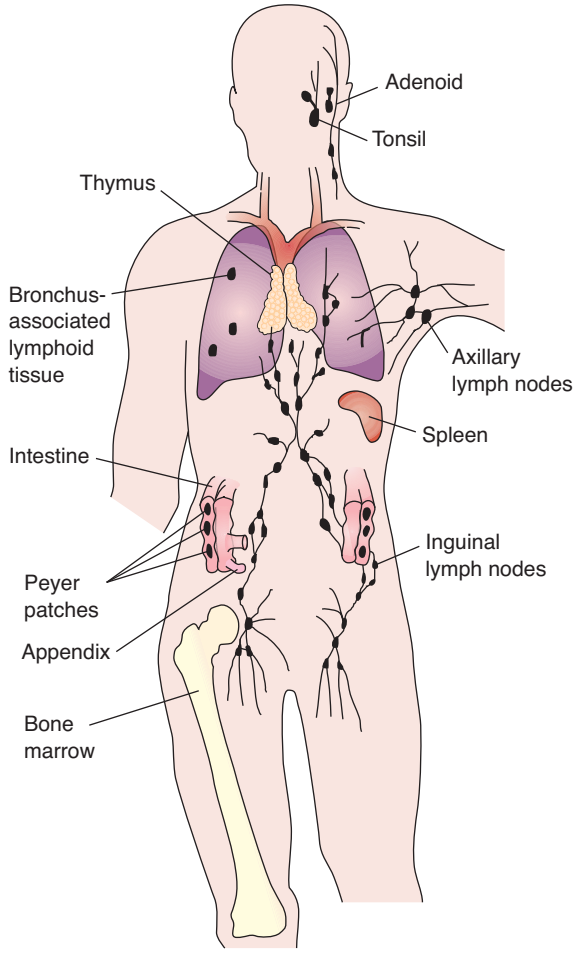


FIGURE 15-2. Central and peripheral lymphoid organs and tissues.

Central Lymphoid Tissues

The central lymphoid tissues in the bone marrow and thymus gland provide the environment for immune cell production and maturation (see Chapter 11). The specialized microenvironment of the bone marrow provides signals both for the development of lymphocyte progenitors from the hematopoietic stem cells and for the subsequent differentiation of B cells.

T-cell progenitors migrate from the bone marrow to the thymus where the process of maturation occurs. The thymus is an elongated, bilobed structure located in the neck region above the heart. The function of the thymus is central to the development of the immune system because it generates mature, immunocompetent T lymphocytes expressing appropriate receptors. The thymus is fully formed and functional at birth. It persists as a large organ until about the time of puberty, when T-cell development and proliferation are reduced and the thymus begins slowly regressing and is replaced by adipose tissue. Nevertheless, some thymus tissue persists and can be restimulated under conditions that demand rapid T-cell proliferation.

Precursor T (pre-T) cells enter the thymus as functionally and phenotypically immature T cells. They undergo cycles of proliferation and selection as they move from the cortical to medullary compartments of the thymus. Rapid cell multiplication, maturation, and selection occur in the cortex under the influence of the microenvironment, thymic hormones, and cytokines. As the T cells multiply and mature, they acquire T-cell receptors, surface markers that distinguish among the different types of T cells, and antigens that distinguish them from nonself. Only those T cells able to recognize foreign antigens and distinguish self from nonself are allowed to mature and leave the thymus. This process is called *thymic selection.* The thymus must be extremely thorough in eliminating self-reactive cells to ensure that autoimmune reactivity and disease do not result. Mature, immunocompetent T-helper and T-cytotoxic cells leave the thymus in 2 to 3 days and enter the peripheral lymphoid tissues through the bloodstream.

The process of B-cell maturation, which is similar to that of T-cell maturation, occurs in the bone marrow. It is here that B cells multiply and mature and acquire immunoglobulin (Ig) signaling molecules and cell markers that distinguish them from nonself. As with T cells, only those B cells that are able to distinguish self from nonself are allowed to mature and leave the bone marrow.

Peripheral Lymphoid Tissues

The peripheral lymphoid structures, which consist of the lymph nodes, the spleen, and other secondary lymphoid tissues, function to concentrate antigen, aid in processing of antigen, and promote the cellular interactions necessary for development of adaptive immune responses.

Lymph Nodes. Lymph nodes are highly organized lymphoid organs located at points of convergence of vessels in the lymphatic system with aggregates of lymph nodes processing lymph from discrete anatomic sites. Many lymph nodes are located in the axillae and groin, and along the great vessels of the neck, thorax, and abdomen (Fig. 15-2).

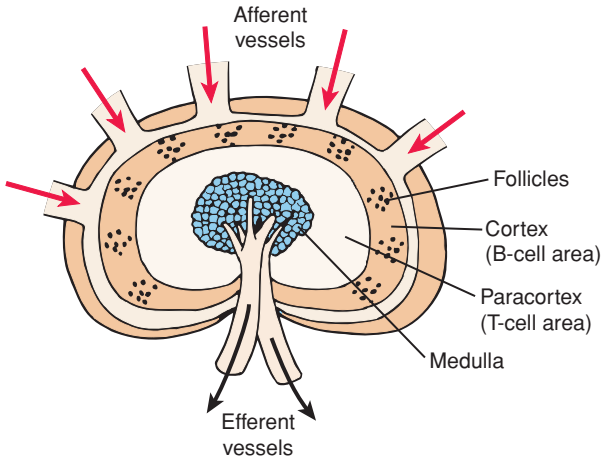


FIGURE 15-3. Structural features of a lymph node. Lymphocytes and macrophages flow slowly through the node, which allows for trapping and interactions of antigens and immune cells.

Lymph nodes are small, bean-shaped, encapsulated lymphoid organs (Fig. 15-3). Lymph enters the node through afferent lymph channels that penetrate the capsule and leaves through the efferent lymph vessels located in the deep indentation of the hilus. Lymphocytes and macrophages flow slowly through the node, which allows trapping and interaction of antigen and immune cells. Lymph nodes have two functions: they function in the removal of foreign material from lymph before it enters the bloodstream and they serve as centers for proliferation and response of immune cells. Fluid from all the epithelia and connective tissues and most parenchymal organs is drained by lymphatics, which transport this fluid, called *lymph,* from the tissue to the lymph nodes. As lymph passes through the lymph nodes, antigen-presenting cells in the nodes are able to sample the antigens that enter through the epithelia. In addition, microbes that bypass the epithelial barriers of the innate immune system are captured by resident dendritic cells and transported to draining lymph nodes.

A lymph node is divided into several specialized areas, an outer cortex, a paracortex, and an inner medulla. The T lymphocytes are more abundant in the paracortex of the node, and the B lymphocytes are more abundant in the follicles and germinal centers located in the outer cortex (see Chapter 11). The T lymphocytes proliferate on antigenic stimulation and migrate to the follicles, where they interact with B lymphocytes. These activated follicles become germinal centers, containing macrophages, follicular dendritic cells, and maturing T and B cells. Activated B cells then migrate to the medulla, where they complete their maturation into plasma cells. These cells stay localized in the lymph node but release large quantities of antibodies into the circulation.

Spleen. The spleen is a large, ovoid secondary lymphoid organ located high in the left abdominal cavity. The

spleen filters antigens from the blood and is important in the response to systemic infections. The spleen is composed of red and white pulp. The red pulp is well supplied with arteries and is the area where senescent and injured red blood cells are removed. The white pulp contains concentrated areas of B and T lymphocytes permeated by macrophages and dendritic cells. A sequence of activation events similar to that seen in the lymph nodes occurs in the spleen.

Other Secondary Lymphoid Tissues. Other secondary lymphoid tissues include the *mucosa-associated lymphoid tissues* (MALT). These nonencapsulated clusters of lymphoid tissues are located around membranes lining the respiratory, digestive, and urogenital tracts. These gateways into the body must harbor the immune cells needed to respond to a large and diverse population of microorganisms. In some tissues, the lymphocytes congregate in loose clusters, but in other tissues such as the tonsils, Peyer patches in the intestine, and the appendix, organized structures are evident (see Fig. 15-2). These tissues contain all the necessary cell components (i.e., T cells, B cells, macrophages, and dendritic cells) for an immune response. Because of the continuous stimulation of the lymphocytes in these tissues by microorganisms constantly entering the body, large numbers of plasma cells are evident. Immunity at the mucosal layers helps to exclude many pathogens and thus protects the vulnerable internal organs.

Cytokines That Mediate and Regulate Immunity

Although cells of both the innate and adaptive immune systems communicate critical information by cell-to-cell contact, many interactions and effector responses depend on the secretion of short-acting soluble molecules called *cytokines*. Chemokines are a family of cytokines that direct leukocyte movement and migration, and colony-stimulating factors are cytokines that promote the proliferation and differentiation of bone marrow progenitor cells. The sources and properties of the main cytokines that participate in innate and adaptive immunity are summarized in Table 15-1.

General Properties of Cytokines

Cytokines are low–molecular-weight regulatory proteins that are produced by cells of the innate and adaptive immune systems and that mediate many of the actions of these cells. The names of specific types of cytokines were derived from the biologic properties first ascribed to them. For example, *interleukins* (ILs) were found to be made by leukocytes and to act on leukocytes, and *interferons* (IFNs) were found to interfere with virus multiplication.

Although cytokines have many diverse actions, all share several important properties. Most cytokines are released at cell-to-cell interfaces, where they bind to specific receptors on the membrane surface of their target cells. All cytokines are secreted in a brief, self-limited manner. They are not usually stored as preformed molecules and their synthesis is limited to new gene transcription resulting from cellular activation. The short half-life of cytokines ensures that excessive immune responses and systemic activation do not occur.

The actions of cytokines are often pleiotropic and redundant. *Pleiotropism* refers to the ability of a cytokine to act on different cell types. For example, IL-2, initially discovered as a T-cell growth factor, is also known to affect the growth of B cells and NK cells. Interferon-γ is the key macrophage-activating cytokine that functions in both innate and adaptive immune responses. Although pleiotropism allows cytokines to mediate diverse effects, it greatly limits their use for therapeutic purposes because of numerous unwanted side effects. *Redundancy* refers to the ability of different cytokines to stimulate the same or overlapping biologic functions. Because of this redundancy, antagonists against a single cytokine may not have functional consequences because other cytokines may compensate.

Not only are the actions of cytokines pleiotropic and redundant, but also the same cytokines may be produced by several different cell types. For example, IL-1 can be produced by virtually all leukocytes, endothelial cells, and fibroblasts. Cytokines often influence the synthesis and actions of other cytokines. The ability of one cytokine to stimulate the production of others often leads to cascades in which the second and third cytokines may mediate the biologic effects of the first. Cytokines may also serve as antagonists to inhibit the action of another cytokine or, in some cases, they may produce additive or greater than anticipated effects.

Cytokine actions may be local or systemic. Most cytokines act close to where they are produced, acting on the same cell that secreted the cytokine (autocrine mechanism), or they may influence the activity of nearby cells in a paracrine fashion. When produced in large amounts, cytokines may enter the bloodstream and exert their action on distant cells in an endocrine manner, the best examples being IL-1 and tumor necrosis factor-α (TNF-α), which produce the systemic acute-phase response during inflammation.

Chemokines

Chemokines are cytokines that stimulate the migration and activation of immune and inflammatory cells. Two major subclasses, termed *CC chemokines* and *CXC chemokines*, are distinguished by the position of the first two cysteines being located adjacent to each other (CC) or separated by an amino acid (CXC). The largest family, the CC chemokines attract mononuclear leukocytes to sites of chronic inflammation. The CXC chemokines attract neutrophils to sites of acute inflammation.

Chemokines are named according to structure, followed by "L" and the number of their gene (e.g., CCL1, CXCL1). Likewise, chemokine receptors are named according to the structure, followed by an "R" and a number (e.g., CCR1, CXCR1). Most receptors recognize more than one chemokine, and most chemokines recognize more than one receptor. Binding of a chemokine to

TABLE 15-1 Cytokines of Innate and Adaptive Immunity

Cytokines	Source	Biologic Activity
Interleukin-1 (IL-1)	Macrophages, endothelial cells, some epithelial cells	Wide variety of biologic effects; activates endothelium in inflammation; induces fever and acute-phase response; stimulates neutrophil production
Interleukin-2 (IL-2)	$CD4^+$, $CD8^+$ T cells	Growth factor for activated T cells; induces synthesis of other cytokines; activates cytotoxic T lymphocytes and NK cells
Interleukin-3 (IL-3)	$CD4^+$ T cells	Growth factor for progenitor hematopoietic cells
Interleukin-4 (IL-4)	$CD4^+$ T_H2 cells, mast cells	Promotes growth and survival of T, B, and mast cells; causes T_H2 cell differentiation; activates B cells and eosinophils and induces IgE-type responses
Interleukin-5 (IL-5)	$CD4^+$ T_H2 cells	Induces eosinophil growth and development
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T lymphocytes	Stimulates the liver to produce mediators of acute-phase inflammatory response; also induces proliferation of antibody-producing cells by the adaptive immune system
Interleukin-7 (IL-7)	Bone marrow stromal cells	Primary function in adaptive immunity; stimulates pre-B cells and thymocyte development and proliferation
Interleukin-8 (IL-8)	Macrophages, endothelial cells	Primary function in adaptive immunity; chemoattracts neutrophils and T lymphocytes; regulates lymphocyte homing and neutrophil infiltration
Interleukin-10 (IL-10)	Macrophages, some T-helper cells	Inhibitor of activated macrophages and dendritic cells; decreases inflammation by inhibiting T_H1 cells and release of IL-12 from macrophages
Interleukin-12 (IL-12)	Macrophages, dendritic cells	Enhances NK cell cytotoxicity in innate immunity; induces T_H1 cell differentiation in adaptive immunity
Type I interferons (IFN-α, IFN-β)	Macrophages, fibroblasts	Inhibit viral replication; activate NK cells; increase expression of MHC-I molecules on virus-infected cells
Interferon-γ (IFN-γ)	NK cells, $CD4^+$ and $CD8^+$ T lymphocytes	Activates macrophages in both innate immune responses and adaptive cell-mediated immune responses; increases expression of MHC-I and -II and antigen processing and presentation
Tumor necrosis factor-α (TNF-α)	Macrophages, T cells	Induces inflammation, fever, and acute-phase response; activates neutrophils and endothelial cells; kills cells through apoptosis
Chemokines	Macrophages, endothelial cells, T lymphocytes	Large family of structurally similar cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from the blood to the tissues
Granulocyte-monocyte CSF (GM-CSF)	T cells, macrophages, endothelial cells, fibroblasts	Promotes neutrophil, eosinophil, and monocyte maturation and growth; activates mature granulocytes
Granulocyte CSF (G-CSF)	Macrophages, fibroblasts, endothelial cells	Promotes growth and maturation of neutrophils consumed in inflammatory reactions
Monocyte CSF (M-CSF)	Macrophages, activated T cells, endothelial cells	Promotes growth and maturation of mononuclear phagocytes

CSF, colony-stimulating factor; NK, natural killer; T_H1, T-helper type 1; T_H2, T-helper type 2; MHC, major histocompatibility complex.

a receptor can result in agonist or antagonist activity, with the same chemokine acting as an agonist at one type of receptor and as an antagonist at another.

Chemokines are implicated in a number of acute and chronic diseases, including atherosclerosis, rheumatoid arthritis, inflammatory bowel disease (Crohn disease, ulcerative colitis), allergic asthma and chronic bronchitis, multiple sclerosis, systemic lupus erythematosus, and HIV infection. To enter target cells, HIV type 1 requires two distinct elements: the CD4 recognition molecule of the helper T cell and either the CXCR4 or CCR5 chemokine. The targeting of T cells and monocytes allows HIV-1 access to sanctuary sites throughout the body and also cripples the $CD4^+$ T-helper cell that orchestrates antiviral immunity (discussed in Chapter 16). Drugs that target these chemokine receptors for HIV are currently in advanced clinical trials.

Colony-Stimulating Factors

Colony-stimulating factors (CSFs) are cytokines that stimulate bone marrow pluripotent stem and progenitor or precursor cells to produce large numbers of platelets, erythrocytes, lymphocytes, neutrophils, monocytes, eosinophils, basophils, and dendritic cells. The CSFs were named according to the type of target cell on which they act (see Table 15-1). Granulocyte-monocyte colony-stimulating factor (GM-CSF) acts on the granulocyte–monocyte progenitor cells to produce monocytes, neutrophils, and dendritic cells; granulocyte colony-stimulating factor (G-CSF) specifically induces neutrophil proliferation; and macrophage colony-stimulating factor (M-CSF) directs the mononuclear phagocyte progenitor. Other cytokines, including IL-3, IL-7, and IL-11, also influence hematopoiesis. Recombinant CSF molecules

are currently being used to increase the success rates of bone marrow transplantations. The availability of recombinant CSFs and cytokines offers the possibility of several clinical therapies where stimulation or inhibition of the immune response or cell production is desirable.

In summary, immunity is the resistance to a disease that is provided by the immune system. Immune mechanisms can be divided into two types: innate and adaptive immunity. Innate immunity is the first line of defense against microbial agents. It can distinguish between self and nonself but not among specific pathogens. Adaptive immunity involves humoral and cell-mediated immune responses that respond to a unique antigen, can amplify and sustain its responses, distinguish self from nonself, and remember the antigen to quickly produce a heightened response on subsequent encounters with the same agent. There is a dynamic interplay between innate and adaptive immunity both in the early initiation stages and the final response to the foreign invader.

The cellular components of the innate and adaptive immunity include the phagocytic cells that are of myeloid lineage and the lymphocytes that are of lymphoid lineage. The phagocytic granulocytes, macrophages, and dendritic cells, along with the NK cells, participate in innate immune responses, and the lymphocytes participate in adaptive immune responses. The tissues of the immune system consist of the generative or central lymphoid organs in which T and B lymphocytes originate and mature and the peripheral lymphoid organs in which adaptive immune responses to microbes is initiated.

Although cells of both the innate and adaptive immune systems communicate critical information about invading pathogens by cell-to-cell contact, many interactions and effector responses depend on the secretion of chemical mediators called *cytokines*. Cytokines are soluble proteins secreted by cells of both the innate and adaptive immune systems that mediate many of the functions of these cells. Some cytokines mediate inflammation or interfere with viral replication. Chemokines are cytokines that stimulate the migration and activation of immune and inflammatory cells. Colony-stimulating factors are cytokines that stimulate the growth and differentiation of bone marrow progenitors of immune cells.

Innate Immunity

The innate immune system consists of the epithelial barriers; phagocytic neutrophils, macrophages, dendritic cells, NK cells, and several plasma proteins, including those of the complement system. These mechanisms are present in the body before an encounter with an infectious agent and are rapidly activated by microbes before the development of adaptive immunity. The innate immune system also interacts with and directs adaptive immune responses.

Innate Immunity

- Innate immunity consists of physical, chemical, cellular, and molecular defenses that are ready for activation and mediate rapid, initial protection against infection.
- Skin and mucous membranes are highly effective physical barriers against microorganisms. Antimicrobial molecules can effectively kill a wide variety of microbes.
- The cells of innate immunity express pattern recognition receptors (PRRs) that bind with broad patterns shared by groups of microbes but not present on mammalian cells. Toll-like receptors, a major type of PRR, are expressed on phagocytes and are potent activators of innate immune system cells and molecules.
- The effector responses of innate immunity involve the inflammatory response, the complement system, natural killer cells, and phagocytosis by neutrophils and monocytes/macrophages.
- Cytokines released from activated leukocytes regulate the activity of other cells, amplify inflammation, stimulate the production of acute-phase proteins, and aid in the initiation of an adaptive immune response.

With the ever-expanding wealth of information on immune system function, it is becoming clear that the innate immune system not only protects against microbial agents, but may also play a role in the pathogenesis of disease. Among the functions of the innate immune system is induction of a complex cascade of events known as the *inflammatory response* (discussed in Chapter 3). Recent evidence suggests that low-grade inflammation and activation of the innate immune system play a key role in the pathogenesis of a number of disorders such as atherosclerosis and coronary artery disease, bronchial asthma, type 2 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus.

Epithelial Barriers

Our outer body surfaces are protected by epithelia, which provide physical and chemical barriers between the internal environment and external world that contains pathogens. Epithelia compromise skin and linings of the respiratory, gastrointestinal, and urogenital tracts. The intact skin is a formidable physical barrier because of its closely packed cells, multiple layering, continuous shedding of cells, and presence of the protective protein keratin. In addition to its barrier function, the skin has chemicals that create a salty and acidic environment and antibacterial proteins, such as the enzyme lysozyme, that inhibit the colonization of microorganisms and aid in their destruction.

The mucous membrane linings of the gastrointestinal, respiratory, and urogenital tracts are protected by sheets of tightly packed epithelial cells that block the entry of microbes and destroy them by secreting antimicrobial enzymes, proteins, and peptides. Specialized cells in these linings secrete a viscous material called *mucus*. Mucus traps and washes away microorganisms, especially with the help of additional secretions such as saliva. Also in the lower respiratory tract, hairlike structures called *cilia* protrude through the epithelial cells. The synchronous action of the cilia moves many microbes trapped in the mucus toward the throat. The physiologic responses of coughing and sneezing further aid in their removal from the body.

Once microbes are trapped, various chemical defenses come into play. These include lysozyme, a hydrolytic enzyme capable of cleaving the walls of bacterial cells; complement, which binds and aggregates bacteria to increase their susceptibility to phagocytosis or disrupt their lipid membrane; and members of the *collectin* family of surfactant proteins (e.g., surfactants [SP]-A and SP-D) in the respiratory tract (see Chapter 21). Both SP-A and SP-D bind a variety of pathogens and are important defense molecules in the lung. The best-defined function of the surfactants is their ability to opsonize pathogens, including bacteria and viruses, and to facilitate phagocytosis by innate immune cells such as macrophages. SP-A and SP-D also regulate production of inflammatory mediators. In the stomach and intestines, death of microbes results from the action of digestive enzymes, acidic conditions, and secretions of *defensins*, small cationic peptides that kill within minutes both gram-positive and gram-negative microorganisms by disrupting the microbial membrane.

Cells of Innate Immunity

Some pathogens can penetrate the epithelial barriers of the host and cause infection, particularly when the barrier has been breached as in wounds, burns, or loss of the body's internal epithelia. The subsequent innate immune response to the penetration of these invaders is initiated by several types of immune cells with receptors for recognition of general groups of microbes. The key cells of innate immunity include phagocytic leukocytes and NK cells.

Several types of phagocytic leukocytes recognize and kill infectious agents during an innate immune response. The early-responding phagocytic cell is the *neutrophil*, followed shortly by the more efficient, multifunctional *macrophage*. Phagocytes are activated to engulf and digest microbes that attach to their cell membrane. Once the cell is activated and the microbe ingested, the cell generates digestive enzymes and toxic oxygen and nitrogen intermediates (i.e., hydrogen peroxide or nitric oxide) that kill the pathogen. The phagocytic killing of microorganisms helps to prevent the spread of infectious agents until adaptive immunity can be marshaled.

Dendritic cells, which are derived from bone marrow cells and related in lineage to the macrophage, also play important roles in the innate immune response to infections and in linking innate and adaptive immune responses (discussed later in the section on antigen-presenting cells). One subpopulation of dendritic cells are specialized early responders to viral infections. They recognize phagocytosed viruses and produce type 1 interferons that have potent antiviral actions.

NK cells are a class of lymphocytes that recognize infected and stressed cells and respond by killing these cells. Activation of NK cells triggers the release of cytoplasmic granules toward the infected cells. These NK granules contain molecules that form pores in the cell membrane and other molecules that induce programmed or apoptotic cell death. NK cells control their responses by using both activating and inhibitory receptors (Fig. 15-4). Their activating receptors (i.e., killer cell receptors)

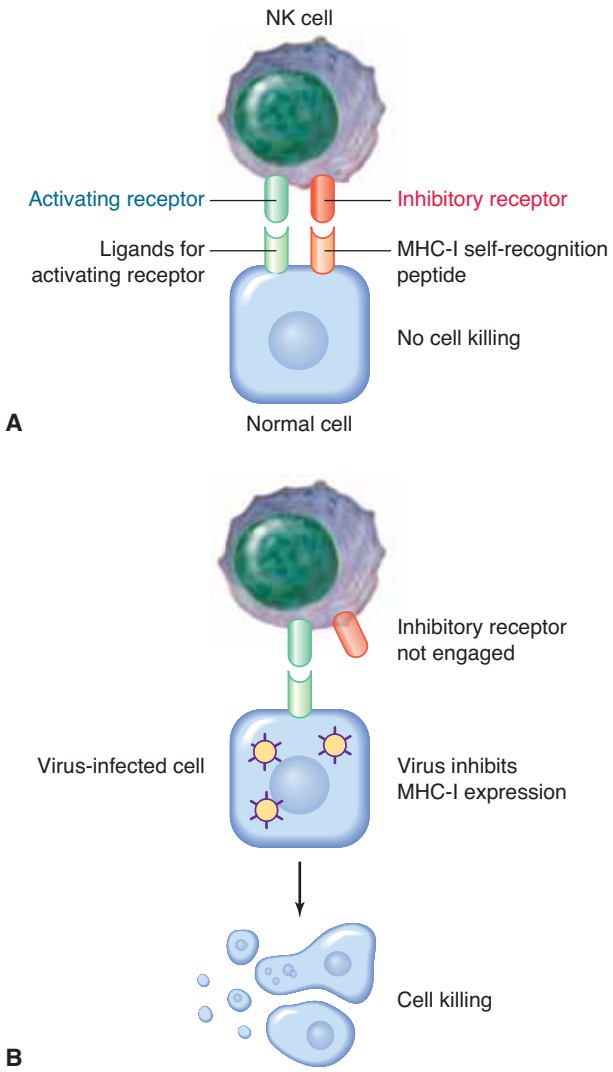


FIGURE 15-4. Natural killer (NK) cell receptors. **(A)** NK cells express activating receptors that respond to ligands from virus-infected or injured cells and inhibiting receptors that bind to the class I major histocompatibility complex (MHC-I) self-recognition molecules expressed by normal cells. Normal cells are not killed because inhibitory signals from normal MHC-I molecules override activating signals. **(B)** In virus-infected or tumor cells, increased expression of ligands for activating receptors and reduced expression or alteration of MHC molecules interrupts the inhibitory signals, allowing activation of NK cells and lysis of target cells.

recognize altered host molecules expressed on stressed tissue cells that may be infected with intracellular microbes. The inhibitory receptors on NK cells recognize molecules on normal host cells and function to stop the killing response of NK cells. This control ensures that normal body cells are not inappropriately destroyed. In contrast to the cytotoxic T lymphocytes of the adaptive immune system, which needs to undergo amplification and maturation to become cytotoxic, the NK cell is programmed directly to kill foreign cells. Depending on the type or combination of NK cell receptors that are activated, the effect is cell death or no response.

Pathogen Recognition

The ability of leukocytes and epithelial cells to participate in innate immunity depends on first recognizing molecules that are a normal component of microbes but not host cells. These components are often essential for infectivity and cannot be mutated to allow the microbe to evade destruction. The receptors that the innate immune system uses to recognize and react against microbes are expressed on phagocytic leukocytes, NK cells, and other cells that participate in defense against various classes of microbes. These receptors are molecules that first tag the microbe and then bind it to the effector cell of the innate immune system. Microbial binding results in effector cell activation, phagocytosis, and subsequent killing of the microbe. Several classes of receptors have been identified that are specific for different types of microbial products including pattern receptors, Toll-like receptors, and serum proteins (i.e., complement proteins) that promote phagocytosis.

Pattern Recognition

Microbes typically bear repeating patterns of molecular structure on their surface. The cell walls of gram-negative and gram-positive bacteria are composed of a matrix of sugars, lipid molecules, proteins, or patterns of modified nucleic acids. The lipopolysaccharides of the outer wall of gram-negative bacteria, for example, are important recognition sites for the innate immune system. Other microbial components also have repetitive structures. Bacterial DNA contains unmethylated cysteine-guanine (CpG) sequences and viruses invariably express double-stranded RNA as part of their life cycle. These repetitive structures are generally known as *pathogen-associated molecular patterns* (PAMPs) and the receptors that recognize them as *pattern recognition receptors* (PRRs).

The recognized structures of PAMPs are essential to the functioning and infectivity of the microbe and are defined as "conserved." The microbe cannot, therefore, evade innate immune recognition through mutation or a lack of production of the molecules because they would not survive. Humans inherit a limited number of germline genes for PRRs that effectively recognize major groups of microbes. One such receptor is the mannose-binding lectin (MBL), which is present as a free protein in the blood plasma. As will be discussed later in this part of the chapter, it can initiate the lectin pathway of the complement system. Pathogen recognition and discrimination of self from nonself by the MBL is due to the particular orientation and spacing of particular sugar residues, which are found only on microbes and not on host cells.

The phagocytic cells of the innate immune system are also equipped with several cell surface receptors that recognize pathogen surfaces directly. Among these is the macrophage-mannose receptor. This receptor binds certain sugars found on the surface of many bacteria and viruses, including HIV. A second set of phagocytic receptors, called the *scavenger receptors,* were originally defined as molecules that bind and mediate endocytosis of oxidized or acetylated low-density lipoproteins (LDLs) that do not interact with the conventional LDL receptor (see Chapter 18). Macrophage scavenger receptors bind a variety of microbes in addition to LDL particles.

Not all receptors that recognize pathogen-specific molecules are phagocytic receptors. The binding of pathogens to some receptors on leukocytes initiates a series of signaling events that lead to the tissue changes associated with acute inflammation. Stimulation of other pattern receptors leads macrophages and dendritic cells to display costimulatory molecules that enable them to act as antigen-presenting cells to lymphocytes and initiate an adaptive immune response.

Toll-Like Receptors

The best defined activation pathway for the pathogen sensors of innate immunity is a family of evolutionary conserved transmembrane receptors called *Toll-like receptors* (TLRs). Interestingly, the first protein to be identified in this family was the *Drosophila* Toll protein, which was found on the fruit fly *Drosophila,* where it functions in embryonic development as well as in protecting the fly from lethal fungal infections.

Eleven different TLRs have so far been identified, each specific for different components of microbes (Table 15-2).

TABLE 15-2 Types of Toll-Like Receptors (TLRs) and Their Recognized Ligands

TRLs	Ligands	Type of Microorganisms
TRL1	Lipopeptides	Mycobacteria
TRL2	Peptidoglycan	Gram-positive bacteria
	Lipoprotein	Mycobacteria
	Zymosan	Yeast and other fungi
TRL3	Double-stranded RNA	Viruses
TRL4	Lipopolysaccharide	Gram-negative bacteria
TRL5	Flagellin	Flagellated bacteria
TRL6	Lipopolypeptide	Mycobacteria
	Zymosan	Yeast and fungi
TRL7	Single-stranded RNA (ssRNA)	Viruses
TRL8	Single-stranded RNA (ssRNA)	Viruses
TRL9	CpG unmethylated dinucleotides	Bacterial DNA
TRLs 10,11	Unknown	

Although most TLRs that recognize extracellular ligands on microbes are found on the surface of the leukocytes, a few are located on the membranes of intracellular compartments of the leukocyte, where they recognize viruses and intracellular pathogens such as *Mycobacterium*. Because there are only 11 recognized TLR genes, the Toll-like receptors have limited specificity compared with the antigen receptors of the adaptive immune system. Although the diversity of the TLRs is limited, they can recognize elements of most microorganisms.

Ligand binding to the TLR at the cell surface leads to recruitment of cytoplasmic signaling molecules and eventual activation of transcription factors that regulate the production of a number of proteins that are important components of innate immunity. These include inflammatory cytokines, endothelial adhesion molecules, and proteins involved in the antimicrobial activities of phagocytic leukocytes. Alterations in the structure of TLRs or mutations in the signaling system associated with TLRs have been suggested to play a pathologic role in disorders such as atherosclerosis, allergies, and certain autoimmune diseases.

Soluble Mediators of Innate Immunity

Although cells of the innate immune system can communicate critical information about microbial agents and self–nonself recognition through cell-to-cell contact, soluble mediators are essential for many other aspects of the response. Development of innate immunity and regulation of the behavior of effector cells all depend on the secretion of soluble mediators such as opsonins, cytokines, and proteins of the complement system.

Opsonins

Various soluble molecules can tag microorganisms for more efficient recognition by phagocytes. The coating of particles, such as microbes, is called *opsonization,* and the coating materials are called *opsonins*. The opsonin bound to the microbe then activates phagocytosis after attachment to a complementary receptor on the phagocyte. Opsonins important in innate immunity and acute inflammation include acute-phase proteins, lectins, and complement. With the activation of adaptive humoral immunity, IgG and IgM antibodies can coat microbes and act as an opsonin by binding to receptors on neutrophils and macrophages. The adaptive immune response can thus enhance the phagocytic function of innate cells.

Inflammatory Cytokines

The cytokines involved in innate immunity include TNF-α; the interleukins IL-1, IL-6, and IL-12; interferons (IFN-γ, IFN-α, IFN-β); and chemokines (see Table 15-1). These cytokines serve various functions. They influence the events of inflammation and innate immunity by producing chemotaxis of leukocytes, stimulating acute-phase protein production, inhibiting viral replication, and affecting the development of cells of the innate and adaptive immune systems. A leukocyte exposed to an external stimulus (i.e., bacteria) can be activated through appropriately triggered receptors (e.g., TLRs) and respond by secreting small amounts of cytokines and other soluble mediators. If many cells are activated, the concentration of cytokines may be sufficient to influence the function of tissues distant from the site of infection, a true endocrine action. The biologic responses associated with cytokines are also regulated by the timing of cytokine receptor expression, which is affected by the stage of activation of a cell. The short half-life of cytokines ensures that an excessive immune response and systemic activation do not usually occur.

Other cytokines of innate immunity are the interferons, so named because of their ability to interfere with virus infections. Although macrophages and NK cells are the major producers of these cytokines, they can also be secreted by tissue cells. IFN-α and IFN-β are classified as type I IFNs and are made by fibroblasts and macrophages. They function to inhibit the replication of viruses and improve the recognition of a virally infected cell by cells of the adaptive immune response. Type I IFNs interact with receptors on neighboring cells to stimulate the translation of an antiviral protein that affects viral synthesis and its spread to uninfected cells. The actions of type I IFNs are effective against different types of viruses and intracellular parasites and are thus part of innate immunity. IFN-γ can activate macrophages in innate immunity and regulates lymphocytes in adaptive immunity. IFN-γ is the most important cytokine produced by the T-helper 1 subclass of T lymphocytes. It is a potent activator of macrophages and enables them to destroy pathogens that proliferate in their vesicles. IFN-γ also stimulates the production of antibodies that promote phagocytosis of microbes through the complement system.

In addition to their local effects, several of the inflammatory cytokines (i.e., TNF-α, IL-1, and IL-6) have important long-range effects that contribute to host defense. One of the most important of these is the initiation of a response called the *acute-phase response*. This involves a shift in the proteins synthesized by the liver into the plasma. Two of these, MBL and C-reactive protein (CRP), are of particular interest because they mimic the action of antibodies of the adaptive immune response, but unlike antibodies, these proteins have broad specificity for PAMPs and depend only on the presence of cytokines for their production. MBL and CRP function as opsonins as well as activators of the complement system.

The Complement System

The complement system is an important effector of both innate and humoral immunity that enables the body to localize and destroy infective agents. The complement system, like the blood coagulation system, consists of a group of proteins that are present in the circulation as functionally inactive precursors. These proteins, mainly proteolytic enzymes, make up 10% to 15% of the plasma proteins. For a complement reaction to occur, the complement components must be activated in the proper sequence. Uncontrolled activation of the complement system is prevented by inhibitor proteins and the instability of the activated complement proteins at each step of the process.

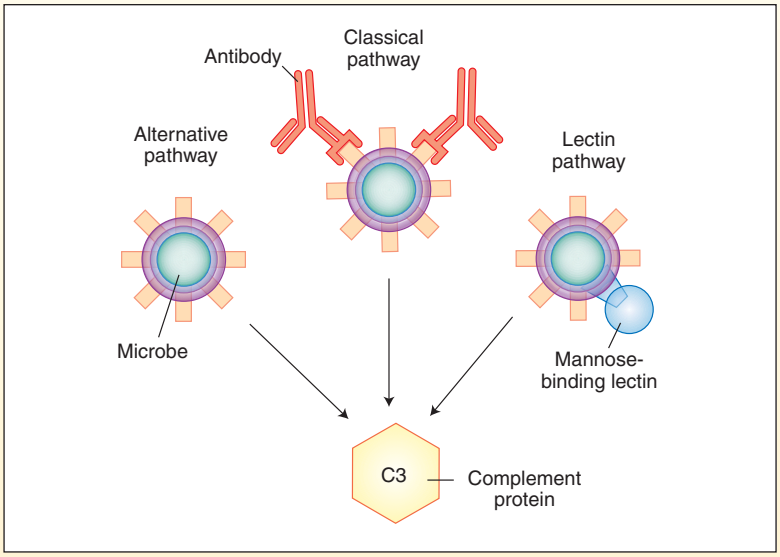
UNDERSTANDING → The Complement System

The complement system provides one of the major effector mechanisms of both humoral and innate immunity. The system consists of a group of proteins (complement proteins C1 through C9) that are normally present in the plasma in an inactive form. Activation of the complement system is a highly regulated process, involving the sequential breakdown of the complement proteins to generate a cascade of cleavage products capable of proteolytic enzyme activity. This allows for tremendous amplification because each enzyme molecule activated by one step can generate multiple activated enzyme molecules at the next step. Complement activation is inhibited by proteins that are present on normal host cells; thus, its actions are limited to microbes and other antigens that lack these inhibitory proteins.

The reactions of the complement system can be divided into three phases: (1) the initial activation phase, (2) the early-step inflammatory responses, and (3) the late-step membrane attack responses.

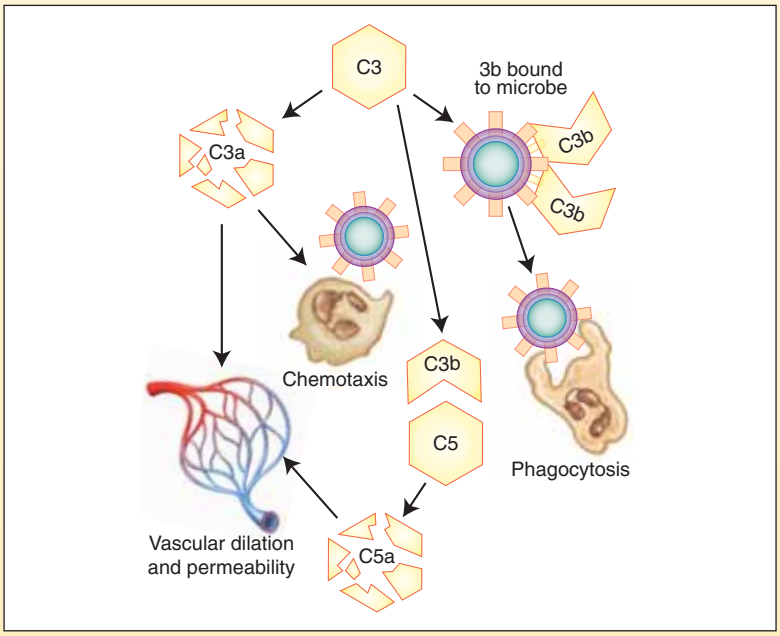
1

Initial Activation Phase. There are three pathways for recognizing microbes and activating the complement system: (1) the alternative pathway, which is activated on microbial cell surfaces in the absence of antibody and is a component of innate immunity; (2) the classical pathway, which is activated by certain types of antibodies bound to antigen and is part of humoral immunity; and (3) the lectin pathway, which is activated by a plasma lectin that binds to mannose on microbes and activates the classical system pathway in the absence of antibody.

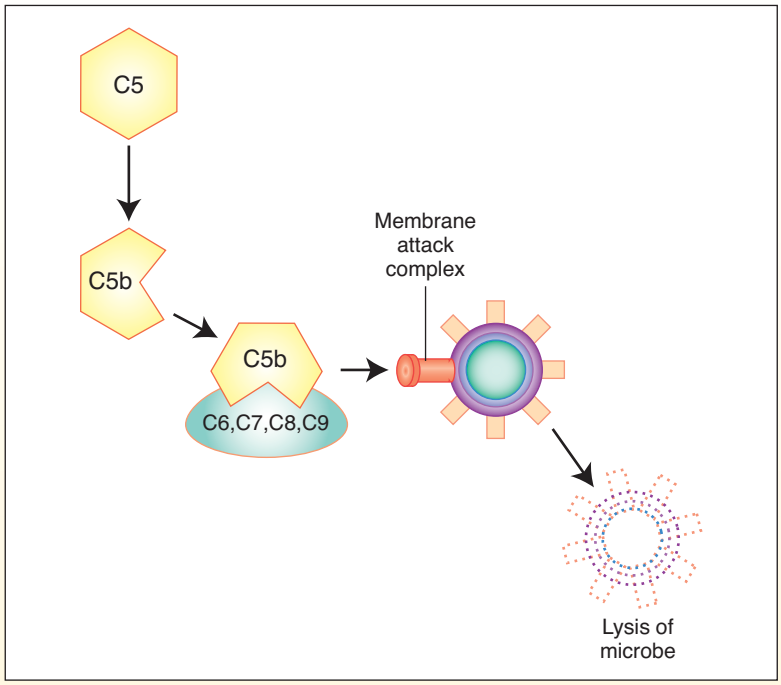


2

Early-Step Inflammatory Responses. The central component of complement for all three pathways is the activation of the complement protein C3 and its enzymatic cleavage into a larger C3b fragment and a smaller C3a fragment. The smaller 3a fragment stimulates inflammation by acting as a chemoattractant for neutrophils. The larger 3b fragment becomes attached to the microbe and acts as an opsonin for phagocytosis. It also acts as an enzyme to cleave C5 into two components: a C5a fragment, which produces vasodilation and increases vascular permeability, and a C5b fragment, which leads to the late-step membrane attack responses.



3 **Late-Step Membrane Attack.** In the late-step responses, C3b binds to other complement proteins to form an enzyme that cleaves C5, generating C5a and C5b fragments. C5a stimulates the influx of neutrophils and the vascular phase of acute inflammation. The C5b fragment, which remains attached to the microbe, initiates the formation of a complex of complement proteins C6, C7, C8, and C9 into a membrane attack complex protein, or pore, that allows fluids and ions to enter and cause cell lysis.



There are three parallel but independent pathways for recognizing microorganisms that result in activation of the complement system: the classical, the lectin, and the alternative pathways. The reactions of the complement systems can be divided into three phases: (1) initiation or activation, (2) amplification of inflammation, and (3) membrane attack response. The pathways differ slightly in the proteins used in the early stage of activation, but all converge in the process by acting on the key complement protein C3, essential for the amplification stage. Activated C3 then affects all subsequent complement molecules (C5 through C9). Inactive circulating complement proteins can be activated by microbial surface polysaccharides, MBL, and other soluble mediators in the lectin or alternative complement pathways that are integral to innate immunity, or by complement-fixing antibodies (IgG, IgM) of adaptive immunity that bind to microbial surfaces or other substances in the classical complement pathway. All activating pathways generate a series of enzymatic reactions that proteolytically cleave successive complement proteins in the pathway. New complement fragments (e.g., C3a, C3b) are regularly generated in this manner.

During the activation process, the enzymatic cleavage of C3 produces C3b, a key opsonin that coats microbes and allows them to be phagocytized after binding to the type 1 complement receptor on leukocytes. The small C3 complement fragment (C3a) can trigger an influx of neutrophils to enhance the inflammatory response. Production of C3a and C5a also leads to the activation of basophils and mast cells and the release of inflammatory mediators that produce smooth muscle contraction, increased vascular permeability, and changes in endothelial cells to enhance migration of phagocytes. The late phase of the complement cascade triggers the assembly of a membrane attack complex (MAC; C5 to C9) that leads to the lytic destruction of many kinds of cells, including bacteria and altered blood cells. The multiple functions of the complement system, including enhanced inflammatory responses, increased phagocytosis, and destruction and clearance of the pathogen from the body, make it an integral component of innate immunity and inflammation. Clinical changes associated with inherited deficiencies of complement range from increased susceptibility to infection to inflammatory tissue damage caused by complement-activated immune complexes not properly cleared by macrophages.

Role of Innate Immunity in Stimulating Adaptive Immunity

In addition to its role as a first-line defense in recognizing microbes and preventing infections, the innate immune responses generate molecules that function as "second signals" together with antigens to activate the adaptive immune response. Full activation of antigen-specific T and B lymphocytes requires two signals. Antigen provides the first signal. Microbes, the response of the innate immune system to microbes, and host cells

damaged by microbes all may provide the second signal. This requirement for a second microbe-initiated signal ensures that lymphocytes respond to microbes (the natural inducers of innate immunity) and not to harmless noninfectious substances. For the purpose of inducing immunity through vaccination, adaptive immune responses may be induced by antigens without microbes. In such instances, the antigens have to be administered with substances called *adjuvants* that elicit the same adaptive immune reactions as microbes do.

The second signals that are necessary for activation of the adaptive immune system can be generated by antigen-presenting dendritic cells and macrophages or by activation of the complement system. Microbes that breach the epithelial barriers of the innate immune system stimulate dendritic cells and macrophages to produce two types of second signals that activate T lymphocytes. First, the dendritic cells and macrophages express surface molecules called *costimulators*, which bind to receptors on naive T cells and function together with antigen recognition to activate T cells. Second, the dendritic cells and macrophages secrete cytokines that stimulate the differentiation of naive T cells into effector cells of cell-mediated adaptive immunity. Blood-borne microbes activate the complement system by the alternative pathway. One of the proteins produced by the complement system becomes covalently attached to the microbe, producing a second signal for activation of B lymphocytes.

In summary, the innate immune system consists of the epithelial cells of the skin and mucous membranes, phagocytes, leukocytes, NK cells, and several stable mediators, including those of the complement system. These defenses are in place before an encounter with a microbial agent and are rapidly activated by microbes before the development of adaptive immunity. The epithelial cells of the skin and mucous membranes, which are the first line of defense, block the entry of infectious agents and secrete antimicrobial enzymes, proteins, and peptides.

The cells of innate immunity include the neutrophils and macrophages, which engulf and digest infectious agents, and NK cells, which kill microbes and foreign agents. These cells express molecules on their membranes that bind repeating patterns of molecular structure on their surface that are essential for their survival. These molecules are expressed on many cell types (neutrophils, macrophages, NK cells) and are potent activators of innate immune cells and molecules. The activation of the TLRs is involved in responses to the widely divergent types of molecules that are present on most pathologic microorganisms.

Development of innate immunity and regulation of the behavior of effector cells all depend on the secretion of soluble molecules, such as opsonins, cytokines, acute-phase proteins, and complement. Opsonins bind to and tag microorganisms for more efficient recognition by phagocytes. Activated leukocytes release cytokines that regulate innate immunity and inflammation by directing the migration of leukocytes, stimulating production of acute-phase proteins, and enhancing phagocytosis.

The complement system is a primary effector system for both the innate and adaptive immune systems and consists of a group of proteins that are activated by microbes and promote inflammation and destruction of the microbes. Recognition of microbes by complement occurs in three ways: by the classical pathway, which recognizes antibody bound to the surface of a microbe or other structure; by the alternative pathway, which recognizes certain microbial molecules; and by the lectin pathway, which uses a plasma protein called the *mannose-binding ligand* that binds to mannose residues on microbial glycoproteins or glycolipids.

Adaptive Immunity

The adaptive immune system is able to recognize and respond to a large number of microbes and nonmicrobial substances. Integral to the adaptive immunity is the ability to distinguish among different, even closely related, microbes and molecules and to "remember" the pathogen by quickly producing a heightened immune response on subsequent encounters with the same agent. The components of the adaptive immune system are lymphocytes and their products. Foreign substances that elicit specific responses are called *antigens*.

There are two types of adaptive immune responses: humoral and cell-mediated immunity. *Humoral immunity* is mediated by secreted molecules and is the principal defense against extracellular microbes and toxins. *Cell-mediated immunity*, or *cellular immunity*, is mediated by specific T lymphocytes and defends against intracellular microbes such as viruses.

Antigens

Before discussing the cells and responses inherent to adaptive immunity, it is important to understand the substances that elicit a response from the host. *Antigens*, also called *immunogens*, are substances foreign to the host that can stimulate an immune response. These foreign molecules are recognized by receptors on immune cells and by secreted proteins, called *antibodies* or *immunoglobulins*, made in response to the antigen. Antigens include bacteria, fungi, viruses, protozoa, and parasites. Nonmicrobial agents such as plant pollens, poison ivy resin, insect venom, and transplanted organs can also act as antigens. Although most antigens are macromolecules, such as proteins and polysaccharides, lipids and nucleic acids occasionally serve as antigens.

Antigens, which in general are large and chemically complex, are biologically degraded into smaller chemical units or peptides. These discrete, immunologically

Adaptive Immunity

- The adaptive immune response involves a complex series of interactions between components of the immune system and the antigens of a foreign pathogen. It is able to distinguish between self and nonself, recognize and specifically react to large numbers of different microbes and pathogens, and remember the specific agents.
- Humoral immunity consists of protection provided by the B lymphocyte–derived plasma cells, which produce antibodies that travel in the blood and interact with circulating and cell surface antigens.
- Cell-mediated immunity consists of protection provided by cytotoxic T lymphocytes, which protect against virus-infected or cancer cells.
- Passive immunity represents a temporary type of immunity that is transferred from another source (e.g., in utero transfer of antibodies from mother to infant), and active immunity is the response by the person's immune system that is acquired through immunization or actually having a disease.

active sites on antigens are called *antigenic determinants*, or *epitopes*. It is the unique molecular shape of an epitope that is recognized by a specific immunoglobulin receptor found on the surface of the lymphocyte or by an antigen-binding site of a secreted antibody (Fig. 15-5). A single antigen may contain multiple antigenic determinants, each stimulating a distinct clone of T and B lymphocytes. For example, different proteins that comprise the influenza virus may function as unique antigens (A, B, C, H, and N antigens), each of which contains several antigenic determinants. Hundreds of antigenic determinants are found on structures such as the bacterial cell wall.

Smaller substances (molecular masses <10,000 daltons) usually are unable to stimulate an adequate immune response by themselves. When these low–molecular-weight compounds, known as *haptens*, combine with larger carrier molecules, they function as antigens. The hapten–carrier complex can stimulate the production of antibodies, some of which combine with the hapten portion of the complex. An allergic response to the antibiotic penicillin is an example of a medically important reaction due to hapten–carrier complexes. Penicillin (molecular mass of approximately 350 daltons) is normally a nonantigenic molecule. However, in some individuals, it can chemically combine with body proteins to form larger complexes that can then generate a potentially harmful immune allergic response.

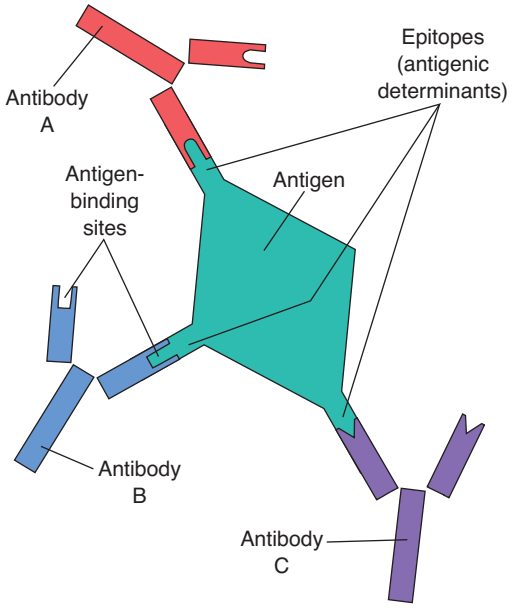


FIGURE 15-5. Multiple epitopes on a complex antigen being recognized by their respective (A, B, C) antibodies.

Cells of Adaptive Immunity

Lymphocytes are the effector cells of the adaptive immune system that specifically recognize and respond to foreign antigens. Accessory cells, such as macrophages and dendritic cells, function as antigen-presenting cells by first processing a complex antigen into epitopes and then displaying the foreign and self-peptides on their membranes so that appropriate activation of lymphocytes occurs. We will begin with a discussion of the antigen-presenting cells, move to the lymphocytes, and end with the MHC molecules that display antigens for recognition by T lymphocytes.

Antigen-Presenting Cells

Macrophages are key members of the mononuclear phagocytic system that engulf and digest microbes and other foreign substances. The monocytes migrate from the blood to various tissues, where they mature into the major tissue phagocyte, the macrophages. As the general scavenger cells of the body, the macrophage can be fixed in a tissue or free to migrate from an organ to lymphoid tissues. The tissue macrophages are scattered in connective tissue or clustered in organs such as the lung (i.e., alveolar macrophages), liver (i.e., Kupffer cells), spleen, lymph nodes, peritoneum, central nervous system (i.e., microglial cells), and other areas.

Dendritic cells share with the macrophage the important task of presenting processed antigen to T lymphocytes. Dendritic cells are found in most tissues where antigen enters the body and in the peripheral lymphoid tissues, where they function as potent antigen-presenting cells. In these different environments, dendritic cells can acquire specialized functions and appearances, as do macrophages. Langerhans cells are specialized dendritic

cells in the skin, whereas follicular dendritic cells are found in the lymph nodes. Langerhans cells are constantly surveying the skin for antigen and can transport foreign material to a nearby lymph node. Skin dendritic cells and macrophages also are involved in cell-mediated immune reactions of the skin such as allergic contact dermatitis.

Lymphocytes

Like other blood cells, T and B lymphocytes are generated from stem cells in the bone marrow. Undifferentiated, immature lymphocytes congregate in the central lymphoid tissues, where they develop into distinct types of mature lymphocytes (Fig. 15-6). B lymphocytes mature in the bone marrow and then move to the peripheral lymphoid tissues where they are exposed to antigen and stimulated to differentiate into antibody-producing plasma cells. T lymphocytes complete their maturation in the thymus and function in the peripheral tissues to produce cell-mediated immunity, as well as aiding in antibody production. The various types of lymphocytes are distinguished by their function and response to antigen, cell membrane molecules and receptors, types of secreted proteins, and tissue location. High concentrations of mature T and B lymphocytes are found in the lymph nodes, spleen, skin, and mucosal tissues, where they can respond to antigen.

T and B lymphocytes possess all of the key properties associated with the adaptive immune response—specificity, diversity, memory, and self–nonself recognition. These cells can exactly recognize a particular microorganism or foreign molecule. Each lymphocyte targets a specific antigen and differentiates it from other substances that may be similar. The approximately 10^{12} lymphocytes in the body have tremendous diversity. They can respond to the millions of different kinds of antigens encountered daily. This diversity occurs because an enormous variety of lymphocyte populations have been programmed and selected during development, each to respond to a different antigen. After lymphocytes have been stimulated by their antigen, they can acquire a memory response. The memory T and B lymphocytes that are generated remain in the body for a longer time and can respond more rapidly on repeat exposure than naive cells. Because of this heightened state of immune reactivity, the immune system usually can respond to commonly encountered microorganisms so efficiently that we are unaware of the response.

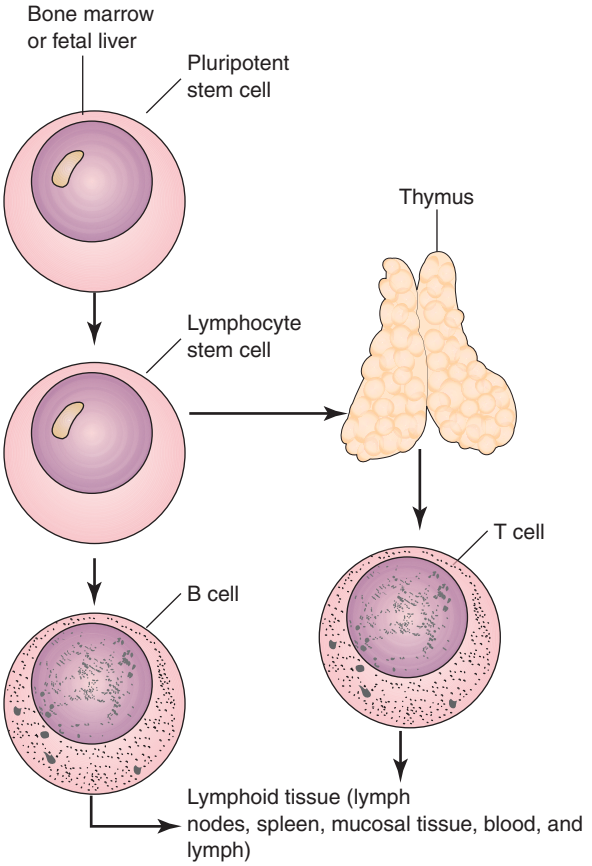


FIGURE 15-6. Pathway for T- and B-cell differentiation.

Adaptive immune responses are initiated when the antigen receptors of lymphocytes recognize antigens. The key trigger for the activation of B and T cells is the recognition of the antigen by unique surface receptors. B-lymphocyte antigen receptors (membrane-bound antibodies) and the antibodies that B cells secrete are able to recognize the shapes of native molecules, including proteins, lipids, carbohydrates, and nucleic acids, as well as simple small chemical groups and parts of larger macromolecules. This broad specificity of B cells for structurally different types of molecules enables antibodies to recognize diverse microbes and toxins. In contrast, the T-cell receptor recognizes only peptides, and only when these peptides are displayed on antigen-presenting cells bound to membrane proteins encoded in the MHC molecule. Thus, T cells are only able to detect cell-associated microbes and antigens.

Activation of the lymphocytes depends on appropriate processing and presentation of antigen to T lymphocytes by antigen-presenting cells such as macrophages and dendritic cells (Fig. 15-7). On recognition of antigen and after additional stimulation by cytokines, the B and T lymphocytes divide several times to form populations or clones of cells that continue to differentiate into effector and memory cells. After antigen binds to a B-cell receptor, the lymphocyte proliferates and differentiates into plasma cells that produce antibodies that are a secreted form of the B-cell receptor and have identical antigen specificity. Thus, the antigen that activates a given B cell becomes the target of the antibody produced by the cell's progeny. After a T cell is activated by its first encounter with an antigen, it proliferates and differentiates into helper or cytotoxic T cells. Helper T cells provide signals that activate antigen-stimulated B cells to differentiate and produce antibody. Some helper T cells also activate macrophages to become more efficient at killing engulfed pathogens. Cytotoxic T cells kill cells that are infected with viruses or other intracellular pathogens.

Major Histocompatibility Complex Molecules

Major histocompatibility complex molecules are membrane-bound proteins encoded by an MHC gene locus

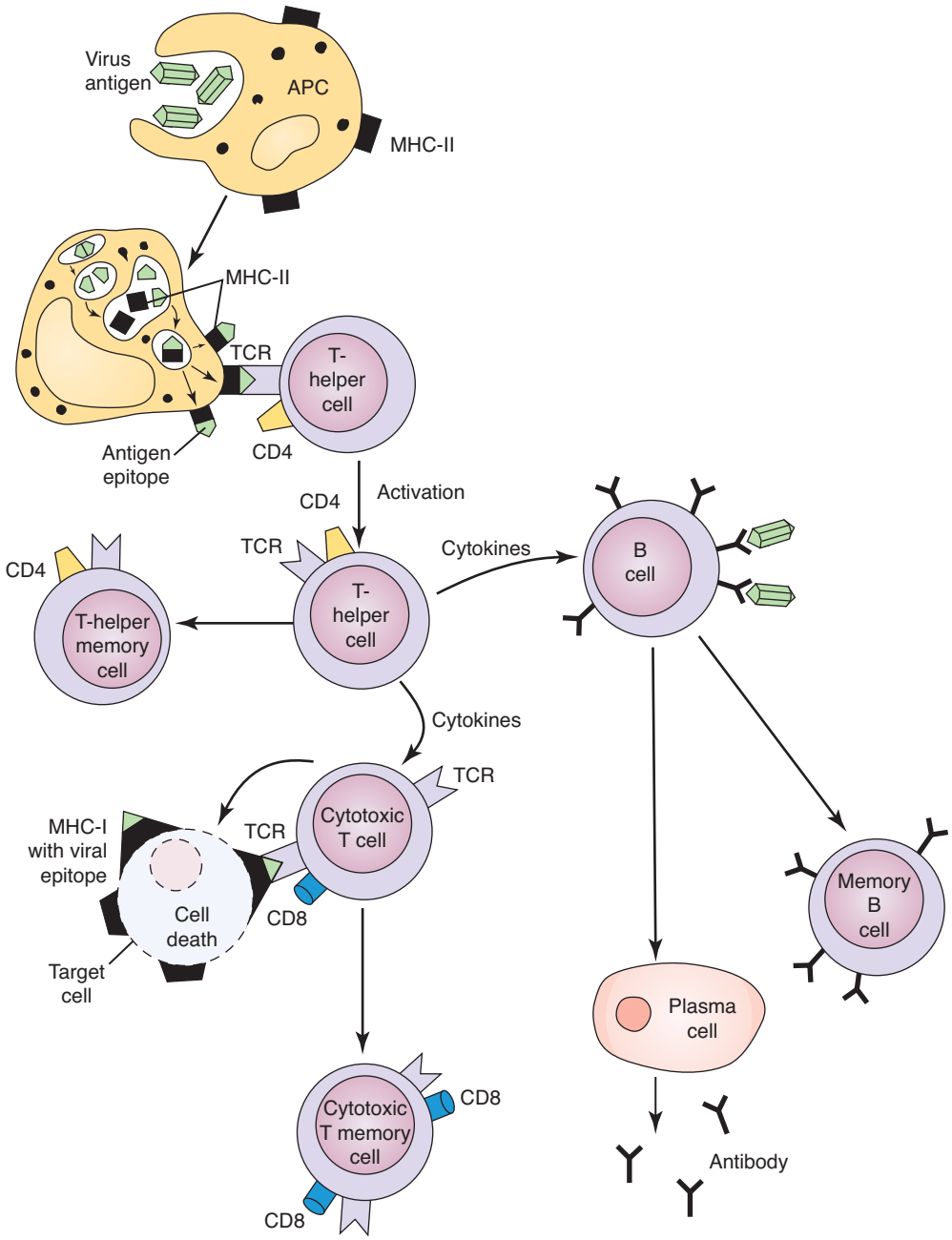


FIGURE 15-7. Pathway for immune cell participation in an adaptive immune response. APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

that serve as peptide display molecules for recognition by T lymphocytes. Although first identified as antigens that evoke rejection of transplanted organs, histocompatibility (i.e., tissue compatibility) molecules are now known to be extremely important for induction and regulation of immune responses. Recall that T cells (in contrast to B cells) can only recognize membrane-bound antigens, and hence histocompatibility molecules are critical to the induction of T-cell immunity. In humans, the genes encoding the most important MHC molecules are located or clustered on a small segment of chromosome 6.

The MHC molecules involved in self-recognition and cell-to-cell communication fall into two classes, class I and class II (Fig. 15-8). *Class I MHC* (MHC-I) molecules, which are expressed on all nucleated cells and platelets, are cell surface molecules that interact with the receptor–antigen peptide complex on $CD8^+$ cytotoxic T cells. *Class II MHC* (MHC-II) molecules, which are expressed mainly on dendritic cells, macrophages, and B lymphocytes, communicate with the antigen receptor and the CD4 molecule on helper T cells.

The MHC-I and MHC-II molecules are membrane-bound proteins that each contain a peptide-binding cleft on the extracellular portion of the molecule. Although the two classes of molecules differ in subunit composition, they are similar in overall structure. The MHC-1

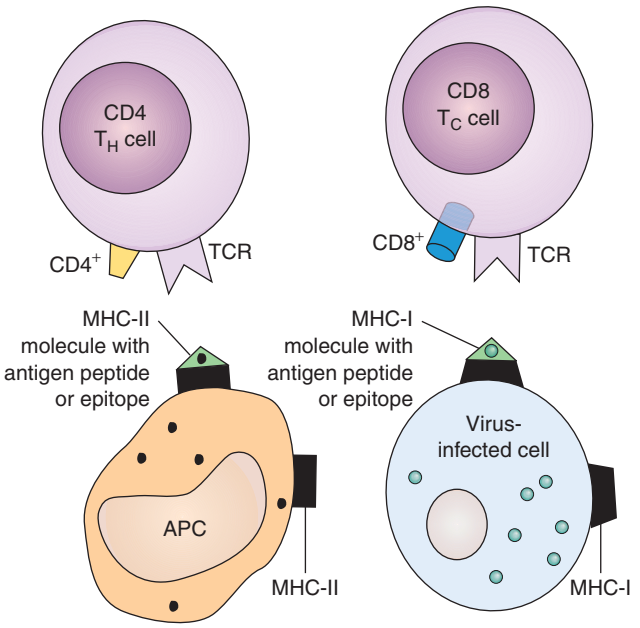


FIGURE 15-8. Recognition by a T-cell receptor (TCR) on a $CD4^+$ helper T (T_H) cell of an epitope associated with a class II major histocompatibility complex (MHC) molecule on an antigen-presenting cell (APC), and by a TCR on a $CD8^+$ cytotoxic T (T_C) cell of an epitope associated with a class I MHC molecule on a virus-infected cell.

molecule contains a cleft that accommodates a peptide fragment of antigen. Cytotoxic T cells can become activated only when they are presented with the foreign antigen peptide associated with the class I MHC molecule. During a typical viral infection of a cell, small peptides from degraded viral proteins associate with MHC-I molecules and are then transported to the infected cell membrane. This complex communicates to the cytotoxic T cell that the cell must be destroyed for the overall survival of the host. The MHC-II molecule's binding cleft accommodates a fragment of antigen from pathogens that have been engulfed and digested by an antigen-presenting cell during the process of phagocytosis. The engulfed pathogen is degraded into peptides in cytoplasmic vesicles and then complexed with the MHC-II molecule. Helper T cells recognize these complexes on the surface of antigen-presenting cells and become activated. These triggered helper T cells multiply quickly and direct other immune cells to respond to the invading pathogen through the secretion of cytokines.

Each individual has a unique collection of MHC proteins, and a variety of MHC molecules can exist in a population. Thus, MHC molecules are both polygenic and polymorphic. The MHC genes are the most polymorphic genes known. Because of the number of MHC genes and the possibility of several alleles for each gene, it is almost impossible for any two individuals to have an identical MHC profile, unless they are identical twins. MHC alleles affect immune responses as well as susceptibility to a number of diseases.

Human MHC proteins are called *human leukocyte antigens* (HLAs) because they were first detected on white blood cells. Because these molecules play a role in transplant rejection and are detected by immunologic tests, they are commonly called antigens. The classic human MHC-I molecules are divided into types called HLA-A, HLA-B, and HLA-C, and the MHC-II molecules are identified as HLA-DR, HLA-DP, and HLA-DQ (Table 15-3). Each of the gene loci that describe HLA molecules can be occupied by multiple alleles or alternative genes. For example, there are more than 350 possible alleles for the A locus, 650 alleles for the B locus, and 180 alleles for the C locus. The genes and their expressed molecules are designated by a letter and numbers (i.e., HLA-B27).

Because the class I and II MHC genes are closely linked on one chromosome, the combination of HLA genes usually is inherited as a unit, called a *haplotype*. Each person inherits a chromosome from each parent and therefore has two HLA haplotypes. The identification or typing of HLA molecules is important in tissue or organ transplantation, forensics, and paternity evaluations. In organ or tissue transplantation, the closer the matching of HLA types, the greater is the probability of identical antigens and the lower the chance of rejection.

B Lymphocytes and Humoral Immunity

Humoral immunity is mediated by antibodies, which are produced by B lymphocytes and their progeny. B lymphocytes can be identified by the presence of membrane immunoglobulin that functions as the antigen receptor, class II MHC proteins, complement receptors, and specific CD molecules. During the maturation process in the

TABLE 15-3 Properties of Class I and II MHC Molecules

Properties	HLA Antigens	Distribution	Functions
Class I MHC	HLA-A, HLA-B, HLA-C	Virtually all nucleated cells	Present processed antigen to cytotoxic $CD8^+$ T cells; restrict cytolysis to virus-infected cells, tumor cells, and transplanted cells
Class II MHC	HLA-DR, HLA-DP, HLA-DQ	Immune cells, antigen-presenting cells, B cells, and macrophages	Present processed antigenic fragments to $CD4^+$ T cells; necessary for effective interaction among immune cells

HLA, human leukocyte antigen; MHC, major histocompatibility complex.

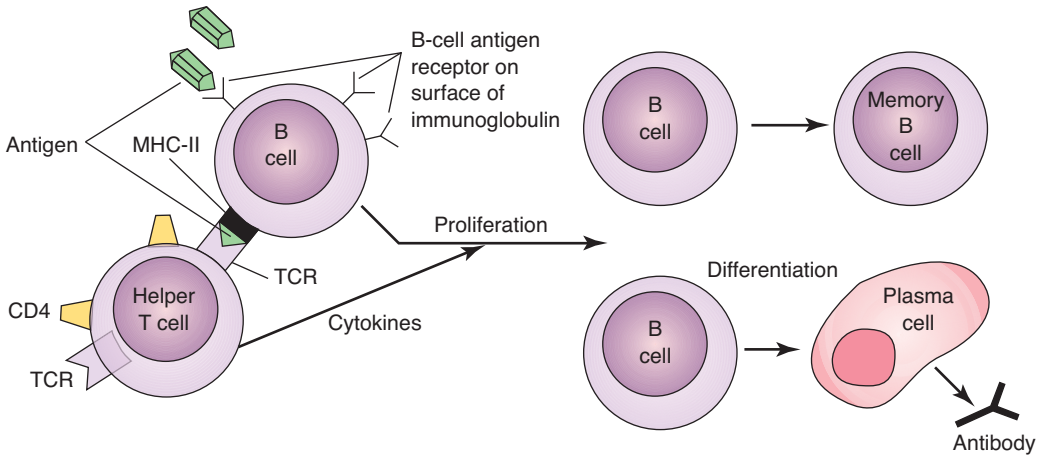


FIGURE 15-9. Pathway for B-cell differentiation. MHC, major histocompatibility class; TCR, T-cell receptor.

bone marrow, B-cell progenitors (pro-B and pre-B cells) develop into mature or naive B cells. The mature B cell leaves the bone marrow, enters the circulation, and migrates to the various peripheral lymphoid tissues, where it is stimulated to respond to a specific antigen. Each of the stages of B-cell development are characterized by a specific pattern of Ig gene expression and the expression of other cell surface proteins that serve as phenotypic markers of these maturational stages.

The commitment of a B-cell line to a specific antigen is evidenced by the expression of the membrane-bound Ig receptors that recognize antigen. B cells that encounter antigen complementary to their surface immunoglobulin receptor and receive T-cell help undergo a series of changes that transform them into antibody-secreting plasma cells or into memory B cells (Fig. 15-9). The antibodies produced by the plasma cells are released into the lymph and blood, where they bind and remove their unique antigen with the help of other immune effector cells and molecules. The longer-lived memory B cells are distributed to the peripheral tissues in preparation for subsequent antigen exposure.

Immunoglobulins

Immunoglobulins or antibodies are secreted proteins of B lymphocytes that function as antigen receptors for B cells or as effector molecules of the humoral immune response. The immunoglobulins have been divided into five classes, IgG, IgA, IgM, IgD, and IgE, each with a different role in the immune defense strategy (Table 15-4). Immunoglobulins have a characteristic four-polypeptide structure consisting of at least two identical antigen-binding sites (Fig. 15-10). Each immunoglobulin is composed of two identical light (L) chains and two identical heavy (H) chains to form a "Y"-shaped molecule. The two forked ends of the immunoglobulin molecule bind antigen and are called *Fab* (i.e., antigen-binding) fragments, and the tail of the molecule, which is called the *Fc fragment*, determines the biologic properties that are characteristic of a particular class of immunoglobulins.

The amino acid sequence of the heavy and light chains shows constant (C) regions and variable (V) regions. The *constant regions* have sequences of amino acids that vary little among the antibodies of a particular class of immunoglobulin. The constant regions are the basis for the separation of immunoglobulins into classes (e.g., IgM, IgG) and allow each class of antibody to interact with certain effector cells and molecules. For example, IgG can tag an antigen for recognition and destruction by phagocytes. The *variable regions* contain the antigen-binding sites of

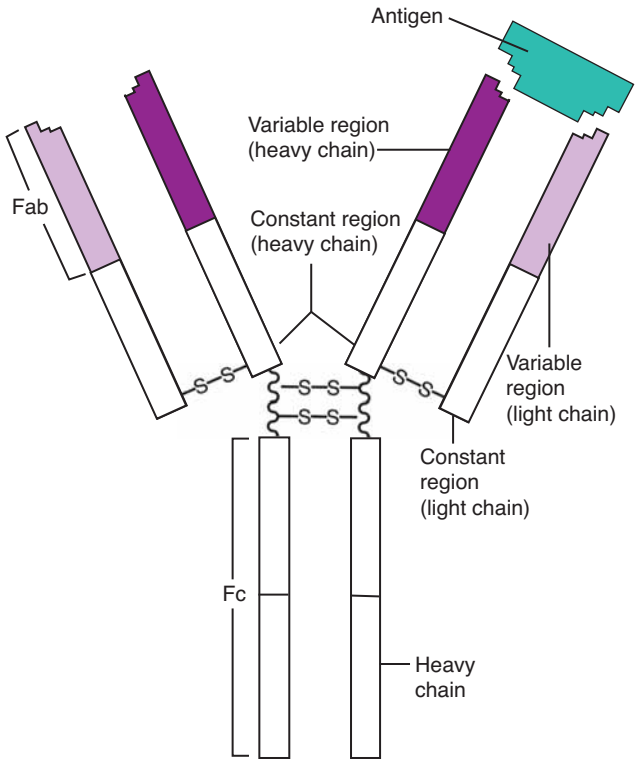
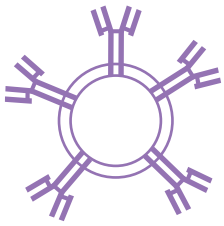
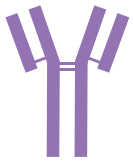
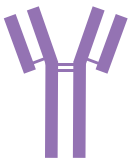


FIGURE 15-10. Schematic model of an immunoglobulin G (IgG) molecule showing the constant and variable regions of the light and heavy chains.

TABLE 15-4 Classes and Characteristics of Immunoglobulins

Figure	Class	Percentage of Total	Characteristics
	IgG	75.0	Displays antiviral, antitoxin, and antibacterial properties; only Ig that crosses the placenta; responsible for protection of newborn; activates complement and binds to macrophages
	IgA	15.0	Predominant Ig in body secretions, such as saliva, nasal and respiratory secretions, and breast milk; protects mucous membranes
	IgM	10.0	Forms the natural antibodies such as those for ABO blood antigens; prominent in early immune responses; activates complement
	IgD	0.2	Found on B lymphocytes; needed for maturation of B cells
	IgE	0.004	Binds to mast cells and basophils; involved in parasitic infections, allergic and hypersensitivity reactions

the molecule. The wide variation in the amino acid sequence of the variable regions seen from antibody to antibody allows this region to recognize its complementary epitope. A unique amino acid sequence in this region determines a distinctive three-dimensional pocket that is complementary to the antigen, allowing recognition and binding. Each B-cell clone produces antibody with one specific antigen-binding variable region or domain. During the course of the immune response, class switching (e.g., from IgM to IgG) can occur, causing the B-cell clone to produce one of the different immunoglobulin types.

IgG (gamma globulin) is the most abundant of the circulating immunoglobulins. It is present in body fluids and readily enters the tissues. IgG is the only immunoglobulin that crosses the placenta and can transfer immunity from the mother to the fetus. This class of immunoglobulin protects against bacteria, toxins, and viruses in body fluids and activates the complement system. This antibody can also bind to target cells and Fc receptors on NK cells and macrophages, leading to lysis of the target cell. There are four subclasses of IgG (i.e., IgG_1, IgG_2, IgG_3, and IgG_4), each of which has some restrictions in its response to certain types of antigens. For example, IgG_2 appears to be responsive to bacteria that are encapsulated with a polysaccharide layer, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

IgA, a secretory immunoglobulin, is found in saliva, tears, colostrum (i.e., first milk of a nursing mother), and bronchial, gastrointestinal, prostatic, and vaginal secretions. This dimeric secretory immunoglobulin is considered a primary defense against local infections in mucosal tissues. IgA prevents the attachment of viruses and bacteria to epithelial cells.

IgM is a macromolecule that forms a polymer of five basic immunoglobulin units. It cannot cross the placenta and does not transfer maternal immunity. It is the first circulating immunoglobulin to appear in response to an

antigen and is the first antibody type made by a newborn. This is diagnostically useful because the presence of IgM suggests a current infection in the infant by a specific pathogen. The identification of newborn IgM rather than maternally transferred IgG to the specific pathogen is indicative of an in utero or newborn infection. *IgD* is found primarily on the cell membranes of B lymphocytes. It serves as an antigen receptor for initiating the differentiation of B cells. *IgE* is involved in inflammation, allergic responses, and combating parasitic infections. It binds to mast cells and basophils. The binding of antigen to mast cell- or basophil-bound IgE triggers these cells to release histamine and other mediators important in inflammation and allergies.

Humoral Immunity

Humoral immunity is the arm of the adaptive immune response that functions to eliminate extracellular microbes and microbial toxins. It depends on the differentiation of B lymphocytes into plasma cells, which produce and secrete antibodies. The combination of antigen with antibody can result in several effector responses, such as precipitation of antigen–antibody complexes, agglutination or clumping of cells, neutralization of bacterial toxins and viruses, lysis and destruction of pathogens or cells, adherence of antigen to immune cells, facilitation of phagocytosis, and complement activation. For example, antibodies can neutralize a virus by blocking the sites on the virus that it uses to bind to the host cell, thereby negating its ability to infect the cell.

Two types of responses occur in the development of humoral immunity: a primary and a secondary response (Fig. 15-11). A *primary immune response* occurs when the antigen is first introduced into the body. During the primary response, there is a latent period or lag before the antibody can be detected in the serum. This latent period involves the processing of antigen by the antigen-presenting cells and its recognition by $CD4^+$ helper T cells. After the antigen receptors on $CD4^+$ helper T cells recognize the antigenic peptide–class II MHC molecules, the T cells become activated and produce cytokines to further stimulate and direct the immune system. In humoral immunity, activated $CD4^+$ helper T cells trigger B cells to proliferate and differentiate into a clone of plasma cells that produce antibody. This activation process takes 1 to 2 weeks, but once generated, detectable antibody continues to rise for several weeks. Recovery from many infectious diseases occurs during the primary response when the antibody concentration is reaching its peak.

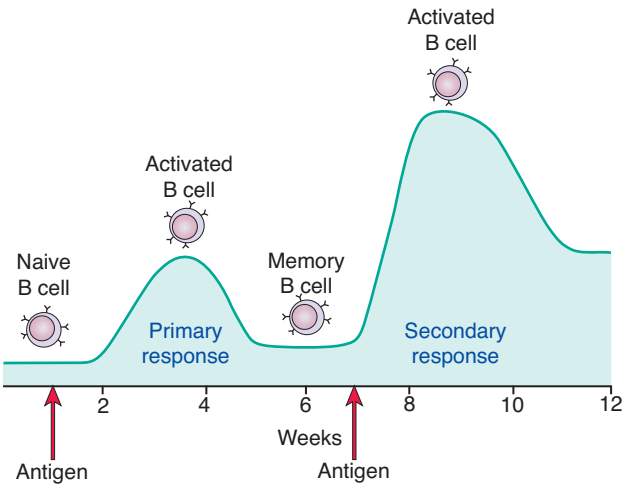


FIGURE 15-11. Primary and secondary or memory phases of the humoral immune response to the same antigen.

The *secondary* or *memory response* occurs on second or subsequent exposures to the antigen. During the primary response, a fraction of activated B cells does not differentiate into plasma cells but forms a pool of memory B cells. In a secondary response, the rise in antibody occurs sooner and reaches a higher level because of available memory cells. The booster immunization given for some diseases, such as tetanus, makes use of the memory response. For a person who has been previously immunized, administration of a booster shot causes an almost immediate rise in antibody to a level sufficient to prevent development of the disease. Activated T cells can also generate primary and secondary cell-mediated immune responses.

T Lymphocytes and Cell-Mediated Immunity

T lymphocytes function in the activation of other T cells and B cells, in the control of intracellular viral infections, in the rejection of foreign tissue grafts, and in delayed hypersensitivity reactions (see Chapter 16). Collectively, these immune responses are referred to as *cell-mediated* or *cellular immunity*.

T lymphocytes arise from bone marrow stem cells, but unlike B cells, pre-T cells migrate to the thymus for their maturation. There the immature T lymphocytes undergo rearrangement of the genes needed for expression of a unique T-cell antigen receptor similar to but distinct from the B-cell receptor. The T-cell receptor is composed of two polypeptide chains that form a groove that recognizes the processed antigen peptide–MHC molecules (Fig. 15-12). Maturation of subpopulations of T cells (i.e., $CD4^+$ and $CD8^+$) also occurs in the thymus. Mature T cells migrate to the peripheral lymphoid tissues and, on encountering antigen, multiply and differentiate into memory T cells and various mature T-cell populations. The two main populations of mature T cells are $CD4^+$ (helper) and $CD8^+$ (cytotoxic) T cells.

Helper T Cells

The $CD4^+$ helper T cell serves as a master regulator for the immune system. Activation of $CD4^+$ helper T cells depends on the recognition of antigen in association with class II MHC molecules. Once activated, the T helper cells secrete cytokines that influence the function of nearly all other cells of the immune system. Differences in the types of cytokines made by the $CD4^+$ helper T cell produce different types of immune responses. These cytokines activate

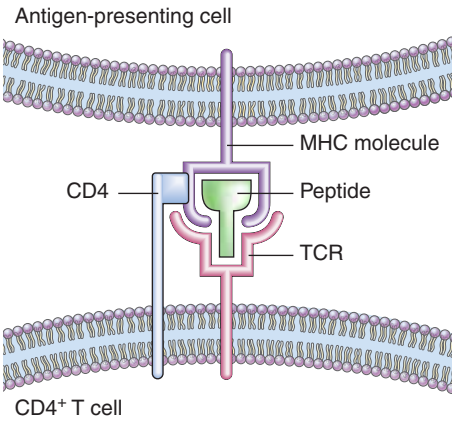


FIGURE 15-12. The T-cell receptor (TCR) on a $CD4^+$ T cell and the interaction of the major histocompatibility complex (MHC) on the antigen-presenting cell. Note that the TCR recognizes the peptide fragment of antigen bound to the MHC class II molecule. The CD4 molecule binds to a portion of the MHC molecule, stabilizing the interaction.

and regulate B cells, cytotoxic T cells, NK cells, macrophages, and other immune cells.

The activated $CD4^+$ helper T cell can differentiate into distinct subpopulations of helper T cells (i.e., T_H1 or T_H2) based on the cytokines secreted by the antigen-presenting cell at the site of activation. The cytokine IL-12 produced by macrophages and dendritic cells directs the maturation of $CD4^+$ helper T cells toward T_H1 cells, whereas IL-4 produced by mast cells and T cells induces differentiation toward T_H2 cells.

The distinct pattern of cytokines secreted by mature T_H1 and T_H2 cells defines these subpopulations of T cells and determines their functions. Activated T_H1 cells stimulate phagocyte-mediated ingestion and killing of microbes. T_H1 cells produce the cytokine IFN-γ which activates macrophages and stimulates B cells to produce IgG antibodies that activate complement and coat pathogens for phagocytosis. T_H2 cells produce IL-4, which stimulates B cells to differentiate into IgE-secreting plasma cells; IL-5, which activates eosinophils; and IL-13, which activates mucosal epithelial cells to secrete mucus and expel microbes. Differentiated $CD4^+$ T cells of the T_H1 subset recognize microbial peptides on macrophages and have the dual function of stimulating the production of IgG antibodies and eliminating cells infected with certain pathogenic intracellular microbes such as mycobacteria; whereas, those of the T_H2 subset tend to recognize protein antigens or chemicals that stimulate the production of IgE and development of allergies. A third subset, called T_H17, has been recently described that produces the cytokine IL-17, which promotes inflammation, and is believed to play a role in some of the T cell-mediated inflammatory disorders.

In most immune responses, a balanced response of T_H1 and T_H2 cells occurs, but immunization or exposure to antigen can skew the response to one or the other subset. For example, the extensive exposure to an allergen in atopic individuals has been shown to shift the naïve $CD4^+$ T cell toward a T_H2 response, with the production of the cytokines that influence IgE production and mast cell priming. An appreciation of these processes has led to clinical research that suggests that redirection of an allergic T_H2 response to a nonallergic T_H1 response can occur in atopic individuals through modified immunization protocols.

Cytotoxic T Cells

Activated $CD8^+$ lymphocytes become cytotoxic T cells after recognition of class I MHC–antigen complexes on target cell surfaces, such as body cells infected by viruses or transformed by cancer (Fig. 15-13). The recognition of class I MHC–antigen complexes on infected target cells ensures that neighboring uninfected host cells, which express class I MHC molecules alone or with self-peptide, are not indiscriminately destroyed. The $CD8^+$ cytotoxic T cells perform their killing function by injecting preformed cytotoxic proteins into target cells, thereby triggering apoptosis or programmed cell death (see Chapter 2). Cytotoxic T cells also produce and release cytokines, such as IFN-γ, which inhibits viral replication and is an important inducer of MHC class 1 molecule expression and macrophage activation. The $CD8^+$ cytotoxic T cells are especially important in controlling replicating viruses and intracellular bacteria

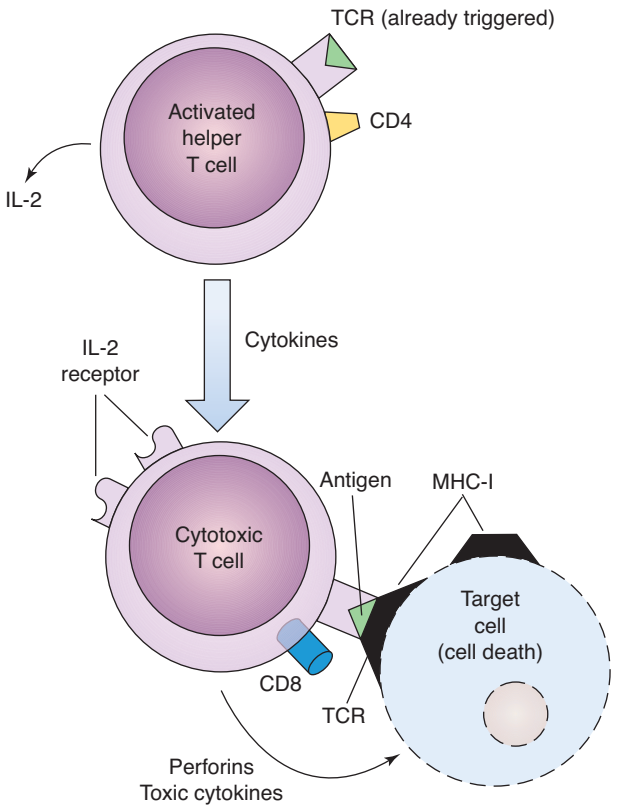


FIGURE 15-13. Destruction of target cell by cytotoxic T cell. Cytokines released from the activated helper T cell enhance the potential of the cytotoxic T cell in destruction of the target cell. IL, interleukin; MHC, major histocompatibility class; TCR, T-cell receptor.

because antibody cannot readily penetrate the membrane of living cells.

Regulatory T Cells

A recently defined type of T lymphocyte is the *regulatory T cell,* which has CD4 and CD25 expressed on its cell membrane. Regulatory T cells, in contrast to $CD4^+$ helper T cells, suppress immune responses by inhibiting the proliferation of other potentially harmful self-reactive lymphocytes. The regulation by these cells is antigen specific and controlled through activation of a T-cell receptor by the antigen and subsequent secretion of the cytokines IL-10 and transforming growth factor-β (TGF-β). These cytokines inhibit the proliferation and activation of lymphocytes and macrophages. There is also recent evidence of regulatory $CD8^+$ T cells that can selectively downregulate T cells that are activated by either self or foreign antigens. These cells are thought to differentiate into effector cells during the primary immune response and function as suppressor cells during the secondary or memory phases of immunity, and are primarily involved in self–nonself discrimination. The potential clinical importance of regulatory T cells is suggested from animal studies showing inhibition of inflammatory bowel disease, experimental allergic encephalitis, and autoimmune diabetes by increased activity of regulatory T cells.

Cell-Mediated Immunity

Cell-mediated immunity is the adaptive immune response against microbes, such as bacteria, parasites, and all viruses that replicate inside cells where they cannot be destroyed by antibodies. Both $CD8^+$ and $CD4^+$ cells contribute to the response, with each having different effector mechanisms for the eradication of the infection. The effector functions of $CD8^+$ cytotoxic T cells, which act against cells infected with viruses, are the most direct. Antigens derived from the virus multiply inside the infected cell and are displayed on the target cell's surface, where they are recognized by antigen receptors on the cytotoxic T cell (Fig. 15-12). Cytotoxic T cells perform their killing function by releasing preformed cytotoxic proteins that induce apoptosis or programmed cell death of the target cell (see Chapter 2).

The principal function of $CD4^+$ cells of the T_H1 subset involves the defense against intracellular pathogens, such as mycobacteria, which grow primarily in phagosomes of macrophages, shielding them from the effects of both antibodies and cytotoxic T cells. T_H1 cells secrete the cytokine IFN-γ, a potent macrophage activator, which stimulates the induction of microbicidal substances in macrophages, leading to the destruction of the ingested microbes. T_H1 cells also produce a range of other cytokines, chemokines, and surface molecules that do not activate infected macrophages, but instead kill chronically infected senescent macrophages, stimulate the production of new macrophages in bone marrow, and recruit fresh macrophages to sites of infection. Thus, the $CD4^+$ T_H1 cell controls and coordinates host defenses against certain intracellular pathogens, a function that helps to explain why a decreased $CD4^+$ count in persons with acquired immunodeficiency syndrome (AIDS) places them at high risk for intracellular pathogen infections.

Active Versus Passive Immunity

Adaptive, or specific, immune responses are designed to protect the body against potentially harmful foreign substances, infections, and other sources of non–self-antigens. It is the specific protection that is acquired through exposure to antigens (active immunity) or through transfer of protective antibodies against an antigen (passive immunity).

Active immunity is acquired through immunization or actually having a disease. It is called *active immunity* because it depends on a response to the antigen by the person's immune system. Active immunity, although long lasting once established, requires a few days to weeks after a first exposure before the immune response is sufficiently developed to contribute to the destruction of the pathogen. However, the immune system usually is able to react within hours to subsequent exposure to the same agent because of the presence of memory B and T lymphocytes and circulating antibodies. The process of acquiring the ability to respond to an antigen after its administration by vaccine is known as *immunization.* An acquired immune response can improve on repeated exposures to an injected antigen or a natural infection.

Passive immunity is immunity transferred from another source. An infant receives passive immunity naturally from the transfer of antibodies from its mother in utero and through breast milk. Maternal IgG crosses the placenta and protects the newborn during the first few months of life. Normally, an infant has few infectious diseases during the first 3 to 6 months owing to the protection provided by the mother's antibodies. Passive immunity also can be artificially provided by the transfer of antibodies produced by other people or animals. Some protection against infectious disease can be provided by the injection of hyperimmune serum, which contains high concentrations of antibodies for a specific disease, or immune serum or gamma globulin, which contains a pool of antibodies from many individuals providing protection against many infectious agents. Passive immunity produces only short-term protection that lasts weeks to months.

Regulation of the Immune Response

Self-regulation is an essential property of the immune system. An inadequate immune response may lead to immunodeficiency, but an inappropriate or excessive response may lead to conditions varying from allergic reactions to autoimmune diseases. This regulation is not well understood and involves all aspects of the immune response—antigen, antibody, cytokines, regulatory T cells, and the neuroendocrine system.

With each exposure to antigen, the immune system must determine the branch of the immune system to be activated and the extent and duration of the immune response. After exposure to an antigen, the immune

response to that antigen develops after a brief lag, reaches a peak, and then recedes. Normal immune responses are self-limited because the response eliminates the antigen, and the products of the response, such as cytokines and antibodies, have a short or limited life span and are secreted only for brief periods after antigen recognition. Evidence suggests that cytokine feedback from the helper T or regulatory T cells controls several aspects of the immune response.

Another facet of immune self-regulation is inhibition of immune responses by tolerance. The term *tolerance* is used to define the ability of the immune system to be nonreactive to self-antigens while producing immunity to foreign agents. Tolerance to self-antigens protects an individual from harmful autoimmune reactions (see Chapter 16). Exposure of an individual to foreign antigens may lead to tolerance and the inability to respond to potential pathogens that cause infection. Tolerance exists not only to self-tissues but also to maternal–fetal tissues. Special regulation of the immune system is evident in privileged sites such as the brain, testes, ovaries, and eyes. Immune damage in these areas could result in serious consequences to the individual and the species.

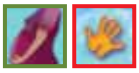
In summary, adaptive immunity involves humoral and cellular mechanisms that respond to a unique antigen, can amplify and sustain its responses, distinguish self from nonself, and remember the antigen to produce quickly a heightened response on subsequent encounters with the same agent. Antigens are substances foreign to the host that can stimulate an immune response. They have antigenic determinant sites or epitopes, which the adaptive immune system recognizes with specific receptors that distinguish the antigens as nonself and as unique foreign molecules.

The principal cells of the adaptive immune system are the lymphocytes. There are two types of lymphocytes: T lymphocytes and B lymphocytes. T lymphocytes differentiate into regulatory (helper T and regulatory T cells) and effector (cytotoxic T cells) cells and provide cell-mediated immunity. Antigen-presenting cells consist of macrophages and dendritic cells that process and present antigen peptides to $CD4^+$ helper T cells. The regulatory $CD4^+$ helper T cells serve as a trigger for the immune response and are essential for the differentiation of B cells into antibody-producing plasma cells and the differentiation of T lymphocytes into effector $CD8^+$ cytotoxic T cells that eliminate intracellular microbes, such as viruses. The cell surface MHC molecules are key recognition molecules that the immune system uses in distinguishing self from nonself. Class I MHC molecules, which are present on all nucleated cells other than those of the immune system, interact with cytotoxic $CD8^+$ T cells in the destruction of cells that have been affected by intracellular pathogens or cancer. Class II MHC molecules, found on antigen-presenting cells and B lymphocytes, aid in cell-to-cell communication between different cells of the immune system. B lymphocytes differentiate into plasma cells that produce antibodies and provide for the elimination of microbes in the extracellular fluid (humoral immunity). Antibodies comprise a class of proteins called *immunoglobulins.* The immunoglobulins have been divided into five classes, IgG, IgA, IgM, IgD, and IgE, each with a different role in the immune defense strategy. T lymphocytes function in the activation of other T cells and B cells (helper T cells), in the control of intracellular pathogens (cytotoxic T cells), and in the regulation of the immune response (regulatory T cells), responses that are collectively referred to as cell-mediated immunity.

Adaptive, or specific, immunity is protection that is acquired through immunization or by having a disease (active immunity), or through transfer of protective antibodies from another source (passive immunity). An acquired immune response can improve with repeated exposure to an injected antigen or a natural infection.

Developmental Aspects of the Immune System

Embryologically, the immune system develops in several stages, beginning at 5 to 6 weeks as the fetal liver becomes active in hematopoiesis. Development of the primary lymphoid organs (i.e., thymus and bone marrow) begins during the middle of the first trimester and proceeds rapidly. Secondary lymphoid organs (i.e., spleen, lymph nodes, and mucosa-associated lymphoid tissues) develop soon after. These secondary lymphoid organs are rather small but well developed at birth and mature rapidly after exposure to microbes during the postnatal period. The thymus is fully formed and functional and is the largest lymphoid tissue relative to body size at birth.



Transfer of Immunity from Mother to Infant

Protection of a newborn against antigens occurs through transfer of maternal antibodies. Maternal IgG antibodies cross the placenta during fetal development and remain functional in the newborn for the first months of life (Fig. 15-14). IgG is the only class of immunoglobulins to cross the placenta. Levels of maternal IgG decrease significantly during the first 3 to 6 months of life, while infant synthesis of immunoglobulins increases. Maternally transmitted IgG is effective against most microorganisms and viruses. The largest amount of IgG crosses the placenta during the last weeks of pregnancy and is stored in fetal tissues, and infants born prematurely may be deficient. Because of transfer of IgG antibodies to the fetus, an infant born to a mother infected with HIV has a positive HIV antibody test result, although the child may not be infected with the virus.

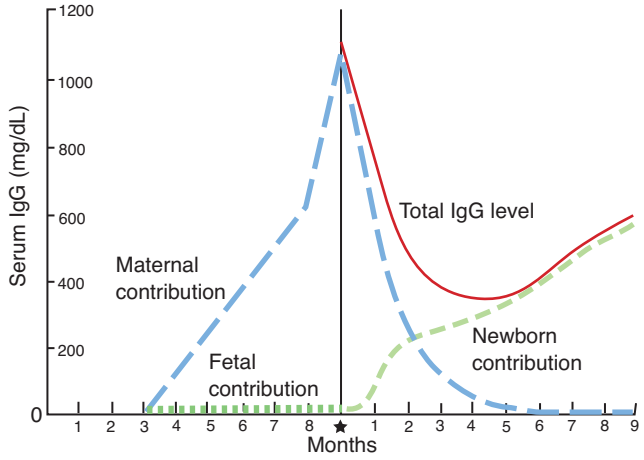


FIGURE 15-14. Maternal/neonatal serum immunoglobulin G levels. (From Allansmith M., McClellan B.H., Butterworth M., et al. [1968]. The development of immunoglobulin levels in man. *Journal of Pediatrics* 72, 289.)

Cord blood does not normally contain IgM or IgA. If present, these antibodies are of fetal origin and represent exposure to intrauterine infection. The infant begins producing IgM antibodies shortly after birth, in response to the immense antigenic stimulation of his or her new environment. Premature infants appear to be able to produce IgM as well as term infants. At approximately 6 days of age the IgM rises sharply, and this rise continues until approximately 1 year of age, when the adult level is achieved.

Serum IgA normally is first detected at approximately 13 days after birth. The level increases during early childhood until adult levels are reached between the sixth and seventh year. Maternal IgA also is transferred to the infant in colostrum, or milk, by breast-feeding. These antibodies provide local immunity for the intestinal system and have been shown to decrease diarrheal infections in underdeveloped countries. These evolutionary adaptations of the immune system have increased the survival of our species and optimized the development of other important organs in the early months of life.

Immune Response in the Elderly

Aging is characterized by a declining ability to adapt to environmental stresses. One of the factors thought to contribute to this problem is a decline in immune responsiveness. This includes changes in cell-mediated and humoral immune responses. Elderly persons tend to be more susceptible to infections, have more evidence of autoimmune and immune complex disorders than younger persons, and have a higher incidence of cancer. Experimental evidence suggests that vaccination is less successful in inducing immunization in older persons than in younger adults. However, the effect of altered immune function on the health of elderly persons is clouded by the fact that age-related changes or disease may affect the immune response.

The alterations in immune function that occur with advanced age are not fully understood. There is a decrease in the size of the thymus gland, which is thought to affect T-cell function. The size of the gland begins to decline shortly after sexual maturity, and by 50 years of age, it usually has diminished to 15% or less of its maximum size. There are conflicting reports regarding age-related changes in the peripheral lymphocytes. A suggested biologic clock in T cells that determines the number of times it divides may regulate cell number with age. Some researchers have reported a decrease in the absolute number of lymphocytes, and others have found little, if any, change. The most common finding is a slight decrease in the proportion of T cells to other lymphocytes and a decrease in $CD4^+$ and $CD8^+$ T cells.

More evident are altered responses of the immune cells to antigen stimulation; increasing proportions of lymphocytes become unresponsive, whereas the remainder continue to function relatively normally. T and B cells show deficiencies in activation. In the T-cell types, the $CD4^+$ subset is most severely affected. Evidence indicates that aged T cells have a decreased rate of synthesis of the cytokines that drive the proliferation of lymphocytes and a diminished expression of the receptors that interact with those cytokines. For example, it has been shown that IL-2, IL-4, and IL-12 levels decrease with aging. Although B-cell function is compromised with age, the range of antigens that can be recognized is not diminished. If anything, the repertoire, including outgrowths of autoreactive B-cell clones, is increased to the extent that B cells begin to recognize some self-antigens as foreign antigens. This may be the basis for the increased incidence of autoimmune disease in the elderly.

In summary, a newborn is protected against antigens in early life by passive transfer of maternal antibodies through the placenta (IgG) and in colostrum (IgA) through breast-feeding. Some changes are seen with aging, including an increase in autoimmune diseases. The impact of alterations in immune function that occur with aging is not fully understood.

REVIEW EXERCISES

1. The systemic manifestations (e.g., generalized muscle aches, chills and fever, loss of appetite) that accompany a severe sore throat or acute respiratory infection are stimulated by reactions to cytokines of the innate immune system rather than by the antibodies or cell-mediated responses of the adaptive immune response.

A. Explain.

2. A nursing student is working in a community clinic as a volunteer. Each time she enters the clinic, she suffers bouts of sneezing and runny nose. She has a history of mold allergy and her younger brother has asthma. Analysis at the allergy clinic indicates a strong reaction to latex. She is advised to avoid exposure to all forms of latex.

A. What class of immunoglobulin and what type of mediator cells are responsible for the symptoms expressed in this individual?
B. What type of T-helper cell and cytokines direct the expression of this humoral immune response?
C. Is this an example of active or passive immunity? Is it a primary or secondary immune response?

3. A child of 5 months of age presents with thrush, a yeast infection of the mouth. In the last 2 months, he has had recurrent bouts of otitis media. His tonsils are very small. Laboratory analysis indicates a low lymphocyte count and no T lymphocytes. Further analysis indicates a genetic mutation in the T-cell receptor that affects maturation of all T cells. The final diagnosis is severe combined immunodeficiency disease. A bone marrow transplant is being pursued with cells from his HLA-matched sibling.

A. Explain why infections were not present in the first few months of this child's life.
B. What would be the impact of an absence of T cells on both humoral and cell-mediated immunity?
C. Why would it not be advisable to administer a live virus vaccine in this child?

BIBLIOGRAPHY

Abbas A.K., Litchman A.H. (2006). *Basic immunology: Functions and disorders of the immune system* (2nd ed., updated edition 2006–2007). Philadelphia: Elsevier Saunders.

Akashi-Takamura S., Miyake K. (2006). Toll-like receptors (TLRs) and immune disorders. *Journal of Infection Chemotherapy* 12, 233–240.

Akira S., Uematsu S., Takeuchi O. (2006). Pathogen recognition and innate immunity. *Cell* 124, 783–801.

Bluestone J.A. (2005). Regulatory T cell therapy: Is it ready for the clinic? *Nature Reviews Immunology* 5, 343–349.

Chapin D.D. (2006). Overview of the human immune response. *Journal of Clinical Immunology* 117, S430–S435.

Clark R., Kupper T. (2005). Old meets new: The interaction between innate and adaptive immunity. *Journal of Investigative Dermatology* 125, 629–637.

Goain A., Gamelli R.L. (2005). A primer on cytokines. *Journal of Burn Care and Rehabilitation* 26, 7–12.

Hoebe K, Janssen E., Beutler B. (2004). The interface between innate and adaptive immunity. *Nature Immunology* 5, 971–974.

Ishii K.J., Akira S. (2006). Innate immune recognition of, and regulation by, DNA. *Trends in Immunology* 27, 525–532.

Jiang H., Chess L. (2006). Regulation of immune responses by T cells. *New England Journal of Medicine* 354, 1166–1176.

Jones S.A. (2005). Directing transition from innate to acquired immunity. *Journal of Immunology* 175, 3463–3468.

Kindt T., Goldsby R., Osbourne B. (2007). *Kuby immunology* (6th ed.). New York: W.H. Freeman.

Lanier L.L. (2005). NK cell recognition. *Annual Review of Immunology* 23, 225–274.

Lasker M.V., Nair S.K. (2006). Intracellular TLR signaling: A structural perspective on human disease. *Journal of Immunology* 177, 11–16.

Murphy K., Travers P., Walport M. (2008). *Janeway's immunobiology.* New York: Garland Publisher.

Nairn R., Helbert M. (2004). *Immunology for medical students.* New York: Mosby/Elsevier.

Rakoff-Nahoum S., Medzhitov R. (2006). Role of the innate immune system and host-commensal mutualism. *Current Topics in Microbiology and Immunology* 308, 1–18.

Ridker P.M., Cannon C.P., Morrow D., et al. (2005). C-reactive protein and outcomes of statin therapy. *New England Journal of Medicine* 351, 20–28.

Roozendaal R., Carroll M.C. (2006). Emerging patterns in complement-mediated pathogen recognition. *Cell* 125, 29–32.

Rossi M., Young J.W. (2005). Human dendritic cells: Potent antigen-presenting cells at the crossroads of innate and adaptive immunity. *Journal of Immunology* 175, 1373–1381.

Russell J.H., Ley T.J. (2002). Lymphocyte mediated cytotoxicity. *Annual Review of Immunology* 20, 323–370.

Staros E.B. (2005). Innate immunity: New approaches to understanding its clinical significance. *American Journal of Clinical Pathology* 123, 305–312.

Sunyer J.O., Boshra H., Lorenzo G., et al. (2003). Evolution of complement as an effector system in innate and adaptive immunity. *Immunologic Research* 27, 549–564.

Takeda K., Kaisho T., Akira S. (2003). Toll-like receptors. *Annual Review of Immunology* 21, 335–376.

Ulevitch R.J. (2004). Therapeutics targeting the innate immune system. *Nature Reviews Immunology* 4, 512–520.

Underhill D.M., Ozinski A. (2002). Phagocytosis of microbes: Complexity in action. *Annual Review of Immunology* 20, 825–852.

Walport M.J. (2001). Complement: Parts 1 and 2. *New England Journal of Medicine* 344, 1058–1066, 1141–1144.

Wright J. (2005). Immunoregulatory functions of surfactant proteins. *Nature Reviews Immunology* 5, 58–68.

Hypersensitivity Disorders
Type I, Immediate Hypersensitivity Disorders
Systemic (Anaphylactic) Reactions
Local (Atopic) Reactions
Type II, Antibody-Mediated Disorders
Complement- and Antibody-Mediated Cell Destruction
Complement- and Antibody-Mediated Inflammation
Antibody-Mediated Cellular Dysfunction
Type III, Immune Complex–Mediated Disorders
Systemic Immune Complex Disorders
Local Immune Complex Reactions
Type IV, Cell-Mediated Hypersensitivity Disorders
Direct Cell-Mediated Cytotoxicity
Delayed-Type Hypersensitivity Disorders
Transplantation Immunopathology
Immune Recognition of Allografts
Solid Organ Rejection
Patterns of Rejection
Transplantation of Hematopoietic Cells
Graft-Versus-Host Disease
Autoimmune Disease
Immunologic Tolerance
B-Cell Tolerance
T-Cell Tolerance
Mechanisms of Autoimmune Disease
Genetic Susceptibility
Environmental Factors
Diagnosis and Treatment of Autoimmune Disease
Immunodeficiency Disorders
Primary Immunodeficiency Disorders
Humoral (B-Cell) Immunodeficiency Disorders
Cellular (T-Cell) Immunodeficiency Disorders
Combined T-Cell and B-Cell Immunodeficiency Disorders
Acquired Immunodeficiency Syndrome
Transmission of HIV Infection
Molecular and Biologic Features of HIV Infection
Classification and Stages of HIV Infection
Opportunistic Infections
Malignancies
Wasting Syndrome and Metabolic Disorders
Diagnosis and Treatment
HIV Infection in Pregnancy and in Infants and Children

Chapter 16

Disorders of the Immune Response

The immune system is a multifaceted defense network that has evolved to protect against invading microorganisms, prevent the proliferation of cancer cells, and mediate the healing of damaged tissue. Under normal conditions, the immune response deters or prevents disease. Occasionally, however, the inadequate, inappropriate, or misdirected activation of the immune system can lead to debilitating or life-threatening illnesses, typified by allergic or hypersensitivity reactions, transplantation rejection, autoimmune disorders, and immunodeficiency states.

Hypersensitivity Disorders

Although activation of the immune system normally leads to production of antibodies and T-cell responses that protect the body against attack by microorganisms, it is also capable of causing tissue injury and disease. Disorders caused by immune responses are collectively referred to as *hypersensitivity reactions*. The term arose from the clinical definition of immunity as "sensitivity" to an antigen.[1]

Hypersensitivity disorders are commonly divided into four types: type I, immediate hypersensitivity disorders; type II, antibody-mediated disorders; type III, immune complex–mediated disorders; and type IV, T-cell–mediated disorders[1–3] (Table 16-1). These categories differ in terms of the type of immune response causing the injury and the nature and location of the antigen that is the target of the response.

Type I, Immediate Hypersensitivity Disorders

Type I hypersensitivity reactions are IgE-mediated reactions that begin rapidly, often within minutes of an antigen challenge. These types of reactions to antigens are often referred to as *allergic reactions*. In the context of an allergic response, the antigens usually are referred to as *allergens*. Typical allergens include the proteins in plant pollens, house dust mites, animal dander, foods, and

Allergic and Hypersensitivity Disorders

- Hypersensitivity disorders result from immune responses to exogenous and endogenous antigens that produce inflammation and cause tissue damage.
- Type 1 immediate hypersensitivity is an IgE-mediated response that leads to the release of inflammatory mediators from sensitized mast cells.
- Type II disorders involve an antibody-mediated response against cell surface or extracellular matrix antigens that results in complement-mediated phagocytosis, inflammation and cell injury, or abnormal physiological responses without cell injury.
- Type III disorders responses result from the generation of circulating antigen–antibody complexes that activate complement resulting in the recruitment and activation of inflammatory cells that release tissue-damaging products.
- Type IV disorders involve tissue damage in which cell-mediated immune responses with sensitized T lymphocytes cause cell and tissue injury.

chemicals like the antibiotic penicillin. Exposure to the allergen can be through inhalation, ingestion, injection, or skin contact. Depending on the portal of entry, type I reactions may occur as a local or atopic reaction that is merely annoying (e.g., seasonal rhinitis) or severely debilitating (asthma) or as a systemic and potentially life-threatening reaction (anaphylaxis).

Two types of cells are central to a type I hypersensitivity reaction: type 2 helper T (T_H2) cells and mast cells or basophils.[1–4] There are two subsets of helper T cells (T_H1 and T_H2) that develop from the same precursor $CD4^+$ T lymphocyte (see Chapter 15). T_H1 cells differentiate in response to microbes and stimulate the differentiation of B cells into IgM- and IgG-producing plasma cells. T_H2 cell differentiation occurs in response to allergens and helminths (intestinal parasites).[1] Cytokines secreted by T_H2 cells stimulate differentiation of B cells into IgE-producing plasma cells, act as growth factors for mast cells, and recruit and activate eosinophils (Fig. 16-1).

Mast cells, which are tissue cells, and basophils, which are blood cells, are derived from hematopoietic precursor cells. Mast cells and basophils have granules that contain mediators that are released to initiate the early events in type I hypersensitivity reactions. These mediators are preformed in the cell or activated through enzymatic processing. Mast cells normally are distributed in connective tissue, especially in areas beneath the skin and mucous membranes of the respiratory, gastrointestinal, and genitourinary tracts and adjacent to blood and lymph vessels.[5,6] This location places them near surfaces that are exposed to environmental antigens and parasites. Mast cells in different parts of the body and even in a single site can have significant differences in mediator content and sensitivity to agents that produce mast cell degranulation.

Type I hypersensitivity reactions begin with mast cell or basophil sensitization. During the sensitization or priming stage, allergen-specific IgE antibodies attach to receptors on the surface of mast cells and basophils. With subsequent exposure, the sensitizing allergen binds to the cell-associated IgE and triggers a series of events that ultimately lead to degranulation of the sensitized mast cells or basophils, causing release of their preformed mediators (Fig. 16-1). Mast cells are also the source of lipid-derived membrane products (e.g., prostaglandins and leukotrienes) and cytokines that participate in the continued response to the allergen.

Many type I hypersensitivity reactions such as bronchial asthma have two well-defined phases: (1) a primary or initial-phase response characterized by vasodilation, vascular leakage, and smooth muscle contraction and (2) a secondary or late-phase response characterized by more intense infiltration of tissues with eosinophils and other

TABLE 16-1 Classification of Hypersensitivity Responses

Type of Hypersensitivity	Immune Mechanism	Mechanism of Injury
Type I, immediate hypersensitivity	IgE antibody	Release of mast cell mediators
Type II, antibody mediated	IgM, IgG antibodies against cell surface or extracellular matrix	Phagocytosis and opsonization of cells; complement- and receptor-mediated recruitment and activation of inflammatory cells (neutrophils, macrophages); abnormalities in cellular functioning (e.g., hormone receptor signaling)
Type III, immune complex mediated	Formation of immune complexes involving circulating antigens and IgM or IgG antibodies	Complement-mediated recruitment and activation of inflammatory cells
Type IV, T-cell mediated	$CD4^+$ T cells (delayed-type hypersensitivity, or $CD8^+$ cytotoxic T-cell–mediated cytolysis)	Macrophage activation of cytokine-mediated inflammation; direct target cell killing, cytokine-mediated inflammation

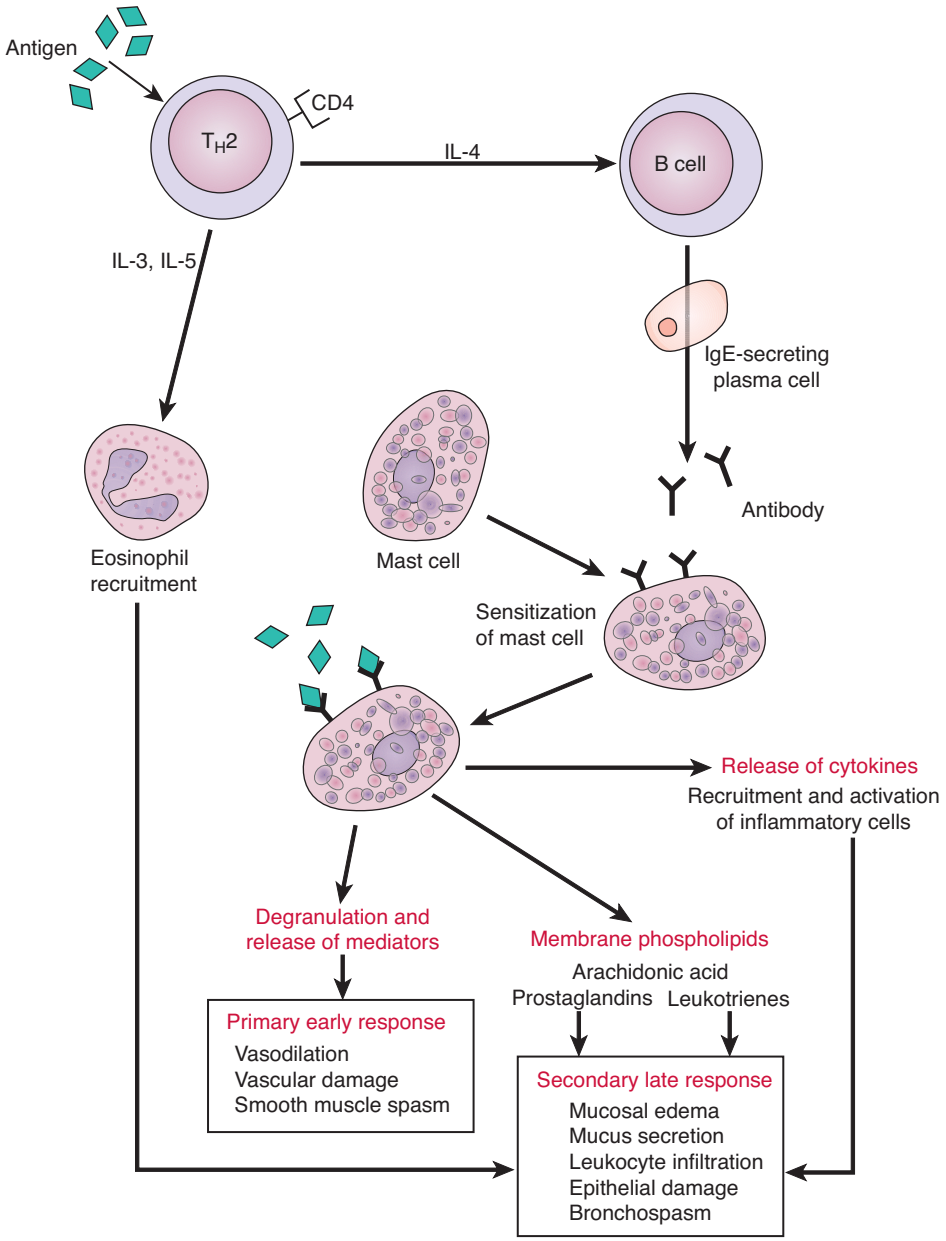


FIGURE 16-1. Type I, IgE-mediated hypersensitivity reaction. The stimulation of B-cell differentiation by an antigen-stimulated type 2 helper T (T_H2) cell leads to plasma cell production of IgE and mast cell sensitization. Subsequent binding of the antigen produces degranulation of the sensitized mast cell with release of preformed mediators that leads to a primary, or early-phase, response. T_H2 T-cell recruitment of eosinophils, along with the release of cytokines and membrane phospholipids from the mast cell, leads to a secondary, or late-phase, response. IL, interleukin.

acute and chronic inflammatory cells, as well as tissue destruction in the form of epithelial cell damage.

The primary or initial-phase response usually occurs within 5 to 30 minutes of exposure to antigen and subsides within 60 minutes. It is mediated by mast cell degranulation and the release of preformed mediators. These mediators include histamine, acetylcholine, adenosine, chemotactic mediators, and enzymes such as chymase and trypsin that lead to generation of kinins. Histamine is a potent vasodilator that increases the permeability of capillaries and venules and causes smooth muscle contraction and bronchial constriction. Acetylcholine produces bronchial smooth muscle contraction and dilation of small blood vessels. The kinins, which are a group of potent inflammatory peptides, require activation through enzymatic modification. Once activated, these peptide mediators (e.g., bradykinin) produce vasodilation and smooth muscle contraction.

The secondary or late-phase response occurs about 2 to 8 hours later and lasts for several days. It results from the action of lipid mediators and cytokines involved in the inflammatory response. The lipid mediators are derived from mast cell membrane phospholipids, which are broken down to form arachidonic acid. Arachidonic acid, in turn, is the parent compound from which the leukotrienes and prostaglandins are synthesized (see Chapter 3). The leukotrienes and prostaglandins produce responses similar to histamine and acetylcholine, although their effects are delayed and prolonged by comparison. Mast cells also produce cytokines and chemotactic factors that prompt the influx of eosinophils and leukocytes to the site of allergen contact, contributing to the inflammatory response.

At this point, it is important to note that not all IgE-mediated responses produce discomfort and disease. Type I hypersensitivity, particularly the late-phase response, plays a protective role in the control of parasitic infections. IgE antibodies directly damage the larvae of these parasites by recruiting inflammatory cells and causing antibody-dependent cell-mediated cytotoxicity. This type of type I hypersensitivity reaction is particularly important in developing countries where much of the population is infected with intestinal parasites.

Systemic (Anaphylactic) Reactions

Anaphylaxis is a systemic life-threatening hypersensitivity reaction characterized by widespread edema, difficulty breathing, and vascular shock secondary to vasodilation[2,7–9] (see section on anaphylactic shock, Chapter 20). It results from the presence of antigen introduced by injection, insect sting, or absorption across the epithelial surface of the skin or gastrointestinal mucosa. The level of severity depends on the level of sensitization. Even small amounts of antigen, such as the presence of residual amounts of peanut that remain on equipment used for preparing foods containing peanuts, can be sufficient to cause anaphylaxis in an extremely sensitive person. Within minutes after exposure, itching, hives, and skin erythema develop, followed shortly by bronchospasm and respiratory distress. Vomiting, abdominal cramps, diarrhea, and laryngeal edema and obstruction follow, and the person may go into shock and die unless effective treatment is instituted.

The initial management of anaphylaxis focuses on establishment of a stable airway and intravenous access, and administration of epinephrine.[8,9] Persons with a history of anaphylaxis should be provided with preloaded epinephrine syringes and instructed in their use. They should also be instructed to seek immediate professional help regardless of the initial response to self-treatment. Family members and caregivers of young children should be trained to inject epinephrine. Prevention of exposure to potential triggers that cause anaphylaxis is particularly important. Finally, all persons with potential for anaphylaxis should be advised to wear or carry a medical alert bracelet, necklace, or other identification to inform emergency personnel of the possibility of anaphylaxis.

Local (Atopic) Reactions

Local or atopic reactions usually occur when the antigen is confined to a particular site by virtue of exposure. The term *atopic* refers to a genetically determined hypersensitivity to common environmental allergens mediated by an IgE–mast cell reaction. Persons with atopic disorders commonly are allergic to more than one, and often many, environmental allergens. The most common atopic disorders are urticaria (hives), allergic rhinitis (hay fever), atopic dermatitis, food allergies, and some forms of asthma. The discussion in this section focuses on allergic rhinitis and food allergy. Allergic asthma is discussed in Chapter 23 and atopic dermatitis in Chapter 46.

The susceptibility to immediate hypersensitivity disorders tends to be inherited.[2] The genetic basis of atopy is unclear; however, linkage studies suggest an association with cytokine genes on chromosome 5q that regulate the expression of circulating IgE.[1] Persons with atopic allergic conditions tend to have high serum levels of IgE and increased numbers of basophils and mast cells. Although the IgE-triggered response is likely a key factor in the pathophysiology of atopic allergic disorders, it is not the only factor and may not be responsible for conditions such as atopic dermatitis and certain forms of asthma.

Allergic Rhinitis. Allergic rhinitis is characterized by symptoms of sneezing, itching, and watery discharge from the nose and eyes (rhinoconjunctivitis). Allergic rhinitis not only produces nasal symptoms but frequently is associated with other chronic airway disorders, such as sinusitis and bronchial asthma.[10,11] Severe attacks may be accompanied by systemic malaise, fatigue, and muscle soreness from sneezing. Fever is absent. Sinus obstruction may cause headache. Typical allergens include pollens from ragweed, grasses, trees, and weeds; fungal spores; house dust mites; animal dander; and feathers. Allergic rhinitis can be divided into perennial and seasonal allergic rhinitis depending on the chronology of symptoms. Persons with the perennial type of allergic rhinitis experience symptoms throughout the year, but those with seasonal allergic rhinitis (i.e., hay fever) are plagued with intense symptoms in conjunction with periods of high allergen (e.g., pollens, fungal spores) exposure. Symptoms that become worse at night suggest a household allergen, and symptoms that disappear on weekends suggest occupational exposure.

Diagnosis depends on a careful history and physical examination, microscopic identification of an increased number of eosinophils on a nasal smear, and skin testing to identify the offending allergens. When possible, avoidance of the offending allergen is recommended. Treatment is symptomatic in most cases and includes the use of oral antihistamines and oral or topical decongestants.[10] Intranasal corticosteroids often are effective when used appropriately. Intranasal cromolyn, a drug that stabilizes mast cells and prevents their degranulation, may be useful, especially when administered before expected contact with an offending allergen. A program of specific immunotherapy ("allergy shots") may be used when symptoms are particularly bothersome.[9,11] Desensitization involves frequent (usually weekly) injections of the offending antigens. The antigens, which are given in increasing doses, stimulate production of high levels of IgG, which acts as a blocking antibody by combining with the antigen before it can combine with the cell-bound IgE antibodies.

Food Allergies. Virtually any food can produce atopic or nonatopic allergies. The primary target of food allergy may be the skin, the gastrointestinal tract, and the respiratory system. The foods most commonly causing these reactions in children are milk, eggs, peanuts, soybeans, tree nuts, fish, and shellfish (i.e., crustaceans and mollusks).[12] In adults, they are peanuts,[13] shellfish, and fish.[12] The allergenicity of a food may be changed by heating or cooking. A person may be allergic to drinking milk but may not have symptoms when milk is included in cooked foods. Both acute reactions (hives and anaphylaxis) and chronic reactions (asthma, atopic dermatitis, and

gastrointestinal disorders) can occur. Anaphylaxis occurs as a multiorgan response associated with IgE-mediated hypersensitivity. The foods most responsible for anaphylaxis are peanuts, tree nuts (e.g., walnuts, almonds, pecans, cashews, hazelnuts), and shellfish.[12,14] One form of food-associated anaphylaxis occurs with exercise.[12,14] Food-associated, exercise-induced anaphylaxis may occur when exercise follows ingestion of a particular food to which IgE sensitivity has been demonstrated, or it may occur after ingestion of any food. Exercise without ingestion of the incriminated food does not produce symptoms.

Food allergies can occur at any age but, similar to atopic dermatitis and rhinitis, they tend to manifest during childhood. The allergic response is thought to occur after contact between specific food allergens and sensitizing IgE in the intestinal mucosa causes local and systemic release of histamine and other mediators of the allergic response. In this disorder, allergens usually are food proteins and partially digested food products. Carbohydrates, lipids, or food additives, such as preservatives, colorings, or flavorings, also are potential allergens. Closely related food groups can contain common cross-reacting allergens. For example, some persons are allergic to all legumes (i.e., beans, peas, and peanuts).

Diagnosis of food allergies usually is based on careful food history and provocative diet testing. Provocative testing involves careful elimination of a suspected allergen from the diet for a time to see if the symptoms disappear and reintroducing the food to see if the symptoms reappear. Only one food should be tested at a time. Treatment focuses on avoidance of the food or foods responsible for the allergy. However, avoidance may be difficult for persons who are exquisitely sensitive to a particular food protein because foods may be contaminated with the protein during processing or handling of the food. For example, contamination may occur when chocolate candies without peanuts are processed with the same equipment used for making candies with peanuts.

Type II, Antibody-Mediated Disorders

Type II (antibody-mediated) hypersensitivity reactions are mediated by IgG or IgM antibodies directed against target antigens on cell surfaces or in connective tissues.[2,3] The antigens may be endogenous antigens that are present on the membranes of body cells or exogenous antigens that are adsorbed on the membrane surface. There are three different types of antibody-mediated mechanisms involved in type II reactions: opsonization and complement- and antibody receptor–mediated phagocytosis, complement- and antibody receptor–mediated inflammation, and antibody-mediated cellular dysfunction[2] (Fig. 16-2).

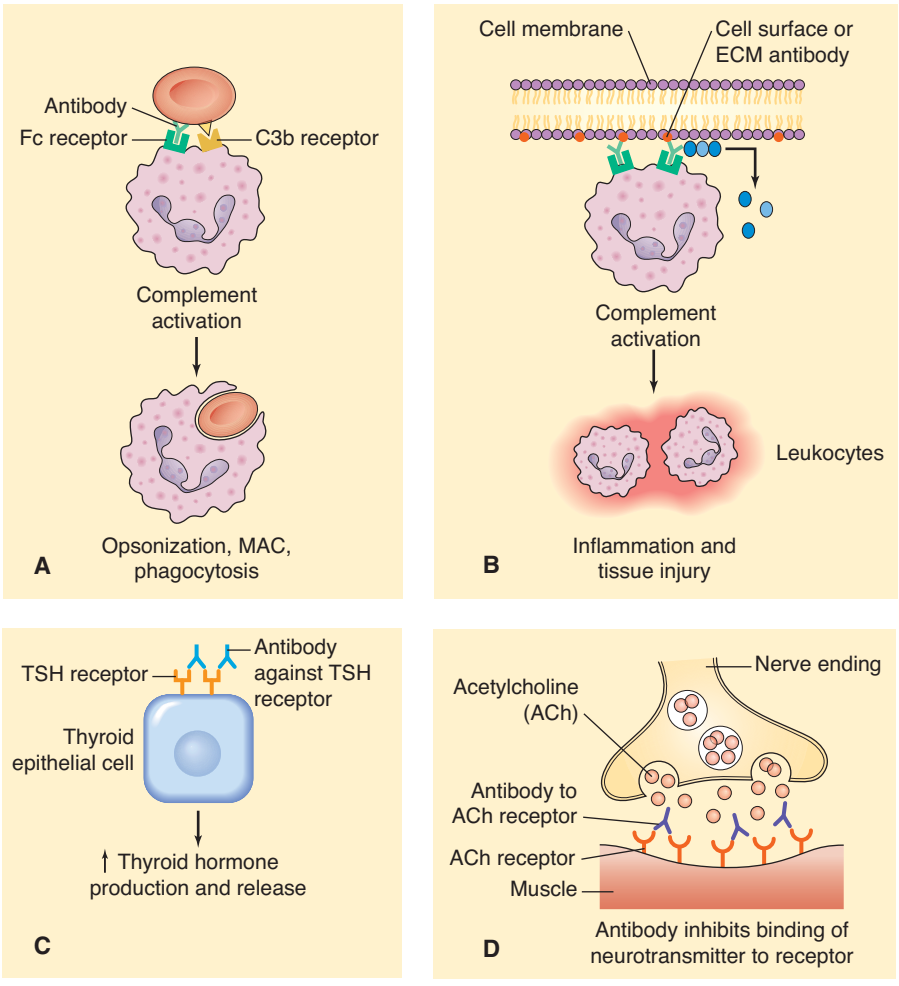


FIGURE 16-2. Type II, hypersensitivity reactions result from binding of antibodies to normal or altered surface antigens. **(A)** Opsonization and complement- or antibody receptor–mediated phagocytosis or cell lysis through membrane attack complex (MAC). **(B)** Complement- and antibody receptor–mediated inflammation resulting from recruitment and activation of inflammation-producing leukocytes (neutrophils and monocytes). Antibody-mediated cellular dysfunction, in which **(C)** antibody against the thyroid-stimulating hormone (TSH) receptor increases thyroid hormone production. **(D)** Antibody to acetylcholine receptor inhibits receptor binding of the neurotransmitter in myasthenia gravis. ECM, extracellular membrane.

Complement- and Antibody-Mediated Cell Destruction

The deletion of cells targeted by antibody can occur by way of either the complement system or by antibody-dependent cell-mediated cytotoxicity (ADCC), which does not require complement.[2,3] Complement-mediated cell destruction can occur because the cells are coated with molecules (opsonized; Fig. 16-2A) that make them attractive to phagocytes or because of the formation of membrane attack proteins that disrupt the integrity of the cell membrane and cause cell lysis (see Chapter 15, Understanding the Complement System). With ADCC destruction, cells that are coated with low levels of IgG antibody are killed by a variety of effector cells that bind to their target by their receptors for IgG, and cell lysis occurs without phagocytosis.

Examples of antibody-mediated cell destruction include mismatched blood transfusion reactions, hemolytic disease of the newborn due to ABO or Rh incompatibility (see Chapter 13), and certain drug reactions. In the latter, the binding of certain drugs or drug metabolites to the surface of red or white blood cells elicits an antibody response that lyses the drug-coated cell. Lytic drug reactions can produce transient anemia, leukopenia, or thrombocytopenia, which are corrected by the removal of the offending drug.

Complement- and Antibody-Mediated Inflammation

When antibodies are deposited in extracellular tissue components, such as basement membranes and matrix, injury results from inflammation rather than phagocytosis or cell lysis (Fig. 16-2B).[2,3] In this case, the deposited antibodies activate complement, generating chemotactic by-products that recruit and activate neutrophils and monocytes. The activated leukocytes release injurious substances, such as enzymes and reactive oxygen intermediates that result in inflammation and tissue damage. Antibody-mediated inflammation is responsible for the tissue injury seen in some forms of glomerulonephritis, vascular rejection of organ grafts, and other diseases. In Goodpasture syndrome, for example, antibody binds to a major structural component of pulmonary and glomerular basement membranes, causing pulmonary hemorrhage and glomerulonephritis[3] (see Chapter 25).

Antibody-Mediated Cellular Dysfunction

In some type II reactions, antibody binding to specific target cell receptors does not lead to cell death, but to a change in cell function (Fig. 16-2C, D). In Graves disease, for example, autoantibody directed against thyroid-stimulating hormone (TSH) receptors on thyroid cells stimulates thyroxine production, leading to hyperthyroidism[2,3] (see Chapter 32). In myasthenia gravis, autoantibodies to acetylcholine receptors on the neuromuscular endplates either block the action of acetylcholine or mediate internalization or destruction of receptors, leading to decreased neuromuscular function (see Chapter 36).

Type III, Immune Complex–Mediated Disorders

Immune complex allergic disorders are mediated by the formation of insoluble antigen–antibody complexes, complement fixation, and localized inflammation[2,3] (Fig. 16-3). Immune complexes formed in the circulation produce damage when they come in contact with the vessel lining or are deposited in tissues, including the renal glomerulus, skin venules, lung tissue, and joint synovium. Once deposited, the immune complexes elicit an inflammatory response by activating complement, thereby leading to chemotactic recruitment of neutrophils and other inflammatory cells. Activation of these inflammatory cells by immune complexes and complement, accompanied by the release of potent inflammatory mediators, is directly responsible for the injury.

Type III reactions are responsible for the vasculitis seen in certain autoimmune diseases such as systemic lupus erythematosus (SLE) or the kidney damage seen with acute glomerulonephritis. As with type I hypersensitivity reactions, type III immune complex disorders present with systemic manifestations or as a local reaction.

Systemic Immune Complex Disorders

Serum sickness is a systemic immune complex disorder that is triggered by the deposition of insoluble antigen–antibody (IgM, IgG, and occasionally IgA) complexes in

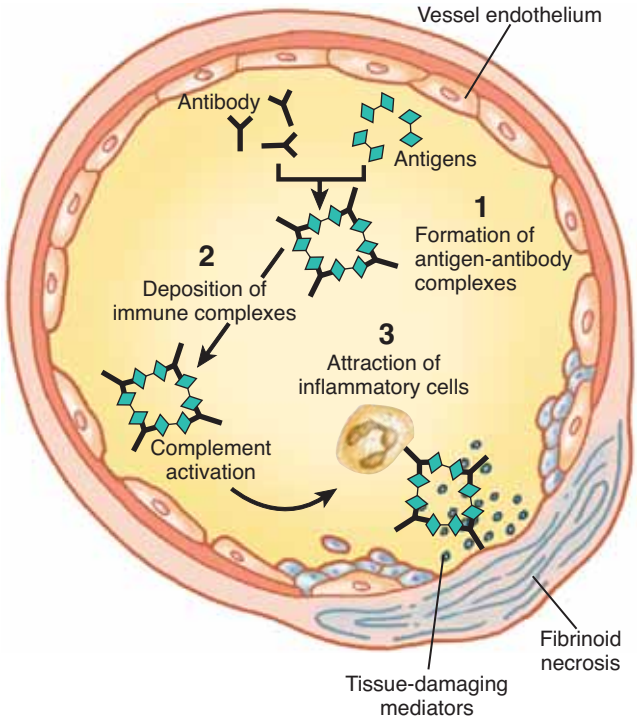


FIGURE 16-3. Type III, immune complex reactions involving complement-activating IgG or IgM immunoglobulins with (*1*) formation of blood-borne immune complexes that are (*2*) deposited in tissues. Complement activation at the site of immune complex deposition (*3*) leads to attraction of leukocytes that are responsible for vessel and tissue injury.

blood vessels, joints, and heart and kidney tissue.[2,3] The deposited complexes activate complement, increase vascular permeability, and recruit phagocytic cells, all of which can promote local tissue damage and edema. The term *serum sickness* was originally coined to describe a syndrome consisting of rash, lymphadenopathy, arthralgias, and occasionally neurologic disorders that appeared 7 or more days after injections of horse antiserum (tetanus). Although this therapy is not used today, the name remains. Currently, the most common causes of this allergic disorder include antibiotics (especially penicillin) and other drugs, various foods, and insect venoms.

The signs and symptoms of systemic immune complex disorders include urticaria, patchy or generalized rash, extensive edema (usually of the face, neck, and joints), and fever. In most cases, the damage is temporary, and symptoms resolve within a few days. However, a prolonged and continuous exposure to the sensitizing antigen can lead to irreversible damage. In previously sensitized persons, severe and even fatal forms of serum sickness may occur immediately or within several days after the sensitizing drug or serum is administered. Treatment usually is directed toward removal of the sensitizing antigen and providing symptom relief. This may include aspirin for joint pain and antihistamines for pruritus. Epinephrine or systemic corticosteroids may be used for severe reactions.

Local Immune Complex Reactions

The *Arthus reaction* is a term used by pathologists and immunologists to describe localized tissue necrosis (usually in the skin) caused by immune complexes. In the laboratory, an Arthus reaction can be produced by injecting an antigen preparation into the skin of an immune animal with high levels of circulating antibody. Within 4 to 10 hours, a red, raised lesion appears on the skin at the site of the injection.[2] An ulcer often forms in the center of the lesion. It is thought that the injected antigen diffuses into local blood vessels, where it comes in contact with specific antibody (IgG) to incite a localized vasculitis (i.e., inflammation of a blood vessel). This experimental model of localized vasculitis is the prototype of many forms of vasculitis seen in humans, such as the cutaneous vasculitides that characterize certain drug reactions.

Type IV, Cell-Mediated Hypersensitivity Disorders

Type IV hypersensitivity reactions involve cell-mediated rather than antibody-mediated immune responses.[2,3] Cell-mediated immunity is the principal mechanism of response to a variety of microorganisms, including intracellular pathogens such as *Mycobacterium tuberculosis* and viruses, as well as extracellular agents such as fungi, protozoa, and parasites. It can also lead to cell death and tissue injury in response to chemical antigens (contact dermatitis) or self-antigens (autoimmunity).

Type IV hypersensitivity reactions, which are mediated by specifically sensitized T lymphocytes, can be divided into two basic types: direct cell-mediated cytotoxicity and delayed-type hypersensitivity (Fig. 16-4).

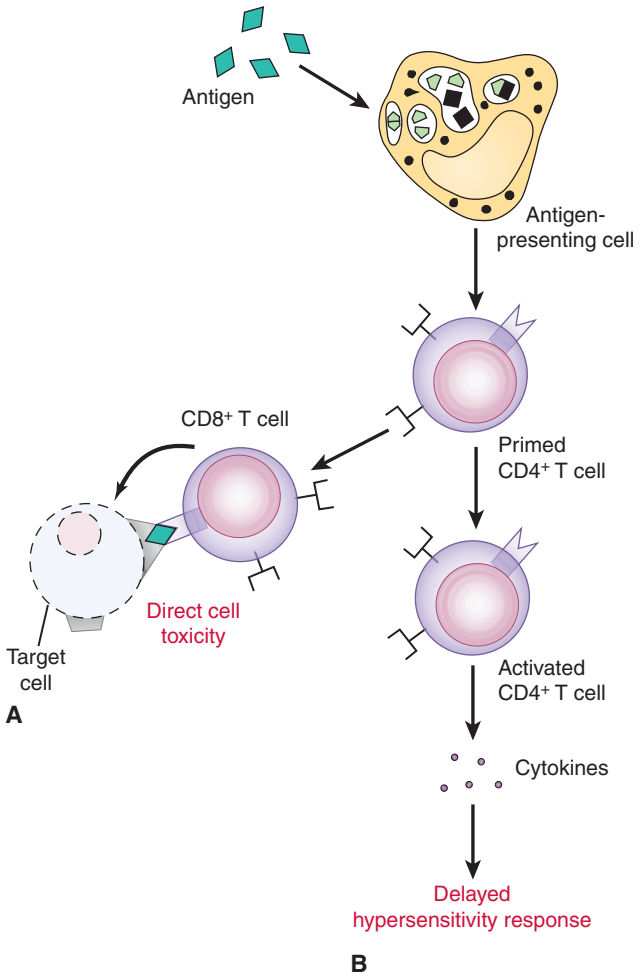


FIGURE 16-4. Type IV, cell-mediated hypersensitivity reactions, which include **(A)** direct cell-mediated cytotoxicity in which $CD8^+$ T cells kill the antigen-bearing target cells, and **(B)** delayed-type hypersensitivity reactions in which presensitized $CD4^+$ cells release cell-damaging cytokines.

Direct Cell-Mediated Cytotoxicity

In direct cell-mediated cytotoxicity (Fig. 16-4A), $CD8^+$ cytotoxic T lymphocytes (CTLs) directly kill target cells that express peptides derived from cytosolic antigens that are presented in association with class I major histocompatibility complex (MHC) molecules (see Chapter 15). In viral infections, CTL responses can lead to tissue injury by killing infected target cells even if the virus itself has no cytotoxic effects.[2] Some viruses directly injure infected cells and are said to be cytopathic, whereas other, noncytopathic viruses do not. Because CTLs cannot distinguish between cytopathic and noncytopathic viruses, they kill virtually all infected cells regardless of whether the infection is harmful. In certain forms of hepatitis, for example, the destruction of liver cells is due to the host CTL response and not the virus.

Delayed-Type Hypersensitivity Disorders

Delayed-type hypersensitivity (DTH) reactions (Fig. 16-4B) occur in response to soluble protein antigens and primarily involve antigen-presenting cells such as macrophages and $CD4^+$ helper T cells of the T_H1 type. During the reaction T_H1 cells are activated and secrete an array of cytokines that recruit and activate macrophages, lymphocytes, fibroblasts, and other inflammatory cells.[7] These T-cell–mediated responses require the synthesis of effector molecules and take 24 to 72 hours to develop, which is why they are called "delayed-type" hypersensitivity disorders.

The best-known DTH response is the reaction to the tuberculin test, in which inactivated tuberculin or purified protein derivative is injected under the skin. In a person who has been sensitized by previous infection, a local area of redness and induration develops within 8 to 12 hours, reaching a peak in 24 to 72 hours. The tuberculin reaction is characterized by perivascular accumulation of T_H1 cells and, to a lesser extent, macrophages. Local secretion of cytokines by these mononuclear inflammatory cells leads to increased microvascular permeability with local redness and swelling. The sequence of events in DTH, as demonstrated by the tuberculin reaction, begins with the first exposure to the tubercle bacilli (see Chapter 22). The T_H1 cells recognize the peptide antigens of the tubercle bacilli in association with class II MHC antigens on the surface of monocytes and antigen-presenting cells that have processed the mycobacterial antigens. This process leads to formation of sensitized T_H1 memory cells that remain in the circulation for years. Subsequent injection of tuberculin into such an individual results in the secretion of T_H1 cell cytokines that are ultimately responsible for the DTH response.

In addition to its beneficial protective role, DTH can also be the cause of disease, including allergic contact dermatitis and hypersensitivity pneumonitis. It also can be involved in transplant rejection and autoimmune disorders.

Allergic Contact Dermatitis. Allergic contact dermatitis denotes an inflammatory response confined to the skin that is initiated by reexposure to an allergen to which a person had previously become sensitized (e.g., cosmetics, hair dyes, metals, topical drugs).[15] The most common form of this condition is the dermatitis that follows an intimate encounter with poison ivy or poison oak antigens, although many other substances can trigger a reaction.

Contact dermatitis is characterized by erythematous, papular, and vesicular lesions associated with intense pruritus and weeping. The affected area often becomes swollen and warm, with exudation, crusting, and development of a secondary infection. The location of the lesions often provides a clue about the antigen causing the disorder. The severity of the reaction associated with contact dermatitis ranges from mild to intense, depending on the person and the allergen. Because this condition follows the mechanism of a DTH response, the reaction does not become apparent for at least 12 hours and usually more than 24 hours after exposure. Depending on the antigen and the duration of exposure, the reaction may last from days to weeks.

Diagnosis of contact dermatitis is made by observing the distribution of lesions on the skin surface and associating a particular pattern with exposure to possible allergens. If a particular allergen is suspected, a patch test can be used to confirm the suspicion. Treatment usually is limited to removal of the irritant and application of topical preparations (e.g., ointments, corticosteroid creams) to relieve symptomatic skin lesions and prevent secondary bacterial infections. Severe reactions may require systemic corticosteroid therapy.

Hypersensitivity Pneumonitis. Hypersensitivity pneumonitis, which is associated with exposure to inhaled organic dusts or related occupational antigens, is another example of a DTH reaction.[16] The disorder is thought to involve a susceptible host and activation of pulmonary T cells, followed by the release of cytokine mediators of inflammation. The inflammatory response that ensues (usually several hours after exposure) produces labored breathing, dry cough, chills and fever, headache, and malaise. The symptoms usually subside within hours after the sensitizing antigens are removed. A primary example of hypersensitivity pneumonitis is "farmer's lung," a condition resulting from exposure to moldy hay. Other sensitizing antigens include tree bark, sawdust, animal dander, and *Actinomycetes* bacteria that are occasionally found in humidifiers, hot tubs, and swimming pools. Exposure to small amounts of antigen for a long period may lead to chronic lung disease with minimal reversibility. This can occur in persons exposed to avian or animal antigens or a contaminated home air humidifier.

The most important element in the diagnosis of hypersensitivity pneumonitis is to obtain a good history (occupational and otherwise) of exposure to possible antigens. Treatment consists of identifying and avoiding the offending antigens. Severe forms of the disorder may be treated with systemic corticosteroid therapy.

In summary, hypersensitivity and allergic disorders are responses to environmental, food, or drug antigens that would not affect most of the population. There are four basic categories of hypersensitivity responses: (1) type I responses, which are mediated by the IgE-class immunoglobulins and include anaphylactic shock, hay fever, and bronchial asthma; (2) type II responses, which involve an antibody-mediated cell destruction (e.g., transfusion reactions and hemolytic anemia), complement- and antibody-mediated inflammation (e.g., some forms of glomerulonephritis), and antibody-mediated cell dysfunction (e.g., Graves disease and myasthenia gravis); (3) type III hypersensitivity reactions, which involve the formation and deposition of insoluble antigen–antibody complexes and are responsible for the vasculitis (seen in SLE or acute glomerulonephritis), systemic immune complex disease (serum sickness), and local immune complex disease (Arthus reaction); and (4) type IV cell-mediated hypersensitivity reactions, which include direct

cell cytotoxicity, in which sensitized $CD8^+$ T cells kill antigen-bearing target cells, and delayed-type hypersensitivity reactions, in which presensitized $CD4^+$ T cells release cytokines that damage and kill antigen-containing cells.

Transplantation Immunopathology

Transplantation is the process of taking cells, tissues, or organs, called a *graft,* from one individual and placing them into another individual. Sometimes grafts are transplanted from another site in the same person. The individual who provided the tissue is called the *donor,* and the individual who receives the graft is called either the *recipient* or the *host*. Transplantation rejection is discussed here because it involves several of the previously discussed immunologic reactions. A major barrier to transplantation is the process of rejection, in which the recipient's immune system recognizes the graft as foreign and attacks it.

The cell surface antigens that determine whether the tissue of transplanted organs is recognized as foreign are the MHC or *human leukocyte antigens* (HLA; see Chapter 15). Transplanted tissue can be categorized as an *autologous* graft if the donor and recipient are the same person, *syngeneic* graft if the donor and recipient are identical twins, and *allogeneic* (genetic variations of same gene within a given species) if the donor and recipient are related or unrelated but share similar HLA types. The molecules that are recognized as foreign on allografts are called *alloantigens*. Donors of solid organ transplants can be living or dead (cadaver) and related or nonrelated (heterologous). Rejection of allografts is a response to MHC molecules, which are so polymorphic that no two individuals are likely to express the same MHC molecules, unless they are identical twins. The likelihood of rejection varies indirectly with the degree of MHC or HLA relatedness between the donor and recipient.

Immune Recognition of Allografts

Rejection of allografts is a complex process that involves cell-mediated immunity and circulating antibodies. Although many cells may participate in the process of acute transplant rejection, only the T lymphocytes seem to be absolutely required.[1,2] The recipient's T cells recognize allogeneic antigens in the graft by two pathways: the direct and indirect recognition pathways.[2]

In the *direct pathway,* T cells of the recipient directly recognize allogeneic MHC molecules on the surface of antigen-presenting cells on the graft. Both the $CD4^+$ and $CD8^+$ cells of the transplant recipient are involved in the reaction. $CD8^+$ cells recognize class I MHC molecules and differentiate into mature CTLs that kill cells in the grafted tissue (see type IV hypersensitivity reactions). The $CD4^+$ helper T-cell subset is triggered into proliferation and differentiation into T_H1 effector cells by recognition of allogeneic class II MHC molecules. As in delayed hypersensitivity reactions, cytokines secreted by activated $CD4^+$ cells cause increased vascular permeability and local accumulation and activation of macrophages, resulting in graft injury.

In the *indirect pathway,* recipient $CD4^+$ T cells recognize donor MHC molecules after they have been picked up, processed, and presented by the recipient's own antigen-presenting cells. Thus, the indirect pathway is similar to the physiologic processing and presentation of other foreign (i.e., microbial) antigens. This form of recognition mainly activates DTH pathways of the type IV hypersensitivity reactions. This indirect pathway is also involved in the production of antibodies against graft alloantigens. If the alloantigens are proteins, they are picked up by host B cells and processed, and their peptides presented to helper T cells, which then stimulate antibody responses.[2]

Solid Organ Rejection

Both T cells and antibodies are involved in rejection of solid organ allografts. T cells recognize allografts by both indirect and direct pathways. CTLs kill cells in the grafted tissue, producing parenchymal, and perhaps more importantly endothelial cell death, resulting in thrombosis and tissue ischemia.[2] Cytokine-secreting T cells trigger DTH reactions with increased vascular permeability and local accumulation of lymphocytes and macrophages.[2] Activated macrophages can injure graft cells and vasculature, leading to tissue ischemia and graft destruction.

Although there is little doubt that T cells are essential to the rejection process, antibodies evoked against alloantigens can also mediate rejection.[2] The process, which is called *humoral rejection,* can take one of two forms. *Hyperacute rejection* occurs when preformed antidonor antibodies are present in the circulation of the recipient. Such antibodies may be present if the recipient has already rejected a kidney transplant or received blood products with nonidentical HLA antigens. When preformed antidonor antibodies are present, rejection occurs immediately after transplantation. The second form of antigen–antibody rejection occurs in recipients who were not previously sensitized, but who develop antibodies to graft alloantigens. The antibodies formed by the recipient may cause injury by several mechanisms, including complement-dependent cytotoxicity, inflammation, and antibody-dependent cell-mediated cytotoxicity. The initial target of these antibodies in rejection appears to be the graft vasculature.

Patterns of Rejection

The basic patterns of transplant rejection have historically been classified as hyperacute, acute, and chronic, based on the clinical tempo of the response and the pathologic mechanisms involved.[1–3] In actual practice, however, there is often an overlap in features. The diagnosis is further complicated by the effects of immunosuppressant drugs or recurrence of the original disease. The following section characterizes the rejection patterns

in the context of renal transplantation. Similar responses occur with other types of organ transplants.

A *hyperacute reaction* occurs almost immediately after transplantation. In kidney transplants, it can often be seen at the time of surgery. As soon as blood flow from the recipient to the donor kidney begins, it takes on a cyanotic, mottled appearance. At other times, the reaction may take hours or days to develop. The hyperacute response is produced by existing recipient antibodies to graft antigens that initiate a type III, Arthus-type hypersensitivity reaction in the blood vessels of the graft. These antibodies usually have developed in response to previous blood transfusions, pregnancies in which the mother makes antibodies to fetal antigens, or infections with bacteria or viruses possessing antigens that mimic MHC antigens.

Acute rejection usually occurs within the first few months after transplantation and is evidenced by signs of organ failure. It also may occur suddenly months or even years later, after immunosuppression has been used and discontinued. T lymphocytes play a central role in acute rejection, responding to antigens in the graft tissue. The activated T cells cause direct lysis of graft cells and recruit and activate inflammatory cells that injure the graft. In vascularized grafts such as kidney grafts, the endothelial cells of blood vessels are the earliest targets of acute rejection.

Chronic rejection occurs over a prolonged period. It manifests with dense intimal fibrosis of blood vessels of the transplanted organ. In renal transplantation, it is characterized by a gradual rise in serum creatinine over a period of 4 to 6 months. The actual mechanism of this type of response is unclear but may include release of cytokines that stimulate fibrosis.

Transplantation of Hematopoietic Cells

Bone marrow transplantation is increasingly being used as therapy for hematopoietic and some nonhematopoietic malignancies, aplastic anemia, and immunodeficiency disorders. Hematopoietic stem cells can be collected from donor bone marrow or peripheral blood. Stem cell aspiration from the bone marrow is the most common form of allograft collection. Peripheral blood offers a less invasive method for obtaining stem cells. Hematopoietic growth factors, such as granulocyte colony-stimulating factor, often are used to induce stem cells to move out of the bone marrow into the blood. Before either bone marrow or peripheral blood stem cells are infused, recipients receive pretreatment conditioning regimes (e.g., total-body irradiation or treatment with cytotoxic drugs) to destroy malignant cells (e.g., in leukemia) and to create a graft bed. Rejection of the allogenic bone marrow transplant appears to be mediated by a combination of reactive T cells and natural killer (NK) cells that are resistant to radiation therapy and chemotherapy.[2]

Graft-Versus-Host Disease

Graft-versus-host-disease (GVHD) occurs when immunologically competent cells or precursors are transplanted into recipients who are immunologically compromised. Although GVHD occurs most often in persons who have undergone allogeneic bone marrow transplantation, it may also follow transplantation of organs rich in lymphoid tissue (e.g., the liver) or follow transfusions with nonirradiated blood.[2] Three basic requirements are necessary for GVHD to develop: (1) the transplant must have a functional cellular immune component, (2) the recipient tissue must bear antigens foreign to the donor tissue, and (3) recipient immunity must be compromised to the point that it cannot destroy the transplanted cells.[1,17,18] The primary agents of GVHD are the donor immunocompetent T cells derived from the donor marrow and the recipient tissue that they recognize as foreign and react against.[2] GVHD results in activation of both $CD4^+$ and $CD8^+$ T cells with ultimate generation of a type IV, cell-mediated DTH and CTL reactions. The greater the difference in tissue antigens between the donor and recipient, the greater is the likelihood of GVHD.

GVHD can occur as an acute or chronic reaction. Acute GVHD, which develops within days to weeks after transplantation, involves the epithelial cells of the skin, liver, and gastrointestinal tract.[2] The organ most commonly affected in acute GVHD is the skin. There is development of a pruritic, maculopapular rash, which begins on the palms and soles and frequently extends over the entire body, with subsequent desquamation. Involvement of the gastrointestinal tract usually parallels the development of skin and liver involvement. Gastrointestinal symptoms include nausea, bloody diarrhea, and abdominal pain. GVHD of the liver is heralded by painless jaundice, hyperbilirubinemia, and abnormal liver function test results. Liver involvement can progress to development of veno-occlusive disease, drug toxicity, viral infection, iron overload, extrahepatic biliary obstruction, sepsis, and coma.[19]

Chronic GVHD may follow acute GVHD or it may develop insidiously. While persons in whom chronic GVHD develops are profoundly immunocompromised, they develop skin lesions resembling systemic sclerosis (discussed in Chapter 44) and manifestations mimicking other autoimmune diseases.

In summary, transplantation is the process of taking cells, tissues, or organs, called an *allograft,* from one individual (a donor) and placing them into another individual (recipient). A major barrier to transplantation is the process of rejection in which the recipient's immune system recognizes the graft as foreign and attacks it. Destruction of the cells or tissues of the graft can result from direct action of the recipient's cytotoxic T cells, from T-cell–generated cytokines and a delayed hypersensitivity reaction, or from antibodies generated against antigens in the graft. Hyperacute rejection occurs almost immediately after transplantation and is caused by existing recipient antibodies to graft antigens that initiate a type III, Arthus-type hypersensitivity reaction in the blood vessels of the graft. Acute rejection occurs within

the first few months after transplantation and occurs when cytotoxic T cells cause direct lysis of graft cells and recruit and activate inflammatory cells that injure the graft. Chronic rejection occurs over a prolonged period and is caused by T-cell–generated cytokines that stimulate fibrosis of graft tissue.

Graft-versus-host disease (GVHD) occurs when immunologically competent cells or precursors are transplanted into recipients who are immunologically compromised. Three basic requirements are necessary for GVHD to develop: (1) the transplant must have a functional cellular immune component, (2) the recipient tissue must bear antigens foreign to the donor tissue, and (3) recipient immunity must be compromised to the point that it cannot destroy the transplanted cells.

Autoimmune Disease

Autoimmune diseases represent a group of disorders that are caused by a breakdown in the ability of the immune system to differentiate between self- and nonself-antigens. Autoimmune diseases can affect almost any cell or tissue in the body. Some autoimmune disorders, such as Hashimoto thyroiditis, are tissue specific, whereas others, such as SLE, affect multiple organs and systems. Chart 16-1 lists some of the probable autoimmune diseases. Many of these disorders are discussed elsewhere in this book.

CHART 16-1 Probable Autoimmune Disease*

Systemic
Mixed connective tissue disease
Polymyositis-dermatomyositis
Rheumatoid arthritis
Scleroderma
Sjögren syndrome
Systemic lupus erythematosus

Blood
Autoimmune hemolytic anemia
Autoimmune neutropenia and lymphopenia
Idiopathic thrombocytopenic purpura

Other Organs
Acute idiopathic polyneuritis
Atrophic gastritis and pernicious anemia
Autoimmune adrenalitis
Goodpasture syndrome
Hashimoto thyroiditis
Type 1 diabetes mellitus
Myasthenia gravis
Premature gonadal (ovarian) failure
Primary biliary cirrhosis
Sympathetic ophthalmia
Temporal arteritis
Thyrotoxicosis (Graves disease)
Crohn disease, ulcerative colitis

*Examples are not inclusive.

Immunologic Tolerance

To function properly, the immune system must be able to differentiate foreign antigens from self-antigens. The ability of the immune system to differentiate self from nonself is called *self-tolerance*. It is the HLAs encoded by MHC genes that serve as recognition markers of self and nonself for the immune system (see Chapter 15). To elicit an immune response, an antigen must first be processed by an antigen-presenting cell (APC), such as a macrophage, which then presents the antigenic determinants along with an MHC II molecule to a $CD4^+$ helper T cell. The dual recognition of the MHC–antigen complex by the T-cell receptor (TCR) of the $CD4^+$ helper T cell acts like a security check. Similar recognition checks occur between $CD8^+$ cytotoxic T cells and the MHC I–antigen complex of tissue cells that have been targeted for elimination. A number of chemical messengers (e.g., interleukins) and costimulatory signals are essential to the activation of immune responses and the preservation of self-tolerance.

Several mechanisms have been postulated to explain the tolerant state, including central tolerance and peripheral tolerance.[2,20–23] *Central tolerance* refers to the elimination of self-reactive T cells and B cells in the central lymphoid organs (i.e., the thymus for T cells and the bone marrow for B cells). *Peripheral tolerance* derives from the deletion or inactivation of autoreactive T cells

Immunologic Tolerance

- Immunologic tolerance is the ability of the immune system to differentiate self from nonself. It results from central and peripheral mechanisms that delete self-reactive immune cells that cause autoimmunity or render their response ineffective in destroying self-cells and self-tissue.
- Central tolerance involves the elimination of self-reactive T and B cells in the central lymphoid organs. Self-reactive T cells are deleted in the thymus and self-reactive B cells in the bone marrow.
- Peripheral tolerance derives from the deletion or inactivation of self-reactive T and B cells that escaped deletion in the central lymphoid organs. It involves mechanisms such as receptor editing, absence of necessary costimulatory signals, production of immunologic ignorance by separating self-reactive immune cells from target tissues, and the presence of suppressor immune cells.

or B cells that escaped elimination in the central lymphoid organs. *Anergy* represents the state of immunologic tolerance to specific antigens. It may take the form of diminished immediate hypersensitivity or delayed-type hypersensitivity, or both.

B-Cell Tolerance

Loss of self-tolerance with development of autoantibodies is characteristic of a number of autoimmune disorders. For example, hyperthyroidism in Graves disease is due to autoantibodies to the TSH receptor (see Fig. 16-2 and Chapter 32). Several mechanisms are available to filter autoreactive B cells out of the B-cell population: clonal deletion of immature B cells in the bone marrow; deletion of autoreactive B cells in the spleen or lymph nodes; functional inactivation or anergy; and receptor editing, a process that changes the specificity of a B-cell receptor when autoantigen is encountered.[20] There is increasing evidence that B-cell tolerance is predominantly due to help from T cells.

T-Cell Tolerance

The central mechanisms of T-cell tolerance involve the deletion of self-reactive T cells in the thymus (Fig. 16-5). T cells develop from bone marrow–derived progenitor cells that migrate to the thymus, where they encounter self-peptides bound to MHC molecules. T cells that display the host's MHC antigens and T-cell receptors for a non–self-antigen are allowed to mature in the thymus (i.e., positive selection). T cells that have a high affinity for host cells are sorted out and undergo apoptosis or cell death (i.e., negative selection). The deletion of self-reactive T cells in the thymus requires the presence of autoantigens. Because many autoantigens are not present in the thymus, self-reactive T cells may escape the thymus, so peripheral mechanisms that participate in T-cell tolerance are required.

Several peripheral mechanisms are available to control the responsiveness of self-reactive T cells in the periphery. Sometimes the host antigens are not available in the appropriate immunologic form or are separated

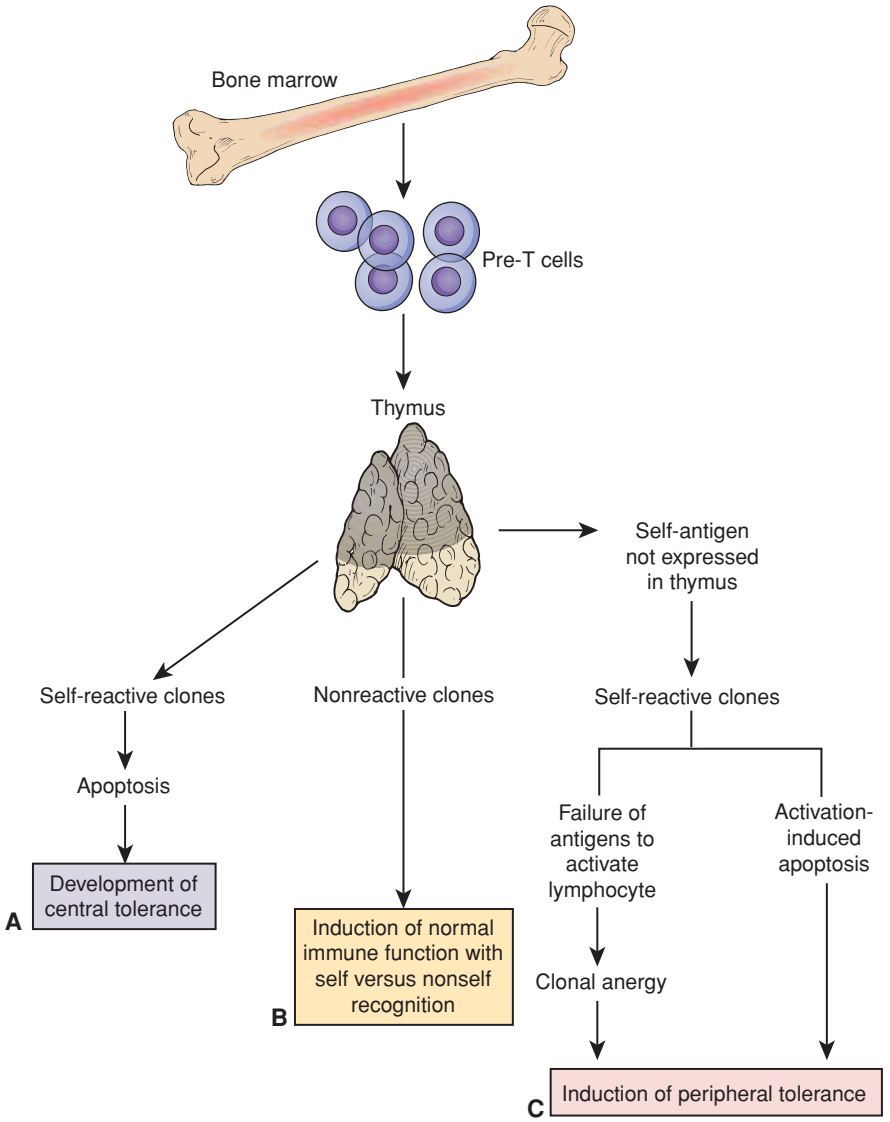


FIGURE 16-5. Development of immunologic tolerance. **(A)** Development of central tolerance with deletion of self-reactive T lymphocytes in the thymus. **(B)** Nonreactive lymphocytes with development of normal immune function. **(C)** Induction of peripheral tolerance in self-reactive cells that are not eliminated in the thymus.

from the T cells (e.g., by the blood-brain barrier) so that corresponding T cells remain *immunologically ignorant* of their presence.[20] In other cases, the autoreactive T cell encounters its corresponding antigen in the absence of the costimulatory signals that are necessary for its activation. The peripheral activation of T cells requires two signals: recognition of the peptide antigen in association with the MHC molecules on the APCs and a set of secondary costimulatory signals. Because costimulatory signals are not strongly expressed on most normal tissues, the encounter of the autoreactive T cells and their specific target antigens frequently results in anergy.[2]

Another mechanism involves the apoptotic death of autoreactive T cells.[20,21,24] This type of apoptosis is mediated by an apoptotic cell surface receptor (called Fas) that is present on the T cell and a soluble membrane messenger molecule (Fas ligand) that binds to the apoptotic receptor and activates the death program (see Chapter 2). The expression of the apoptotic Fas receptor is markedly increased in activated T cells; thus, coexpression of the Fas messenger molecule by the same cohort of activated autoreactive T cells may serve to induce their death.

Suppressor T cells with the ability to down-regulate the function of autoreactive T cells are also thought to play an essential role in peripheral T-cell tolerance. These cells are believed to be a distinct subset of $CD4^+$ and $CD8^+$ T cells.[25,26] The mechanism by which these T cells exert their suppressor function is unclear. They may secrete cytokines that suppress the activity of self-reactive immune cells, or they may delete the self-reactive T-cell clones.

Mechanisms of Autoimmune Disease

It is not known what triggers autoimmunity, but both inheritance and environmental factors appear to play a role. Gender may also play a role in the development of autoimmune disorders. A number of autoimmune disorders such as SLE occur more commonly in women than men, suggesting that estrogens may play a role in the development of autoimmune disease. Evidence suggests that estrogens stimulate and androgens suppress the immune response.[27,28] For example, estrogen stimulates a DNA sequence that promotes the production of interferon-γ, which is thought to assist in the induction of an autoimmune response.

Genetic Susceptibility

Genetic factors can increase the incidence and severity of autoimmune diseases, as shown by the familial clustering of several autoimmune diseases and the observation that certain inherited HLA types occur more frequently in persons with a variety of immunologic and lymphoproliferative disorders.[2,22,23] For example, 90% of persons with ankylosing spondylitis carry the HLA-B27 antigen, compared with 7% of persons without the disease.[2] Other HLA-associated diseases are Reiter syndrome and HLA-B27, rheumatoid arthritis and HLA-DR4, and SLE and HLA-DR3 (see Chapter 44). The molecular basis for these associations is unknown. Because autoimmunity does not develop in all persons with genetic predisposition, it appears that other factors such as a "trigger event" interact to precipitate the altered immune state. The event or events that trigger the development of an autoimmune response are unknown. It has been suggested that the "trigger" may be a virus or other microorganism, a chemical substance, or a self-antigen from a body tissue that has been hidden from the immune system during development.

Environmental Factors

Although environmental factors, such as infectious agents, appear to be involved in the pathogenesis of autoimmune disorders, their precise role in initiating or perpetuating the autoreactive response is largely unknown. Among the proposed mechanisms involved in loss of self-tolerance are breakdown of T-cell anergy, release of sequestered antigens, molecular mimicry, and superantigens.

Breakdown in T-Cell Anergy. *Anergy* is a state of unresponsiveness to antigen.[2] It involves the prolonged or irreversible inactivation of lymphocytes, such as that induced by an encounter with self-antigens. Activation of antigen-specific $CD4^+$ T cells requires two signals: (1) recognition of the antigen in association with class II MHC molecules on the surface of an antigen-presenting cell and (2) a set of costimulatory signals provided by the antigen-presenting cell. If the second costimulatory signal is not delivered, the T cell becomes anergic. Most normal tissues do not express the costimulatory molecules and thus are protected from autoreactive T cells. However, this protection can be broken if the normal cells that do not normally express the costimulatory molecules are induced to do so. Some inductions can occur after an infection or in situations where there is tissue necrosis and local inflammation.

Release of Sequestered Antigens. Normally the body does not produce antibodies against self-antigens. Thus, any self-antigen that was completely sequestered during development and then reintroduced to the immune system is likely to be regarded as foreign. Among the sequestered tissues that could be regarded as foreign are spermatozoa and ocular antigens such as those found in uveal tissue. Posttraumatic uveitis and orchiditis after vasectomy may fall into this category.

Changes in antigen structure or release of hidden antigens may also account for the persistence of autoimmune disorders. Once an autoimmune disorder has been induced, it tends to be progressive, sometimes with sporadic relapses and remissions. A possible mechanism for the persistence and evolution of autoimmunity is the phenomenon called *epitope spreading*.[2] Infections, and even the initial autoimmune episode, may expose self-antigens that have been hidden from the immune system. The result is continued activation of new lymphocytes that recognize the previously hidden epitopes.

Molecular Mimicry. Many autoimmune diseases are associated with infections, and clinical flare-ups are often preceded by infectious processes. One proposed link

between infections and autoimmunity is *molecular mimicry,* in which a microbe shares an immunologic epitope with the host.[29,30] In rheumatic fever and acute glomerulonephritis, for example, a protein in the cell wall of group A β-hemolytic streptococci has considerable similarity with antigens in heart and kidney tissue, respectively. After infection, antibodies directed against the microorganism cause a classic case of mistaken identity, which leads to inflammation of the heart or kidney. Not everyone exposed to group A β-hemolytic streptococci has an autoimmune reaction. The reason that only certain persons are targeted for autoimmune reactions to a particular self-mimicry molecule may be determined by differences in HLA types. The HLA type determines exactly which fragments of a pathogen are displayed on the cell surface for presentation to T cells. One individual's HLA may bind self-mimicry molecules for presentation to T cells, and another's HLA type may not. In the spondyloarthropathies, particularly Reiter syndrome and reactive arthritis, there is a clear relationship between arthritis and a prior bacterial infection, combined with the inherited HLA-B27 antigens.

Superantigens. Superantigens are a family of related substances, including staphylococcal and streptococcal exotoxins, that can short-circuit the normal sequence of events in an immune response, leading to inappropriate activation of $CD4^+$ helper T cells. Superantigens do not require processing and presentation of antigen by APCs to induce a T-cell response.[31] Instead, they are able to interact with a T-cell receptor outside the normal antigen-binding site. This distinctive mode of activation, together with the ability of superantigens to bind to a wide variety of MHC class II molecules, leads to activation of large numbers of T cells regardless of their MHC/peptide specificity. Superantigens are involved in several diseases, including food poisoning and toxic shock syndrome.

Diagnosis and Treatment of Autoimmune Disease

Suggested criteria for determining whether a disorder is an autoimmune disease are evidence of an autoimmune reaction, determination that the immunologic findings are not secondary to another condition, and lack of other identified causes for the disorder. Currently, the diagnosis of autoimmune disease is based primarily on clinical findings and serologic testing. In the future, it is likely that autoimmune disorders will be diagnosed by directly identifying the genes responsible for the condition.

The basis for most serologic assays is the demonstration of antibodies directed against tissue antigens or cellular components. For example, a child with a chronic or acute history of fever, arthritis, and a macular rash along with high levels of antinuclear antibody has a probable diagnosis of SLE. The detection of autoantibodies in the laboratory usually is accomplished by one of three methods: indirect fluorescent antibody assay (IFA), enzyme-linked immunosorbent assay (ELISA), or particle agglutination of some kind. The rationale behind each of these methods is similar: the patient's serum is diluted and allowed to react with an antigen-coated surface (i.e., whole, fixed cells for the detection of antinuclear antibodies). In the case of IFA and ELISA, a second "labeled" antibody is added, which binds to the patient's antibody and forms a visible reaction. Particle agglutination assays are much simpler—the binding of the patient's antibody to antigen-coated particles causes a visible agglutination reaction. For most serologic assays, the patient's serum is serially diluted until it no longer produces a visible reaction (e.g., 1:100 dilution). This is called a *positive titer.* Healthy persons sometimes have low titers of antibody against cellular and tissue antigens, but their titers usually are far lower than in patients with autoimmune disease.

Treatment of autoimmune disease is based on the tissue or organ that is involved, the effector mechanism involved, and the magnitude and chronicity of the effector processes. Ideally, treatment should focus on the mechanism underlying the autoimmune disorder. Corticosteroids and immunosuppressive drugs may be used to arrest or reverse the downhill course of some autoimmune disorders. Purging autoreactive cells from the immune repertoire, through the use of plasmapheresis, is also an option in some severe cases of autoimmunity.

Recent research has focused on the cytokines involved in the inflammatory response that accompanies many of the autoimmune disorders (e.g., interferon-β for multiple sclerosis and tumor necrosis factor-α [TNF-α] antibodies for rheumatoid arthritis and Crohn disease).

In summary, autoimmune diseases represent a disruption in self-tolerance that results in damage to body tissues by the immune system. Autoimmune diseases can affect almost any cell or tissue of the body. The ability of the immune system to differentiate self from nonself is called *self-tolerance.* Normally, self-tolerance is maintained through central and peripheral mechanisms that delete autoreactive B or T cells or otherwise suppress or inactivate immune responses that would be destructive to host tissues. Defects in any of these mechanisms could impair self-tolerance and predispose to development of autoimmune disease.

The ability of the immune system to differentiate foreign from self-antigens is the responsibility of HLA encoded by MHC genes. Antigen is presented to receptors of T cells in combination with MHC molecules. Among the possible mechanisms responsible for development of autoimmune disease are failure of T-cell–mediated immune suppression; aberrations in MHC–antigen–TCR interactions; molecular mimicry; and superantigens. The suggested criteria for determining that a disorder results from an autoimmune disorder are evidence of an autoimmune reaction, determination that the immunologic findings are not secondary to another condition, and lack of other identifiable causes for the disorder.

Immunodeficiency Disorders

Immunodeficiency can be defined as an abnormality in one or more branches of the immune system that renders a person susceptible to diseases normally prevented by an intact immune system. Two major categories of immune mechanisms defend the body against infectious or neoplastic disease: humoral or antibody-mediated immunity (i.e., B lymphocytes) and cell-mediated immunity (i.e., T lymphocytes and cytokines).

Abnormalities of the immune system can be classified as primary (i.e., congenital or inherited) or secondary if the immunodeficiency is acquired later in life. Secondary immunodeficiencies are more common than primary disorders of genetic origin. Secondary deficiencies in humoral immunity can develop as a consequence of selective loss of immunoglobulins through the gastrointestinal or genitourinary tracts. Secondary deficiencies of T-cell function have been described in conjunction with acute viral infections (e.g., measles virus, cytomegalovirus) and with certain malignancies (e.g., Hodgkin disease and other lymphomas). Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS; to be discussed) is the most devastating example of a secondary immunodeficiency. Regardless of the cause, primary and secondary deficiencies can produce the same spectrum of disease. The severity and symptomatology of the various disorders depend on the type and extent of the deficiency.

Primary Immunodeficiency Disorders

Until recently, little was known about the causes of primary immunodeficiency diseases. However, this has changed with recent advances in genetic technology.[1,32–35] To date, more than 100 primary immunodeficiency syndromes have been identified, and specific molecular defects have been identified in more than one third of these diseases.[32,35] Most are transmitted as recessive traits, several of which are caused by mutations in genes on the X chromosome and others by mutations on autosomal chromosomes. Many of these disorders have been traced to mutations affecting signaling pathways (e.g., cytokines and cytokine signaling, receptor subunits, and metabolic pathways) that dictate immune cell development and function. Furthermore, it has been shown that the immune system is a carefully balanced system that is designed to distinguish between self and nonself; therefore, symptoms of autoimmunity often are observed with primary immunodeficiency disease.[32]

Early detection is possible for most primary immunodeficiency diseases, is critical for the success of some treatments, and can be lifesaving. For infants with severe combined T- and B-cell immunodeficiency, early diagnosis is essential in terms of not only preventing life-threatening infections, but also preventing administration of live attenuated virus vaccines (e.g., measles, mumps, rubella, varicella), which could prove fatal.[32] The first clinical clue for diagnosis of primary immunodeficiency disease is usually a history of infections that are persistent, difficult to treat, or caused by unusual microbes. The Jeffrey Modell Foundation/Immune Deficiency Foundation has developed a set of warning signs that serve as an excellent tool for determining what should be considered abnormal (Chart 16-2).[36] Because these disorders are frequently inherited, a positive

Primary Immunodeficiency Disorders

- Primary immunodeficiency disorders are congenital or inherited abnormalities of immune function that render a person susceptible to diseases normally prevented by an intact immune system.
- Disorders of B-cell function impair the ability to produce antibodies and defend against microorganisms and toxins that circulate in body fluids (IgM and IgG) or enter the body through the mucosal surface of the respiratory or gastrointestinal tract (IgA). Persons with primary B-cell immunodeficiency are particularly prone to pyogenic infections due to encapsulated organisms.
- Disorders of T-cell function impair the ability to orchestrate the immune response ($CD4^+$ helper T cells) and to protect against viral ($CD8^+$ cytotoxic T cells), intracellular bacterial, fungal, and protozoan infections. T cells also play an important role in surveillance against oncogenic viruses and tumors; hence, persons with impaired T-cell function are at increased risk for certain types of cancers.
- Combined T-cell and B-cell immunodeficiency states affect all aspects of immune function. Severe combined immunodeficiency represents a life-threatening absence of immune function that requires bone marrow or stem cell transplantation for survival.

CHART 16-2 Ten Warning Signs of Primary Immunodeficiency

- Eight or more new ear infections within 1 year
- Two or more serious sinus infections within 1 year
- Two or more months on antibiotics with little effect
- Two or more pneumonias within 1 year
- Failure of an infant to gain weight or grow normally
- Recurrent, deep skin or organ abscesses
- Persistent thrush in mouth or elsewhere on skin, after 1 year of age
- Need for intravenous antibiotics to clear infections
- Two or more deep-seated infections
- A family history of primary immunodeficiency

From the Jeffrey Modell Foundation. (n.d.). [Online] Available: www.info4pi.org.

family history is also a key diagnostic tool. The type of infection can provide information regarding the type of defect that is present. Infections with bacterial organisms are frequently observed in cases of antibody deficiency, whereas severe viral, fungal, and opportunistic infections characterize T-cell deficiencies. Recurrent *Streptococcus pneumoniae* or *Neisseria* infections characterize persons with complement deficiencies, and recurrent infections with staphylococcal and other catalase-positive organisms indicate disorders of phagocytosis.

Humoral (B-Cell) Immunodeficiency Disorders

Of all the primary immunodeficiency diseases, those affecting antibody production and humoral immunity are the most common.[35] Antibody production depends on the differentiation of hematopoietic stem cells into mature B lymphocytes and the antigen-dependent generation of immunoglobulin-producing plasma cells[37,38] (Fig. 16-6). This maturation cycle initially involves the production of surface IgM, migration from the bone marrow to the peripheral lymphoid tissue, and switching to the production of specialized IgM-, IgA-, IgD-, IgE-, or IgG-secreting plasma cells after antigenic stimulation. Primary humoral immunodeficiency disorders can interrupt the production of one or all of the immunoglobulins.

Defects in humoral immunity increase the risk of recurrent pyogenic infections, including those caused by *S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and gram-negative organisms such as *Pseudomonas* species. Humoral immunity usually is not as important in defending against intracellular bacteria (mycobacteria), fungi, and protozoa. Viruses usually are handled normally, except for the enteroviruses that cause gastrointestinal infections.

Transient Hypogammaglobulinemia of Infancy. During the first few months of life, infants are protected from infection by IgG antibodies that have been transferred from the maternal circulation during fetal life. IgA, IgM, IgD, and IgE do not normally cross the placenta. The presence of elevated levels of IgA or IgM in the infant cord blood suggests premature antibody production in response to an intrauterine infection. An infant's level of maternal IgG gradually declines over a period of approximately 6 months (see Chapter 15, Fig. 15-14). Concomitant with the loss of maternal antibody, the infant's immature humoral immune system begins to function, and between the ages of 1 and 2 years, the child's antibody production reaches adult levels.

Any abnormality that interferes with the production of immunoglobulin-producing plasma cells can produce a state of immunodeficiency. For example, certain infants may experience a delay in IgG production (IgM and IgA levels are normal) beyond 6 months of age. The total number and antigenic response of circulating B cells are normal, but the chemical communication between B and T cells that leads to clonal proliferation of antibody-producing plasma cells seems to be reduced.[35] This condition is referred to as *transient hypogammaglobulinemia of infancy.* The result of this condition usually is limited to repeated bouts of upper respiratory and middle ear infections. This condition usually resolves by the time the child is 2 to 4 years of age.

X-Linked Agammaglobulinemia. X-linked (Bruton) agammaglobulinemia is a recessive trait that affects only boys.[32–35,37,39] As the name implies, persons with this disorder have essentially undetectable levels of all serum immunoglobulins. Therefore, they are susceptible to meningitis and recurrent otitis media and to sinus and pulmonary infections with encapsulated organisms such as *S. pneumoniae, H. influenzae* type b, *S. aureus,* and *Neisseria meningitidis.*[33]

The abnormal gene in X-linked agammaglobulinemia maps to the long arm of the X chromosome and encodes

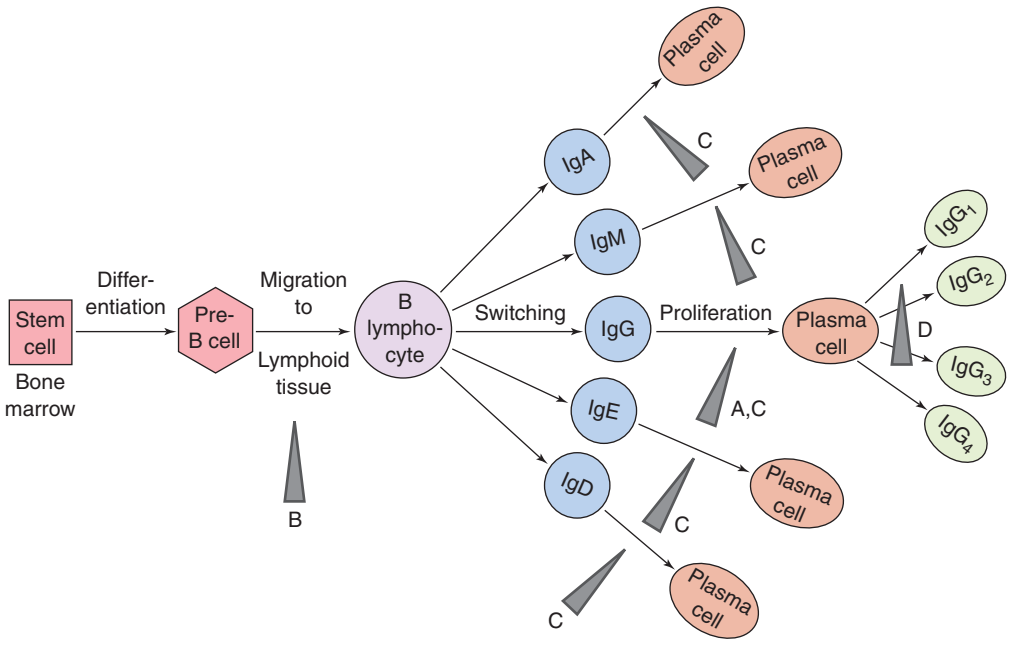


FIGURE 16-6. Stem cells to mature immunoglobulin-secreting plasma cells. *Arrows* indicate the stage of the maturation process that is interrupted in **(A)** transient hypogammaglobulinemia, **(B)** X-linked agammaglobulinemia, **(C)** common variable immunodeficiency, and **(D)** IgG subclass deficiency.

the B-cell protein tyrosine kinase (Bruton tyrosine kinase [*Btk*]). *Btk* appears to be necessary for pre–B-cell expansion and maturation into surface immunoglobulin-expressing B cells, but probably has a role in all stages of B-cell development. Mutation in the *Btk* gene results in an absence of mature circulating B cells and plasma cells. T lymphocytes, however, are normal in number and function.

Most boys with the disorder remain asymptomatic until 6 to 9 months of life because of the presence of maternal antibodies. A clue to the presence of the disorder is the failure of an infection to respond completely and promptly to antibiotic therapy. Diagnosis is based on demonstration of low or absent serum immunoglobulins. Therapy consists of prophylaxis with intravenous immunoglobulin (IVIG) and prompt antimicrobial therapy for suspected infections. The prognosis of this condition depends on the prompt recognition and treatment of infections. Chronic pulmonary disease is an ever-present danger.

Common Variable Immunodeficiency. Another disorder of B-cell maturation, which is similar to X-linked agammaglobulinemia, is a condition called *common variable immunodeficiency* (CVID). In this syndrome, the terminal differentiation of mature B cells to plasma cells is blocked.[37,38] More than 80% of persons with this disorder have a normal number of B lymphocytes, but when the lymphocytes are presented with antigen, they fail to differentiate into antibody-secreting cells.[38] Some persons may also have increased apoptosis of helper T cells and decreased T-cell function and signaling.

The symptomatology of CVID is similar to that of X-linked agammaglobulinemia (i.e., recurrent otitis media and sinus and pulmonary infections with encapsulated organisms), but the onset of infections occurs much later, usually between the ages of 15 and 35 years. In contrast to X-linked agammaglobulinemia, the sex distribution in CVID is almost equal. Most persons with CVID have no identified molecular diagnosis. Because the disorder occurs in first-degree relatives of persons with IgA deficiency, and some persons with IgA deficiency develop agammaglobulinemia, these disorders may have a common genetic basis.

Persons with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes, and approximately 25% have splenomegaly.[35] They have an increased tendency toward development of interstitial lung disease, autoimmune disorders, hepatitis, and chronic diarrhea with associated intestinal malabsorption. There is also an increased risk of gastric cancer and non-Hodgkin B-cell lymphoma.

Treatment methods for CVID are similar to those used for X-linked agammaglobulinemia, with IVIG being the cornerstone of therapy. Anaphylaxis to IgA in the IVIG can occur in persons with CVID who are IgA deficient. The use of IgA-depleted IVIG has greatly reduced this risk.

Selective Immunoglobulin A Deficiency. Selective IgA deficiency is the most common type of immunoglobulin deficiency, affecting 1 in 400 to 1 in 1000 persons.[34] The syndrome is characterized by moderate to marked reduction in levels of serum and secretory IgA. It is likely that the cause of this deficiency is a block in the pathway that promotes terminal differentiation of mature B cells to IgA-secreting plasma cells. The occurrence of IgA deficiency in both men and women and in members of successive generations within families suggests autosomal inheritance with variable expressivity. The disorder has also been noted in persons treated with certain drugs (e.g., phenytoin, sulfasalazine), suggesting that environmental factors may trigger the disorder.[35]

Approximately two thirds of persons with selective IgA deficiency have no overt symptoms, presumably because IgG and IgM levels are normal and compensate for the defect. At least 50% of affected children overcome the deficiency by the age of 14 years. Persons with markedly reduced levels of IgA often experience repeated upper respiratory and gastrointestinal infections and have an increased incidence of allergic manifestations, such as asthma, and autoimmune disorders. Persons with IgA deficiency also can develop antibodies against IgA, which can lead to severe anaphylactic reactions when blood components containing IgA are given.[5] Therefore, only specially washed erythrocytes from normal donors or erythrocytes from IgA-deficient donors should be used.

There is no treatment available for selective IgA deficiency unless there is a concomitant reduction in IgG levels. Administration of IgA immune globulin is of little benefit because IgA has a short half-life and is not secreted across the mucosa. There also is the risk of anaphylactic reactions associated with IgA antibodies in the immune globulin.

Immunoglobulin G Subclass Deficiency. An IgG subclass deficiency can affect one or more of the IgG subtypes, despite normal levels or elevated serum concentrations of IgG. As discussed in Chapter 15, IgG immunoglobulins can be divided into four subclasses (IgG_1 through IgG_4) based on structure and function. Most circulating IgG belongs to the IgG_1 (70%) and IgG_2 (20%) subclasses. In general, antibodies directed against protein antigens belong to the IgG_1 and IgG_3 subclasses, and antibodies directed against carbohydrate and polysaccharide antigens are primarily IgG_2 subclass. As a result, persons who are deficient in IgG_2 subclass antibodies can be at greater risk for development of sinusitis, otitis media, and pneumonia caused by polysaccharide-encapsulated microorganisms such as *S. pneumoniae, H. influenzae* type b, and *N. meningitidis*.

Children with mild forms of the deficiency can be treated with prophylactic antibiotics to prevent repeated infections. IGIV can be given to children with severe manifestations of this deficiency. The use of polysaccharide vaccines conjugated to protein carriers can provide protection against some of these infections, rather than the protein conjugated to protein carriers that would stimulate an IgG_1 response.

Cellular (T-Cell) Immunodeficiency Disorders

Unlike B cells, in which a well-defined series of differentiation steps ultimately leads to the production of immunoglobulins, mature T lymphocytes consist of

distinct subpopulations whose immunologic assignments are diverse. T cells can be functionally divided into two subtypes ($CD4^+$ helper and $CD8^+$ cytotoxic T cells). Collectively, T lymphocytes protect against fungal, protozoan, viral, and intracellular bacterial infections; control malignant cell proliferation; and are responsible for coordinating the overall immune response.

In general, persons with cell-mediated immunodeficiency disorders have infections or other clinical problems that are more severe than those seen with antibody disorders. Children with defects in this branch of the immune response rarely survive beyond infancy or childhood unless immunologic reconstitution is achieved through bone marrow transplantation.[35] However, exceptions are being recognized as newer T-cell defects, such as the X-linked hyper-IgM syndrome, are identified. Other recently identified primary T-cell immunodeficiency disorders result from defective expression of the TCR complex, defective cytokine production, and defects in T-cell activation.

For children with potentially fatal forms of T-cell defects, transplantation of thymic tissue or MHC-compatible bone marrow is currently the treatment of choice.[34] Stem cell transplantation, an alternative to bone marrow transplantation, has also proved useful in treating some disorders. The major risk to recipients of bone marrow transplantation is that of graft-versus-host disease. Gene replacement therapy remains a distant goal for most immunodeficiencies at present. The main obstacles to this type of therapy are purifying self-renewing stem cells, which are the ideal target for introduction of the replacement gene, and lack of methods for introducing the genes into the stem cell.

Thymic Hypoplasia: DiGeorge Syndrome. DiGeorge syndrome stems from an embryonic developmental defect. The defect is thought to occur before the 12th week of gestation, when the thymus gland, parathyroid gland, and parts of the head, neck, and heart are developing. The disorder affects both sexes. Because familial occurrence is rare, it seems unlikely that the disorder is inherited. Formerly thought to be caused by a variety of factors, including extrinsic teratogens, this defect has been traced to microdeletion of specific deoxyribonucleic acid (DNA) sequences from chromosome 22 (22q11).[35,39]

Infants born with this defect have partial or complete failure in development of the thymus and parathyroid glands and have congenital defects of the head, neck, and heart. The extent of immune and parathyroid abnormalities is highly variable, as are the other defects. Occasionally, a child has no heart defect. In some children, the thymus is not absent but is in an abnormal location and is extremely small. These infants can have partial DiGeorge syndrome, in which hypertrophy of the thymus occurs with development of normal immune function. The facial disorders can include hypertelorism (i.e., increased distance between the eyes); micrognathia (i.e., abnormally small jaw); low-set, posteriorly angulated ears; split uvula; and high-arched palate (Fig. 16-7). Urinary tract abnormalities also are common. The most frequent presenting sign is hypocalcemia and tetany that develop in the first 24 hours of life. It is caused by the absence of the parathyroid gland and is resistant to standard therapy.

FIGURE 16-7. An infant with DiGeorge syndrome. The surgical scar on the chest indicates repair of heart disease caused by truncus arteriosus or interrupted aortic arch, which is common in this syndrome. The infant also has the facial features of a child with DiGeorge syndrome, as illustrated by hypertelorism, low-set ears, hypoplastic mandible, and bowing upward of the upper lip. (From Roberts R. *Atlas of infectious diseases.* Edited by Gerald Mandell (series editor), Catherine M. Wilfert. © 1998 Current Medicine, Inc.)

Children who survive the immediate neonatal period may have recurrent or chronic infections because of impaired T-cell immunity. Children also may have an absence of immunoglobulin production, caused by a lack of helper T-cell function. For children who do require treatment, thymus transplantation can be performed to reconstitute T-cell immunity. Bone marrow transplantation also has been successfully used to restore normal T-cell populations. If blood transfusions are needed, as during corrective heart surgery, special processing is required to prevent graft-versus-host disease.

Hyper-IgM Syndrome. The X-linked immunodeficiency of hyper-IgM, also known as the *hyper-IgM syndrome,* is characterized by low IgG and IgA levels with normal or,

more frequently, high IgM concentrations. Being X-linked, the disorder is confined to boys. Formerly classified as a B-cell defect, it now has been traced to a T-cell defect. The disorder results from the inability of T cells to signal B cells to undergo isotype switching to IgG and IgA; thus, they produce only IgM.[39] Although the disorder was identified on the basis of an antibody defect, its primary cause is a defect in cell-mediated immunity.

Like boys with X-linked agammaglobulinemia, affected boys become symptomatic during the first and second years of life. They have recurrent pyogenic infections, including otitis media, sinusitis, tonsillitis, and pneumonia. They are also susceptible to opportunistic infections, especially *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), because of the defect in cell-mediated immunity. Persons with the syndrome are also at increased risk for development of autoimmune diseases of the formed elements of the blood, including hemolytic anemia, thrombocytopenia, and recurrent severe neutropenia.[39]

Combined T-Cell and B-Cell Immunodeficiency Disorders

Disorders that affect both B and T lymphocytes, with resultant defects in both humoral and cell-mediated immunity, fall under the broad classification of combined immunodeficiency syndrome (CIDS). A single mutation in any one of the many genes that influence lymphocyte development or response, including lymphocyte receptors, cytokines, or MHC antigens, could lead to combined immunodeficiency. Regardless of the affected gene, the net result is a disruption in the normal communication system between B and T lymphocytes and deregulation of the immune response. The spectrum of disease resulting from combined immunodeficiency disorders ranges from mild to severe to ultimately fatal forms.

Severe Combined Immunodeficiency Disorders. Combined B-cell and T-cell immunodeficiency disorders account for approximately 20% of primary immunodeficiency disorders. In the most pronounced forms of the disorder, often referred to as *severe combined immunodeficiency* (SCID), genetic mutations lead to absence of all T- and B-cell function and, in some cases, a lack of NK cells.[35,40,41] Affected infants have a disease course that resembles AIDS, with failure to thrive, chronic diarrhea, and opportunistic infections. Survival beyond the first year of life is rare without prompt immune reconstitution through bone marrow or hematopoietic stem cell transplantation. Early diagnosis is critical because the chances of successful treatment are highest in infants who have not experienced severe opportunistic infections. Both X-linked and autosomal recessive inheritances are involved.

The most common form of SCID, accounting for half of all cases, is X-linked, and hence SCID is more common in boys than girls. It is caused by a genetic defect in a transmembrane receptor that is responsible for proliferation of T-lymphocyte precursors.[41] These mutations are recessive, so that heterozygous girls are usually normal carriers of the gene, whereas boys who inherit the abnormal chromosome manifest the disease. Children with this disorder appear similar to those with other forms of SCID except for having uniformly low percentages of T and NK cells and an elevated percentage of B cells. However, the B cells do not produce immunoglobulin in a normal manner because of a lack of T-cell help.

The remaining cases of SCID show an autosomal recessive pattern of inheritance, with approximately half of these caused by mutations in adenine deaminase (ADA), an enzyme involved in purine metabolism.[41,42] ADA deficiency results in accumulation of adenine and deoxyadenosine triphosphate metabolism, both of which inhibit DNA synthesis and are toxic to lymphocytes. Infants with ADA-deficiency SCID usually have a much more profound lymphopenia than do infants with other forms of SCID, often manifesting as absolute lymphocyte counts of less than 500/mm^3. The absolute numbers of both T and B cells are very low. Although the number of NK cells is low, their function is normal. Other distinguishing features of ADA deficiency include the presence of rib cage deformity and numerous skeletal deformities. Bone marrow transplantation has been successful in treating children with ADA-deficiency SCID.[35,40] Enzyme replacement therapy also may be used in the management of persons with this form of SCID. However, it should not be used if bone marrow transplantation is anticipated because it can predispose to graft rejection.[35,40]

Immune Deficiency with Thrombocytopenia and Eczema: Wiskott-Aldrich Syndrome. Wiskott-Aldrich syndrome is an X-linked recessive disorder characterized by thrombocytopenia, eczema, and marked susceptibility to bacterial infections.[2,43] Bleeding episodes or symptoms due to infection usually begin within the first 6 months of life. Abnormalities of humoral immunity include decreased serum levels of IgM and markedly elevated serum IgA and IgE concentrations. T-cell dysfunction initially is mild but progressively deteriorates, and children with the disorder become increasingly susceptible to development of malignancies of the mononuclear phagocytic system, including Hodgkin lymphoma and leukemia. Children with Wiskott-Aldrich syndrome typically are unable to produce antibody to polysaccharide antigens and therefore are susceptible to infections caused by encapsulated microorganisms. They also are prone to septicemia and meningitis caused by these organisms. Varicella infection can be lethal to children with this condition.

Management of children with Wiskott-Aldrich syndrome focuses on treatment of eczema, control of infections, and management of bleeding episodes. If an infection is suspected, careful evaluation for bacterial, viral, and fungal causes followed by administration of appropriate antimicrobial therapy is required. Bone marrow transplantation has been successful in children with Wiskott-Aldrich syndrome. Splenectomy, sometimes recommended for children with thrombocytopenia, effectively stops the bleeding episodes but increases the risk of septicemia.[43]

Acquired Immunodeficiency Syndrome

AIDS is a disease caused by infection with HIV and is characterized by profound immunosuppression with associated opportunistic infections, malignancies, wasting, and central nervous system degeneration. HIV is a retrovirus that selectively attacks the $CD4^+$ T lymphocytes, the immune cells responsible for orchestrating and coordinating the immune response to infection. As a consequence, persons with HIV infection have a deteriorating immune system, and thus are more susceptible to severe infections with ordinarily harmless organisms.

Because the disease affects an exceptionally high proportion of the population throughout the world, it is often referred to as a *pandemic*. As a national and global epidemic, the degree of morbidity and mortality caused by HIV, as well as its impact on health care resources and the economy, is tremendous and unrelenting. In 2007 alone, it was estimated that there were nearly 33 million people worldwide living with HIV/AIDS and 2 million people died of HIV-related causes.[44] During the same year, 2.7 million people were newly infected with HIV, with women and young people (i.e., those 15 to 24 years of age) accounting for nearly 50% of the infections. Because the reporting of cases is not uniform throughout the world, many countries may not be accurately represented in this number.[44]

Transmission of HIV Infection

HIV is transmitted through conditions that facilitate the exchange of blood or body fluids that contain the virus or virus-infected cells.[2,3,45,46] The major routes of transmission of HIV infection are sexual contact; contaminated blood, either through sharing needles or syringes used for illicit drugs; or passage from infected mothers to their newborns. It is estimated that more than 90% of children living with HIV acquired the virus in utero, during the birth process, or through breast-feeding (to be discussed).[44] HIV is not transmitted through casual contact. Several studies involving more than 1000 uninfected, nonsexual household contacts with persons with HIV infection (including siblings, parents, and children) have shown no evidence of casual transmission.[47]

Sexual contact is the most frequent mode of HIV transmission. There is a risk of transmitting HIV when semen or vaginal fluids come in contact with a part of the body that lets them enter the bloodstream. This can include the vaginal mucosa, anal mucosa, and wounds or sores on the skin. Condoms are highly effective in preventing the transmission of HIV. Unprotected sex between men is still the main mode of transmission in both Canada and the United States (40% of new HIV cases in Canada in 2006 and 53% in the United States in 2005).[44] During the same years, 32% of newly diagnosed HIV/AIDS cases in the United States and 33% of newly diagnosed cases in Canada were attributable to high-risk heterosexual intercourse.[44] However, in Canada, a substantial proportion of those infections were in people born in countries with a high HIV prevalence.

Intact mucosal surfaces represent a significant barrier to HIV infection. Thus, the risk of HIV infection is increased in the presence of genital ulcerative sexually transmitted infections (STIs; i.e., syphilis, herpes simplex virus infection, and chancroid) and nonulcerative STIs (i.e., gonorrhea, chlamydial infection, and trichomoniasis).[46] HIV also increases the duration and recurrence of STI lesions, treatment failures, and atypical presentation of genital ulcerative diseases because of the suppression of the immune system.

Because HIV is found in blood, the use of needles, syringes, and other drug injection paraphernalia is a direct route of transmission. Transmission by multiple use of contaminated injecting equipment accounted for almost 20% of newly diagnosed cases of HIV infection in the United States (18% in 2005) and Canada (19% in 2006).[44] Although alcohol, cocaine, and other noninjected drugs do not directly transmit infection, their use alters perception of risk and reduces inhibitions about engaging in behaviors that pose a high risk of transmitting HIV infection.

Transfusions of whole blood or blood products, such as clotting factors, used in treatment of hemophilia before 1985 resulted in the transmission of HIV. Since 1985, all blood donations in the United States have been screened for HIV, so this is no longer a transmission risk.[2] Currently, all donated blood and plasma are screened for antibody to HIV and HIV-associated p24 antigen (detectable before the development of antibodies). The U.S. Food and Drug Administration (FDA) requires blood collection centers to screen potential donors through interviews designed to identify behaviors known to present a risk for HIV infection. In addition, nucleic acid amplification testing (NAAT) of blood donors has reduced the risk of transfusion transmission of HIV and hepatitis C virus to approximately 1 in 2 million blood units.[48] Although HIV infection devastated the adult hemophiliac population early in the AIDS epidemic, the availability of recombinant clotting factors and changes in processing of plasma-derived products have eliminated this risk.

Occupational HIV infection among health care workers is uncommon. Universal Blood and Body Fluid Precautions should be used in encounters with all patients in the health care setting because HIV status is not always known. Occupational risk of infection for health care workers most often is associated with percutaneous

The AIDS Epidemic and Transmission of HIV

- AIDS is caused by HIV.
- HIV is transmitted through blood, semen, vaginal fluids, and breast milk.
- Persons with HIV infection are infectious even when asymptomatic.

inoculation (i.e., needle stick) of blood from a patient with HIV infection. Transmission is associated with the size of the needle, amount of blood present, depth of the injury, type of fluid contamination, stage of illness of the patient, and viral load of the patient. The average risk for HIV infection from percutaneous exposure to HIV-infected blood is about 0.3%, and about 0.09% after a mucous membrane exposure.[49]

The HIV-infected person is infectious even when no symptoms are present. The point at which an infected person converts from being negative for the presence of HIV antibodies in the blood to being positive is called *seroconversion*. Seroconversion typically occurs within 1 to 3 months after exposure to HIV, but can take up to 6 months. Recent data suggest that 50% of transmissions occur during primary HIV infection and early HIV infection.[50] The time after infection and before seroconversion is known as the *window period*. During the window period, a person's HIV antibody test result will be negative but he or she can still transmit the virus.

Molecular and Biologic Features of HIV Infection

The primary etiologic agent of AIDS is HIV, an enveloped ribonucleic acid (RNA) retrovirus that carries its genetic material in RNA rather than DNA. Two genetically different but antigenically related forms of HIV, HIV-1 and HIV-2, have been isolated in people with AIDS.[1–3] HIV-1 is the type most commonly associated with AIDS in the United States, Europe, and central Africa, whereas HIV-2 causes a similar disease principally in western Africa. HIV-2 appears to be transmitted in the same manner as HIV-1; it can also cause immunodeficiency as evidenced by a reduction in the number of $CD4^+$ T cells and the development of AIDS. Although the spectrum of disease for HIV-2 is similar to that of HIV-1, it spreads more slowly and causes disease more slowly than HIV-1. Specific tests are now available for HIV-2, and blood collected for transfusion is routinely screened for HIV-2. The remaining discussion focuses on HIV-1, but the information is generally applicable to HIV-2 as well.

HIV infects a limited number of cell types in the body, including $CD4^+$ T lymphocytes, macrophages, and dendritic cells (see Chapter 15). The $CD4^+$ T cells are necessary for normal immune function. Among other functions, the $CD4^+$ T cell recognizes foreign antigens and helps activate antibody-producing B lymphocytes. The $CD4^+$ T cells also orchestrate cell-mediated immunity, in which cytotoxic $CD8^+$ T cells and NK cells directly destroy virus-infected cells, tubercle bacilli, and foreign antigens. The phagocytic function of monocytes and macrophages is also influenced by $CD4^+$ T cells.

The HIV virion is spherical and contains an electron-dense core surrounded by a lipid envelope[1–3] (Fig. 16-8A). The virus core contains the major capsid protein p24, two copies of the genomic RNA, and three viral enzymes (protease, reverse transcriptase, and integrase). Because p24 is the most readily detected antigen, it is the target for the antibodies used in screening for HIV infection. The viral core is surrounded by a matrix protein called *p17*, which lies beneath the viral envelope. The viral envelope is studded with two viral glycoproteins, gp120 and gp41, which are critical for the infection of cells.

Pathophysiology of HIV/AIDS

- HIV is a retrovirus that destroys the body's immune system by taking over and destroying $CD4^+$ T cells.
- In the process of taking over the $CD4^+$ T cell, the virus attaches to receptors on the $CD4^+$ cell, fuses to and enters the cell, incorporates its RNA into the cell's DNA, and then uses the $CD4^+$ cell's DNA to reproduce large amounts of HIV, which are released into the blood.
- The three phases of HIV are primary HIV acute infection; latency, during which there are no signs or symptoms of disease; and overt AIDS, during which the $CD4^+$ cell count falls to low levels and signs of opportunistic infections and other disease manifestations develop.
- As the $CD4^+$ T-cell count decreases, the body becomes susceptible to opportunistic infections.

Replication of HIV occurs in eight steps[2,3] (see Fig. 16-8B). Each of these steps provides insights into the development of methods used for preventing or treating the infection. The *first step* involves the binding of the virus to the $CD4^+$ T cell. Once HIV has entered the bloodstream, it attaches to the surface of a $CD4^+$ T cell by binding to the CD4 molecule, which acts as a high-affinity receptor for the virus. This process is known as *attachment*. However, attaching to the CD4 molecule is not sufficient for infection; the virus must also bind with other surface molecules (chemokine coreceptors, such as CCR5 and CXCR4) that bind the gp120 and gp41 envelope glycoproteins. The chemokine coreceptors are critical components of the HIV infection process: the virus can only infect cells expressing $CD4^+$ and the coreceptors. It has been reported that people with defective coreceptors are more resistant to development of HIV infection, despite repeated exposure.[51] Research aimed at developing coreceptor-targeted viral entry inhibitors raises new hope for bridging the gap toward a cure of HIV infection.

The *second step* of the replication process allows for internalization of the virus. After attachment, the viral envelope peptides fuse to the $CD4^+$ T-cell membrane. Fusion results in an *uncoating* of the virus, allowing the contents of the viral core (the two single strands of viral RNA and the reverse transcriptase, integrase, and protease enzymes) to enter the host cell. The *third step* consists of DNA synthesis. In order for HIV to reproduce, it must change its RNA into DNA. It does this by using the *reverse transcriptase* enzyme. Reverse transcriptase makes a copy of the viral RNA, and then in reverse makes a complementary DNA (cDNA) strand. The result is a double-stranded

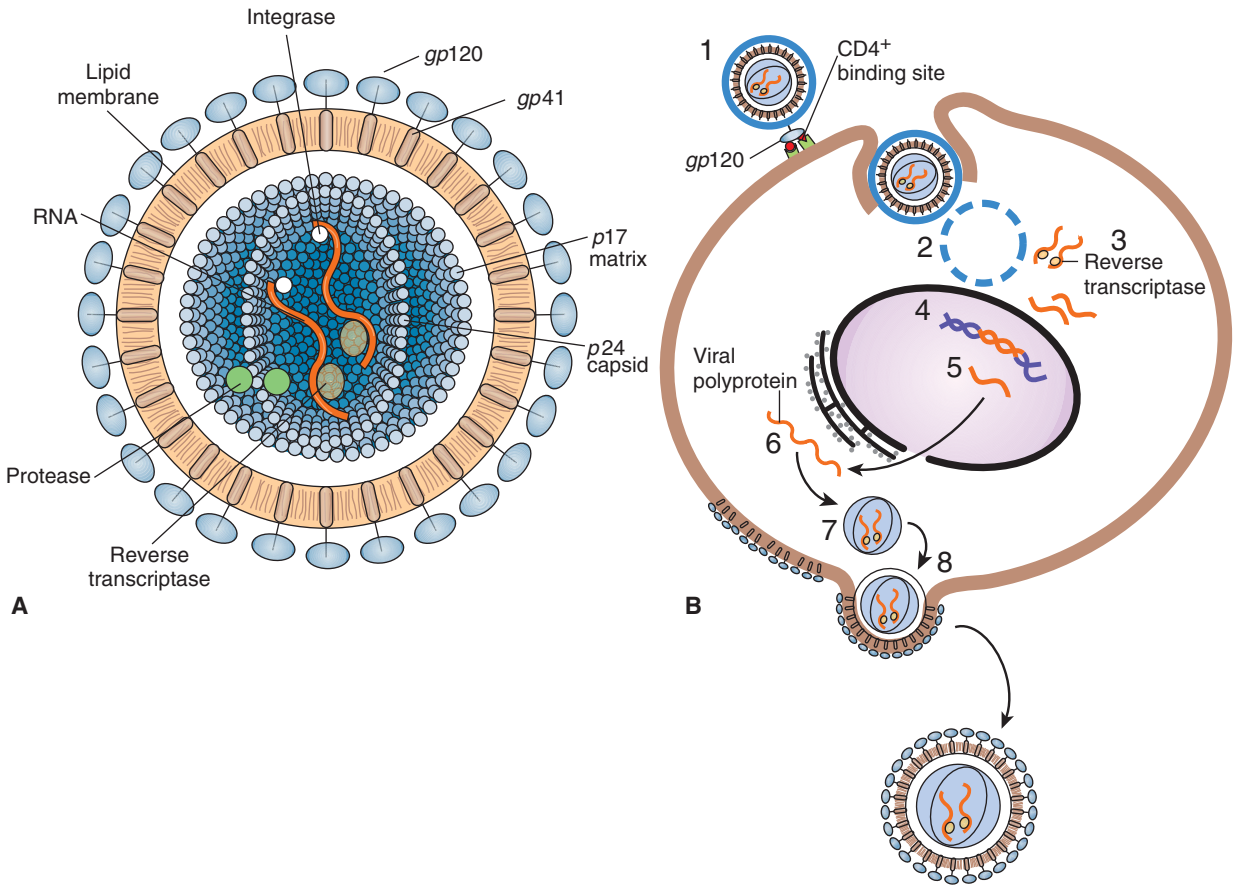


FIGURE 16-8. **(A)** Structure of the human immunodeficiency virus (HIV). **(B)** Life cycle of HIV-1. (*1*) Attachment of the HIV virus to $CD4^+$ T-cell receptor; (*2*) internalization and uncoating of the virus with viral RNA and reverse transcriptase; (*3*) reverse transcription, which produces a mirror image of the viral RNA and double-stranded DNA molecule; (*4*) integration of viral DNA into host DNA using the integrase enzyme; (*5*) transcription of the inserted viral DNA to produce viral messenger RNA; (*6*) translation of viral messenger RNA to create viral polyprotein; (*7*) cleavage of viral polyprotein into individual viral proteins that make up the new virus; and (*8*) assembly and release of the new virus from the host cell.

DNA that carries instructions for viral replication. In quiescent T cells, the proviral cDNA may remain in the cytoplasm in a linear extrachromosomal form.

The *fourth step* is called *integration*. In dividing cells, the cDNA enters the nucleus and becomes part of the $CD4^+$ T cell and, with the help of the enzyme integrase, is inserted into the cell's original DNA. The integrated virus is called a *provirus*. The *fifth step* involves *transcription* of the double-stranded viral DNA to form a single-stranded messenger RNA (mRNA) with the instructions for building new viruses. Transcription involves activation of the T cell and induction of host cell transcription factors. Alternatively, the provirus may remain nontranscribed within infected cells for months or years, hidden from the host's immune system and even from antiviral therapies. Long-lived reservoirs of HIV are established within the first month of acute infection.[46] These reservoirs of latently infected cells do not spontaneously produce virus unless activated. Their long life span constitutes one of the main barriers to HIV eradication by current antiviral therapies.

The *sixth step* includes translation of the viral mRNA. During *translation,* ribosomal RNA (rRNA) uses the instructions in the mRNA to create a chain of proteins and enzymes called a *polyprotein*. These polyproteins contain the components needed for the next stages in the construction of new viruses. The *seventh step* is called *cleavage*. During cleavage, the protease enzyme cuts the polyprotein chain into the individual core proteins that will make up the new viruses. Finally, during the *eighth step,* the core proteins migrate to the cell membrane, where they acquire a lipid envelope that buds off from the cell membrane. Productive infections, associated with extensive viral budding, lead to cell death.[2] It is important to note that although HIV can infect resting cells, the initiation of transcription and viral replication occurs only when the infected cell is activated by exposure to antigens or cytokines.

Within 72 hours of a transmission event, local virus replication occurs at the site of infection and the draining lymph nodes.[46] Infection becomes systemic by the end of the first week, as the virus disseminates to other lymphoid tissue compartments. By day 10 after infection, most circulating $CD4^+$ T cells have either been infected or interacted with HIV. The availability and rapid consumption of

targets during this early period leads to massive viral replication, accounting in part for the high levels of viremia and genital shedding achieved by the end of the first month. Once infection has become truly systemic, virus loads grow exponentially, with doubling time of approximately 0.3 days during the first 2 to 3 weeks of infection.

The problem is that over years, the $CD4^+$ T-cell count gradually decreases through this process, and the number of viruses detected in the blood of persons infected with HIV increases. The depletion of $CD4^+$ T cells after infection is due to the cytopathic effect of the virus, resulting from production of viral particles, as well as death of unaffected cells. Other infected cells, such as macrophages and dendritic cells, may also die, resulting in destructive changes in the lymphoid organs. Until the $CD4^+$ T-cell count falls to a very low level, a person infected with HIV can remain asymptomatic, although active viral replication is still taking place and serologic tests can identify antibodies to HIV. These antibodies, unfortunately, do not convey protection against the virus. Although symptoms are not evident, the infection proceeds on a microbiologic level, including the invasion and selective destruction of $CD4^+$ T cells. The continual decline of $CD4^+$ T cells, which are pivotal cells in the immune response, strips the person with HIV of protection against common organisms and cancerous cells.

Classification and Stages of HIV Infection

HIV Infection and AIDS Case Definition Classification. The definitions and classification systems for HIV and AIDS have been evolving since the beginning of the HIV epidemic, due in part to improvements in diagnostic and therapeutic capabilities, including increased use of new HIV-testing technologies. In 1993, the Centers for Disease Control and Prevention (CDC) implemented a classification system for HIV infection and an AIDS case definition for adolescents and adults that emphasized the clinical importance of the $CD4^+$ T-cell count.[52] The 1993 classification system, which was revised in 2008, defined three categories that corresponded to $CD4^+$ T-cell counts per microliter (μL) of blood: *category 1:* >500 cells/μL, *category 2:* 200 to 499 cells/μL, and *category 3:* <200 cells/μL. This system also included three clinical categories: *category A* that included persons who are asymptomatic or had persistent generalized lymphadenopathy or symptoms of primary HIV infection (i.e., acute seroconversion illness); *category B* that included persons with symptoms of immune deficiency not serious enough to be AIDS defining; and *Clinical category C* that included persons with AIDS-defining illnesses listed in the AIDS surveillance case definition shown in Chart 16-3.[52]

The 2008 revised CDC classification system, which requires laboratory-confirmed evidence of HIV infection, has been greatly simplified.[54] It highlights the central importance of the $CD4^+$ T-cell count and percentages, which are objective measures of immunosuppression routinely used in the care of HIV-infected persons (Table 16-2). It has also eliminated the A, B, and C clinical categories, because they include many conditions that are not discrete diseases, are not necessarily associated with immunodeficiency, and poorly match current treatment measures. The three $CD4^+$ T-cell categories used in the 1993 system have been renamed for the stages of HIV infection, increasing from stage 1 through stage 3 (AIDS). An undetermined stage has also been included.

CHART 16-3 Conditions Included in the 1993 AIDS Surveillance Case Definition

Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive*
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcer(s) (>1 month's duration) or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium-intracellulare complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary* or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent*
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of the brain
Wasting syndrome due to HIV

*Added to the 1993 expansion of the AIDS surveillance case definition.

(Centers for Disease Control and Prevention. [1992]. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report* 41[RR-17], 19.)

Stages of HIV Infection. The typical course of HIV infection is defined by three phases, which usually occur over a period of 8 to 12 years. The three phases are the primary infection phase, chronic asymptomatic or latency phase, and overt AIDS phase (Fig. 16-9).[52]

Many persons, when they are initially infected with HIV, have an acute mononucleosis-like syndrome known as *primary infection*. This acute phase (stage 1) may include fever, fatigue, myalgias, sore throat, night sweats,

Table 16-2 The Revised CDC Classification System for Human Immunodeficiency Virus (HIV) Infection in Adults and Adolescents Aged >13 Years.*

Stage	$CD4^+$ T-cell Count cells/L ($CD4^+$ T-cell Percentage)	AIDS-defining Conditions (ADC)
Stage 1	≥500 (29%)	No ADC
Stage 2	200–499 (14%–28%)	No ADC
Stage 3	<200 (<14%)	No documented ADC
Stage undetermined	No information	No information

*A confirmed case meets the laboratory diagnosis of HIV infection and one of the four stages. Although cases with no information on AIDS-defining characteristics can be classified as stage unknown, every effort should be made to obtain $CD4^+$ T-cell counts and percentages and the presence of AIDS-defining conditions at the time of diagnosis.
Developed from Schneider E., Whitmore S., Glynn M.K., et al. (2008). Revised case definitions for HIV infections among adults, adolescents, and children aged <18 months and for children aged 18 months to <13 years—United States, 2008. MMWR 57(RR10), 1–8.

gastrointestinal problems, lymphadenopathy, maculopapular rash, and headache. Fever and malaise are the symptoms most commonly associated with primary infection.[46,54] During primary infection, there is an increase in viral replication, which leads to very high viral loads, sometimes greater than 1,000,000 copies/mL, and a decrease in the $CD4^+$ T-cell count. The signs and symptoms of primary HIV infection usually appear 1 to 4 weeks after exposure to HIV, and have an average duration of 7 to 10 days.[54] After several weeks, the immune system acts to control viral replication and reduces the viral load to a lower level, where it often remains for several years. People who are diagnosed with HIV infection while they are in the primary infection phase may have a unique opportunity for treatment. Some experts hypothesize that if started early, treatment may reduce the number of HIV-infected $CD4^+$ memory T cells; protect the functioning of HIV-infected $CD4^+$ T cells and cytotoxic T cells; and potentially help to maintain a homogeneous viral population that will be better controlled by antiretroviral therapy and the immune system.[46,55]

The primary stage is followed by a latent period (stage 2) during which the person has no signs or symptoms of illness. The median time of the latent period is about 10 years. During this time, the $CD4^+$ T-cell count falls gradually from the normal range of 800 to 1000 cells/μL to 200 to 400 cells/μL (14% to 28%). More recent data suggest that the $CD4^+$ T-cell decline may not fall in an even slope based on HIV RNA levels, and factors related to the variability in the decline in $CD4^+$ T cells are under investigation.[56] Lymphadenopathy (i.e., swollen lymph nodes for more than 3 months in at least two locations, not including the groin) develops in some persons with HIV infection during this phase. The lymph nodes may be sore or visible externally.

The third phase (stage 3), overt AIDS, occurs when a person has a $CD4^+$ T-cell count of less than 200 cells/μL (<14%) or an AIDS-defining illness.[53] Without antiretroviral therapy, this phase can lead to death within 2 to 3 years. The risk of opportunistic infections and death increases significantly when the $CD4^+$ T-cell count falls below 200 cells/μL.

Clinical Course. The clinical course of HIV varies from person to person. In the absence of treatment, most people with HIV infection progress to AIDS after 7 to 10 years.[2,53] These people are the *chronic or typical progressors*. Another 10% to 20% are *rapid progresors* who

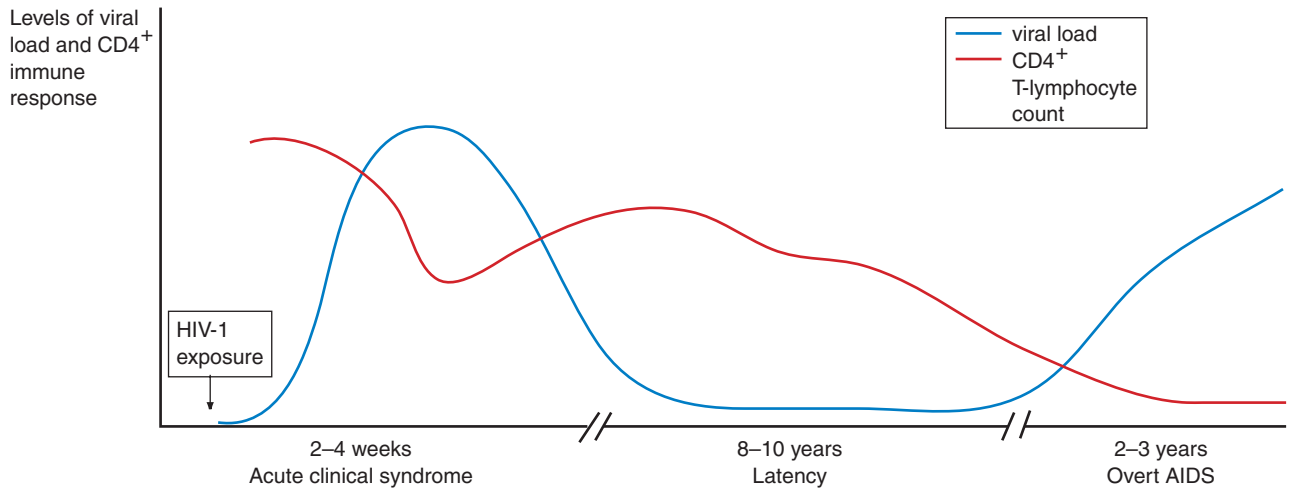


FIGURE 16-9. Viral load and $CD4^+$ cell count during the phases of HIV infection.

develop AIDS within 2 to 3 years after primary infection. The final 5% to 15% are *long-term nonprogressors,* who remain asymptomatic for 10 years or more after seroconversion, with stable $CD4^+$ T-cell counts and low plasma HIV RNA levels. A subset of these long-term nonprogressors, called *elite controllers,* have plasma HIV RNA levels that are below the level of detection. These people have been attracted great attention in hopes that studying them may help to identify host and viral factors that influence disease progression.[2]

Opportunistic Infections

Opportunistic infections begin to occur as the immune system becomes severely compromised. The number of $CD4^+$ T cells directly correlates with the risk of development of opportunistic infections. In addition, the baseline HIV RNA level contributes and serves as an independent risk factor.[2,3] Opportunistic infections involve common organisms that do not produce infection unless there is impaired immune function. Although a person with AIDS may live for many years after the first serious illness, as the immune system fails, these opportunistic illnesses become progressively more severe and difficult to treat.

Opportunistic infections are most often categorized by the type of organism (e.g., fungal, protozoal, bacterial and mycobacterial, viral). Bacterial and mycobacterial opportunistic infections include bacterial pneumonia, salmonellosis, bartonellosis, *Mycobacterium tuberculosis* (TB), and *Mycobacterium avium-intracellulare* complex (MAC). Fungal opportunistic infections include candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, penicilliosis, and pneumocystosis. Protozoal opportunistic infections include cryptosporidiosis, microsporidiosis, isosporiasis, and toxoplasmosis. Viral infections include those caused by cytomegalovirus (CMV), herpes simplex and zoster viruses, human papillomavirus, and JC virus, a virus that is the causative agent of progressive multifocal leukoencephalopathy (PML).

Respiratory Tract Infections. The most common causes of respiratory disease in persons with HIV infection are bacterial pneumonia, *P. jiroveci* pneumonia, and pulmonary TB. Other organisms that cause opportunistic pulmonary infections in persons with AIDS include CMV, MAC, *Toxoplasma gondii,* and *Cryptococcus neoformans.*[2] Pneumonia also may occur because of more common bacterial pulmonary pathogens, including *S. pneumoniae, Pseudomonas aeruginosa,* and *H. influenzae.* Some persons may become infected with multiple organisms, and it is not uncommon to find more than one pathogen present. Kaposi sarcoma (to be discussed) also can occur in the lungs.

P. jiroveci (formerly known as *P. carinii*) pneumonia (PCP) was the most common presenting manifestation of AIDS during the first decade of the epidemic. PCP is caused by *P. jiroveci,* an organism that is common in soil, houses, and many other places in the environment. In persons with healthy immune systems, *P. jiroveci* does not cause infection or disease. In persons with HIV infection,

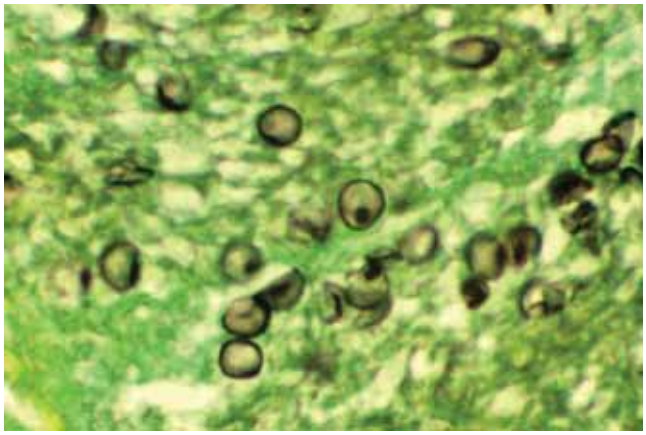


FIGURE 16-10. *Pneumocystis jiroveci* pneumonia. Histopathology of lung shows characteristic cysts with cup forms and dotlike wall thickening (methenamine silver stain). (From Centers for Disease Control and Prevention Public Image Library. [Online] Available: http://www.phil.cdc. gov/phil/details. asp.)

P. jiroveci can multiply quickly in the lungs and cause pneumonia. As the disease progresses, the alveoli become filled with a foamy exudate that forms cup-shaped cyst walls within the exudate (Fig. 16-10). Since highly active antiretroviral therapy (HAART) and prophylaxis for PCP were instituted, the incidence has decreased.[57] PCP still is common in people unaware of their HIV-positive status, in those who choose not to treat their HIV infection or take prophylaxis, and in those with poor access to health care. The best predictor of PCP is a $CD4^+$ cell count below 200 cells/μL,[57] and it is at this point that antimicrobial (trimethoprim-sulfamethoxazole or an alternative agent in the case of adverse reactions to sulfa drugs) is strongly recommended. The symptoms of PCP may be acute or gradually progressive. Patients may present with complaints of a mild cough, fever, shortness of breath, and weight loss. Diagnosis of PCP is made on recognition of the organism in pulmonary secretions.

Tuberculosis is the leading cause of death for people with HIV infection worldwide, and is often the first manifestation of HIV infection. At least one third of the 40 million people estimated to be living with HIV are likely to be infected with TB (UNAIDS press release, March 20, 2007). TB cases in the United States decreased from the 1950s to 1985; then, in 1986, the number of TB cases began to increase (see Chapter 22).[58] A number of factors contributed to this increase, including changes in immigration patterns and increased numbers of people living in group settings like prisons, shelters, and nursing homes, but the most profound factor was HIV infection. The lungs are the most common site of *M. tuberculosis* infection, but extrapulmonary infection of the kidney, bone marrow, and other organs also occurs in people with HIV infection. Whether a person has pulmonary or extrapulmonary TB, most persons present with fever, night sweats, cough, and weight loss. Persons infected with *M. tuberculosis* (i.e., those with positive tuberculin skin test results) are more likely to develop reactivated TB if they become infected with HIV. Coinfected individuals (i.e., those with both HIV and TB infection) are

also more likely to have a rapidly progressive form of TB. Equally important, HIV-infected persons with TB coinfection usually have an increase in viral load, which decreases the success of TB therapy. They also have an increased number of other opportunistic infections and an increased mortality rate.

Since the late 1960s, most persons with TB have responded well to therapy. However, in 1991, there were outbreaks of multidrug-resistant (MDR) TB. Since the original outbreak of MDR TB in the early 1990s, new cases of MDR TB have declined, largely because of improved infection control practices and the expansion of directly observed therapy programs.

Gastrointestinal Manifestations. Diseases of the gastrointestinal tract are some of the most frequent complications of HIV infection and AIDS. Esophageal candidiasis, CMV infection, and herpes simplex virus infection are common opportunistic infections that cause esophagitis in people with HIV infection.[59] Aphthous ulcers presumed secondary to HIV are also common. Persons experiencing these infections usually complain of painful swallowing or retrosternal pain. The clinical presentation can range from asymptomatic to a complete inability to swallow and resulting dehydration. Endoscopy or barium esophagography is required for definitive diagnosis.

Diarrhea or gastroenteritis is a common complaint in persons with HIV infection. Patients should be evaluated for the same common causes of diarrhea as in the general population. The most common protozoal opportunistic infection that causes diarrhea is due to *Cryptosporidium parvum*. The clinical features of cryptosporidiosis can range from mild diarrhea to severe, watery diarrhea with a loss of up to several liters of water per day. The most severe form usually occurs in persons with a $CD4^+$ cell count of less than 50 cells/μL and also can include malabsorption, electrolyte disturbances, dehydration, and weight loss. Other organisms that cause gastroenteritis and diarrhea are *Salmonella,* CMV, *Clostridium difficile, Escherichia coli, Shigella, Giardia,* and microsporidia.[59] These organisms are identified by examination of stool cultures or endoscopy.

Nervous System Manifestations. HIV infection, particularly in its late stages of severe immunocompromise, leaves the nervous system vulnerable to an array of neurologic disorders, including neurocognitive disorders, toxoplasmosis, and progressive multifocal leukoencephalopathy. These disorders can affect the peripheral nervous system or CNS and contribute to the morbidity and mortality of persons with HIV infection.

HIV-associated neurocognitive disorders (HANDs) refer to the cognitive disorders associated with HIV/AIDS. In 2007, the National Institute of Mental Health and National Institute of Neurologic Diseases and Stroke developed a new classification with standardized diagnostic criteria for HAND. The three conditions comprising HAND are HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD, formerly AIDS dementia complex).[60] HAND is a syndrome of cognitive impairment with motor dysfunction or behavioral/psychosocial symptoms associated with HIV infection itself.[60] HAD is usually a late complication of HIV infection. The clinical features of HAD are impairment of attention and concentration, slowing of mental speed and agility, slowing of motor speed, and apathetic behavior. The diagnosis of HAD is one of exclusion, and all other potential etiologies need to be excluded. Treatment of HAD consists of HAART to decrease symptoms and may result in significant improvement of both motor and cognitive skills.

Toxoplasmosis is a common opportunistic infection in persons with AIDS. The organism responsible, *T. gondii,* is a parasite that most often affects the CNS.[61] Toxoplasmosis usually is a reactivation of a latent *T. gondii* infection that has been dormant in the CNS. The typical presentation includes fever, headaches, and neurologic dysfunction, including confusion and lethargy, visual disturbances, and seizures. Computed tomography scans or, preferably, magnetic resonance imaging (MRI) should be performed immediately to detect the presence of neurologic lesions. Prophylactic treatment with trimethoprim-sulfamethoxazole, dapsone-pyrimethamine, or atovaquone is effective against *T. gondii* when the $CD4^+$ cell count falls below 100 cells/μL. Given that these medications are also used for prevention of PCP, almost all persons under care with a $CD4^+$ count lower than 200 cells/μL will be receiving effective toxoplasmosis prophylaxis.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the white matter of the brain caused by the JC virus, a DNA papovavirus that attacks the oligodendrocytes.[62] PML advances slowly, and it can be weeks to months before the patient seeks medical care. PML is characterized by progressive limb weakness, sensory loss, difficulty controlling the digits, visual disturbances, subtle alterations in mental status, hemiparesis, ataxia, diplopia, and seizures.[62] The mortality rate is high, and the average survival time is 2 to 4 months. Diagnosis is based on clinical findings and an MRI, and confirmed by the presence of the JC virus.[62] There is no proven cure for PML, but improvement can occur after starting effective HAART.

Malignancies

Persons with AIDS have a high incidence of certain malignancies, especially Kaposi sarcoma (KS), non-Hodgkin lymphoma, and noninvasive cervical carcinoma. The increased incidence of malignancies probably is a function of impaired cell-mediated immunity. As persons with HIV infection are living longer, there have been reports of the increasing incidence of age- and gender-specific malignancies.[63] Persons with HIV infection appear to have an increased risk of lung cancer even after adjusting for tobacco history. Non–AIDS-defining malignancies account for more morbidity and mortality than AIDS-defining malignancies in the antiretroviral therapy era. Traditional risk factors play a significant role in the increased risk of non–AIDS-defining malignancies for HIV-infected individuals, but do not entirely explain the excess cancer risk.[63]

Kaposi sarcoma is a malignancy of the endothelial cells that line small blood vessels.[64] An opportunistic cancer, KS occurs in immunosuppressed persons (e.g., transplant recipients or persons with AIDS). KS was one of the first opportunistic cancers associated with AIDS, and still is the most frequent malignancy related to HIV infection. There is evidence linking KS to a herpesvirus (herpesvirus 8 [HHV-8], also called *KS-associated herpes virus* [KSHV]).[64] The virus is readily transmitted through homosexual and heterosexual activities; however, there is a disproportionately higher incidence of KS in men who have sex with men compared with women and other men. Maternal–infant transmission also can occur. The virus has been detected in saliva from infected persons, and other modes of transmission are suspected.

The lesions of KS can be found on the skin and in the oral cavity, gastrointestinal tract, and lungs. More than 50% of people with skin lesions also have gastrointestinal lesions. The disease usually begins as one or more macules, papules, or violet skin lesions that enlarge and become darker (Fig. 16-11). They may enlarge to form raised plaques or tumors. Tumor nodules frequently are located on the trunk, neck, and head, especially the tip of the nose. They usually are painless in the early stages, but discomfort may develop as the tumor develops. Invasion of internal organs, including the lungs, gastrointestinal tract, and lymphatic system, commonly occurs. Gastrointestinal tract KS is often asymptomatic, but can cause pain, bleeding, or obstruction.[64] Pulmonary KS usually is a late development of the disease and causes dyspnea, cough, and hemoptysis.[64]

FIGURE 16-11. Kaposi sarcoma. **(A)** Intraoral Kaposi sarcoma of the hard palate secondary to HIV infection. **(B)** Cutaneous brown Kaposi sarcoma lesions located over the maximal left ankle and foot. (From Centers for Disease Control and Prevention Public Image Library. [Online] Available: http://phil.cdc.gov/phil/details.asp.

With prolonged survival, the number of persons with AIDS who develop *non-Hodgkin lymphoma* has increased steadily.[2] The clinical features are fever, night sweats, and weight loss (see Chapter 11). Because the manifestations of non-Hodgkin lymphoma are similar to those of other opportunistic infections, diagnosis often is difficult. Diagnosis can be made by biopsy of the affected tissue.

The human papillomavirus (HPV) has been linked to the development of *cervical carcinoma* and anal carcinoma in both HIV-positive men and women.[2] This is attributable to the high prevalence of human papillomavirus infection in persons with AIDS whose immune system has been compromised. This virus is associated with squamous cell carcinoma of the cervix and its precursor lesions, cervical dysplasia (see Chapter 40). Hence, gynecologic examination should be part of the routine evaluation of HIV-infected women. A quadrivalent vaccine to prevent HPV infection became available in 2007. The safety and immunogenicity of this vaccine among HIV-infected men and women are being studied.[65]

Wasting Syndrome and Metabolic Disorders

Wasting Syndrome. In 1997, wasting became an AIDS-defining illness. The syndrome is common in persons with HIV infection or AIDS. Wasting is characterized by involuntary weight loss of at least 10% of baseline body weight in the presence of diarrhea, more than two stools per day, or chronic weakness and a fever.[66] This diagnosis is made when no other opportunistic infections or neoplasms can be identified as causing these symptoms. Factors that contribute to wasting are anorexia, metabolic abnormalities, endocrine dysfunction, malabsorption, and cytokine dysregulation. Treatment for wasting includes nutritional interventions like oral supplements or enteral or parenteral nutrition. There also are numerous pharmacologic agents used to treat wasting, including appetite stimulants, cannabinoids, and megestrol acetate.

Metabolic Disorders. A wide range of metabolic and morphologic disorders are associated with HIV infection, including insulin resistance and diabetes, lipodystrophy, hyperlipidemia, and mitochondrial disorders. Many of these disorders are associated with treatment regimens used in the disorder. Metabolic complications among people with HIV infection on HAART have been

increasing since the introduction of potent HAART.[67] Insulin resistance and diabetes appear to be higher among those with HIV infection compared with the general population, although traditional risk factors contribute significantly.[68] Insulin resistance and diabetes also appear to be more associated with the use of specific nucleosides in combination with protease inhibitors rather than just the protease inhibitors, as initially thought. It is still not known why insulin resistance occurs in people with HIV infection, and most experts believe it is secondary to dysregulation of metabolic pathways or to indirect effects through mitochondrial toxicity linked to adipocyte toxicity.

The term *lipodystrophy* is frequently used to describe the body composition changes with or without the other metabolic derangements. Lipodystrophy related to HIV infection includes symptoms that fall into two categories: changes in body composition and metabolic changes.[69] The alterations in body appearance are an increase in abdominal girth, buffalo hump development (abnormal distribution of fat in the supraclavicular area), wasting of fat from the face and extremities, and breast enlargement in men and women. Most individuals experience either lipohypertrophy or lipoatrophy. Mixed patterns of fat changes are less common.[70] The metabolic changes include elevated serum cholesterol, low HDL cholesterol, elevated triglyceride levels, and insulin resistance. Originally attributed to the use of protease inhibitors, the pathogenesis of these metabolic derangements is complex and there may be multiple confounding factors.[71]

The mitochondria control many of the oxidative chemical reactions that release energy from glucose and other organic molecules. The mitochondria transform this newly released energy into adenosine triphosphate (ATP), which cells use as an energy source. In the absence of normal mitochondrial function, cells revert to anaerobic metabolism with generation of lactic acid. The mitochondrial disorders seen in persons with HIV infection are attributed to a class of drugs called the *nucleoside/nucleotide analog reverse transcriptase inhibitors* (NRTIs), particularly the thymidine analogs.[72] The most common presentations are lipoatrophy and peripheral neuropathy, although patients may not experience both. Patients may also present with nonspecific gastrointestinal symptoms, including nausea, vomiting, and abdominal pain. They may develop altered liver function and lactic acidosis. Since the recognition of the ascending polyneuropathy syndrome and reports of hepatic failure due to combination therapy with stavudine and didanosine, reports of life-threatening events due to mitochondrial toxicities have dramatically decreased.

Diagnosis and Treatment

A diagnosis of HIV infection may be prompted by a number of scenarios, including positive results of a screening test, accompanying signs and symptoms of an acute HIV infection, or manifestations of an immunodeficiency state. Unfortunately, there are approximately 250,000 persons living with HIV infection in the United States who are not aware of their infection, their risk of transmitting the infection, and missed opportunity to benefit from early treatment.

Diagnostic Methods. The most accurate and inexpensive method for identifying HIV infection is the HIV antibody test. The first commercial assays for HIV were introduced in 1985 to screen donated blood. Since then, use of antibody detection tests has been expanded to include evaluating persons at increased risk for HIV infection. The HIV antibody test procedure consists of screening with an *enzyme immunoassay* (EIA), also known as *enzyme-linked immunosorbent assay*, followed by a confirmatory test such as the *Western blot assay,* which is performed if the EIA is positive.[73] The EIA detects antibodies produced in response to HIV infection. In an EIA, antibodies to HIV in the blood sample bind to HIV antigens in the test material.[52] The Western blot is a more sensitive assay than the EIA that looks for the presence of antibodies to specific viral antigens.[52] In the case of a false-positive EIA result, the Western blot test can identify the person as uninfected. *Polymerase chain reaction* (PCR) is a technique for detecting HIV DNA (see Chapter 14). PCR detects the presence of the virus rather than the antibody to the virus, which the EIA and Western blot tests detect. PCR is useful in diagnosing HIV infection in infants born to infected mothers because these infants have their mothers' HIV antibody regardless of whether the children are infected.

Technologic advances have led to new forms of testing, such as the oral test, home testing kits, and the new rapid blood test. Oral fluids contain antibodies to HIV. In the late 1990s, the FDA approved the OraSure test. The OraSure uses a cotton swab, which is inserted into the mouth for 2 minutes, placed in a transport container with preservative, and then sent to a laboratory for EIA and Western blot testing. Home HIV testing kits can be bought over the counter. The kits, approved by the FDA, allow persons to collect their own blood sample through a finger-stick process, mail the specimen to a laboratory for EIA and confirmatory Western blot tests, and receive results by telephone in 3 to 7 days. In November 2002, the FDA approved the Ora Quick Rapid HIV-1 Antibody Test.[74] The Ora Quick uses a whole-blood specimen from a finger stick and can provide results in about 20 minutes. Reactive, or positive, test results require confirmation using Western blot testing. Persons with a reactive result need to be told that the preliminary test was positive, but that they need a confirmatory test. The use of a rapid test should facilitate people receiving the results of their HIV test more regularly because they do not need to return for their test results 2 weeks later unless it is positive or there is concern that the person may be in the window period before seroconversion.

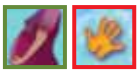
Treatment. Currently, there is no cure for HIV infection. The medications that are currently available to treat HIV infection decrease the amount of virus in the body, but they do not eradicate HIV.[75] The treatment of HIV infection is one of the most rapidly evolving fields in medicine.

There currently are five different classes of HIV antiretroviral medications: nucleoside and nucleotide analog reverse transcriptase inhibitors; nonnucleoside reverse transcriptase inhibitors; protease inhibitors; entry inhibitors; and the newest class, integrase inhibitors. Each class of agents attempts to interrupt the life cycle of

the HIV at different points (see Fig. 16-8). *Reverse transcriptase inhibitors* inhibit HIV replication by acting on the enzyme reverse transcriptase. *Nucleoside analog reverse transcriptase inhibitors* and *nucleotide reverse transcriptase inhibitors* act by blocking the elongation of the DNA chain by stopping more nucleosides from being added. *Nonnucleoside reverse transcriptase inhibitors* work by binding to the reverse transcriptase enzyme so it cannot copy the virus's RNA into DNA. *Protease inhibitors* bind to the protease enzyme and inhibit its action. This inhibition prevents cleavage of the polypeptide chain into individual proteins, which would be used to construct a new virus. The two newest classes of antiretroviral therapy are the *entry inhibitors* and *integrase inhibitors*. The entry inhibitors prevent HIV from entering or fusing with the $CD4^+$ cell, thus blocking the virus from inserting its genetic information into the $CD4^+$ T cell, whereas the integrase inhibitors block the integration step of the viral cycle, thus preventing the HIV genome from integrating into the host's genome.

Because different drugs act at different stages of the replication cycle, optimal treatment includes a combination of at least three antiretroviral drugs, often referred to as highly active antiretroviral therapy. The goal of HAART is a sustained suspension of HIV replication, resulting in an undetectable viral load and increasing $CD4^+$ cell count. In general, antiviral therapies are prescribed to slow the progression of AIDS and improve the overall quality of life and survival time of persons with HIV infection.

Preventive and therapeutic vaccines for HIV are also being investigated.[76] The preventive vaccine would be given to someone who is HIV negative, with the goal of preventing infection if exposed to HIV. These vaccines have focused mainly on inducing neutralizing antibodies to prevent infections. The second type of vaccine would be used in people who are already infected with HIV as a therapeutic strategy to control HIV replication. The goal of these vaccines would be to better control the HIV viremia by lowering the viral load set point, changing the viral load trajectories, and preserving immune function for longer periods of time. These vaccines have focused on bringing about cellular immune responses and preparing the immune system for the lysis of infected cells. To date, these strategies have proved disappointing.



HIV Infection in Pregnancy and in Infants and Children

Early in the epidemic, children who acquired HIV could have become infected through blood products or perinatally. Now, transmission from mother to infant is the most common way that children become infected with HIV. HIV may be transmitted from infected women to their offspring in utero, during labor and delivery, or through breast-feeding.[77] Most transmissions from mother to child occur during childbirth when the mother's infected blood in the birth canal infects the baby. Breast-feeding, particularly in poor countries, can account for one third to one half of all mother-to-child transmission. Screening programs for pregnant women and antiretroviral prophylaxis are available for preventing mother-to-child transmission in HIV-positive women. Epidemiologic estimates suggest that coverage for antiviral prophylaxis to HIV-positive women for prevention of mother-to-child transmission in low- to middle-income countries increased from 9% in 2004 to 33% in 2007.[44]

Diagnosis and Treatment. Diagnosis of HIV infection in children born to HIV-infected mothers is complicated by the presence of maternal anti-HIV IgG antibody, which crosses the placenta to the fetus.[78] Consequently, infants born to HIV-infected women can be HIV antibody positive by ELISA for up to 18 months of age even though they are not infected with HIV. PCR testing for HIV DNA is used most often to diagnose HIV infection in infants younger than 18 months of age. Two positive PCR tests for HIV DNA are needed to diagnose a child with HIV infection. Children born to mothers with HIV infection are considered uninfected if they become HIV antibody negative after 6 months of age, have no other laboratory evidence of HIV infection, and have not met the case definition criteria for AIDS in children.

The landmark Pediatric AIDS Clinical Trials Group (PACTG) 076 reported that perinatal transmission could be lowered by two thirds, from 26% to 8%, by administering zidovudine to the mother during pregnancy and labor and delivery and to the infant when it is born.[79] The U.S. Public Health Service therefore recommends that HIV counseling and testing should be offered to all pregnant women.[80] The recommendations also stress that women who test positive for HIV antibodies should be informed of the perinatal prevention benefits of zidovudine therapy and offered HAART, which often includes zidovudine. This is done because it has now been found that women receiving antiretroviral therapy who also have a viral load less than 1000 copies/mL have very low rates of perinatal transmission. One caveat to antiretroviral therapy in pregnancy is that efavirenz cannot be used during the first trimester because it is a teratogen, causing neural tube defects. Benefits of voluntary testing for mothers and newborns include reduced morbidity because of intensive treatment and supportive health care, the opportunity for early antiretroviral therapy for mother and child, and information regarding the risk of transmission from breast milk.

Clinical Manifestations. Children may have a different clinical presentation of HIV infection than adults.[78] Failure to thrive, CNS abnormalities, and developmental delays are the most prominent primary manifestations of HIV infection in children. Children born with HIV infection usually weigh less and are shorter than noninfected infants. A major cause of early mortality for HIV-infected children is PCP. As opposed to adults, in whom PCP occurs in the late stages, PCP occurs early in children, with the peak age of onset at 3 to 6 months. For this reason, prophylaxis with trimethoprim-sulfamethoxazole should be started beginning at 4 to 6 weeks for all infants born to HIV-infected mothers, regardless of their $CD4^+$ cell count or infection status.[81]

In summary, an immunodeficiency is defined as an absolute or partial loss of the normal immune response, which places a person in a state of compromise and increases the risk for development of infections or malignant complications. Immunodeficiency states can affect components of the innate or adaptive immune systems. The variety of defects known to involve the immune response can be classified as primary (i.e., congenital or inherited) or secondary (i.e., due to another disease or condition). The extent to which any or all of these components are compromised dictates the severity of the immunodeficiency.

Immunodeficiency can affect the humoral or cellular components of the adaptive immune system. B-cell or humoral immunodeficiency disorders can selectively involve a single immunoglobulin (e.g., IgA immunodeficiency) or all of the immunoglobulins (agammaglobulinemia). Defects in humoral immunity increase the risk of recurrent pyogenic infections but have less effect on the defense against intracellular bacteria (mycobacteria), fungi, protozoa, and viruses (except for the enteroviruses that cause gastrointestinal infections). T lymphocytes protect against fungal, protozoan, viral, and intracellular bacterial infections; control malignant cell proliferation; and are responsible for coordinating the overall immune response. T-cell or cellular immune disorders can present as selective T-cell immunodeficiency states or as combined T- and B-cell immunodeficiency disorders. Infants with severe combined immunodeficiency have a disease course that resembles AIDS, with failure to thrive, chronic diarrhea, and opportunistic infections. Survival beyond the first year of life is rare without prompt immune reconstitution through bone marrow or hematopoietic stem cell transplantation.

AIDS, the most common type of secondary immunodeficiency, is caused by HIV infection. The virus is most commonly transmitted from one person to another through sexual contact, through blood exchange, or perinatally. HIV is a retrovirus that infects the body's $CD4^+$ T cells and macrophages. The destruction of $CD4^+$ cells constitutes an attack on the entire immune system because this subset of lymphocytes exerts critical regulatory and effector functions that involve both humoral and cellular immunity. The clinical course of HIV infection can be divided into three phases: a primary phase that occurs shortly after infection and is usually manifested by mononucleosis-like symptoms, a latency phase that may last for years, and an overt AIDS phase that is characterized by a marked decrease in $CD4^+$ T cells and the development of opportunistic infections of the respiratory, gastrointestinal, and nervous systems; malignancies such as Kaposi sarcoma and non-Hodgkin lymphoma; wasting syndrome; and metabolic disorders. There is no cure for AIDS. Treatment largely involves the use of drugs that interrupt the replication of HIV and prevention or treatment of complications such as opportunistic infections.

Women who are infected with HIV may transmit the virus to their offspring in utero, during labor and delivery, or through breast milk. Diagnosis of HIV infection in children born to HIV-infected mothers is complicated by the presence of maternal HIV antibody, which crosses the placenta to the fetus. This antibody usually disappears within 18 months in uninfected children. The administration of antiretroviral therapy to the mother during pregnancy and labor and delivery and to the infant when it is born decreases perinatal transmission.

REVIEW EXERCISES

1. A 32-year-old man presents in the allergy clinic with complaints of allergic rhinitis or hay fever. His major complaints are those of nasal pruritus (itching), nasal congestion with profuse watery drainage, sneezing, and eye irritation. The physical examination reveals edematous and inflamed nasal mucosa and redness of the ocular conjunctiva. He relates that this happens every fall during "ragweed season."

A. Explain the immunologic mechanisms that are responsible for this man's symptoms.
B. What type of diagnostic test might be used?
C. What type(s) of treatment might be used to relieve his symptoms?

2. Persons with intestinal parasites and those with allergies may both have elevated levels of eosinophils in their blood.

A. Explain.

3. A 20-year-old woman has been diagnosed with IgA deficiency. She has been plagued with frequent bouts of bronchitis and sinus infections.

A. Why are these types of infections particularly prominent in persons with an IgA deficiency?
B. She has been told that she needs to be aware that she could have a severe reaction when given unwashed blood transfusions. Explain.

4. Persons with impaired cellular immunity may not respond to the tuberculin test, even when infected with *Mycobacterium tuberculosis*.

A. Explain.

5. A 29-year-old woman presents to the clinic for her initial obstetric visit, about 10 weeks into her pregnancy.

A. This woman is in a monogamous relationship. Should an HIV test be a part of her initial blood work? Why?
B. The woman's HIV test comes back positive. What should be done to decrease the risk of her passing on HIV to her child?
C. The infant is born, and its initial antibody test is positive. Does this mean the infant is infected? How is the diagnosis of HIV infection in a child younger than 18 months made, and why is this different than the diagnosis for adults?

6. A 40-year-old man presents to the clinic very short of breath, and after a radiograph and an examination, he is diagnosed with PCP. His provider does an HIV test, which comes up positive. Upon further testing, the man's $CD4^+$ cell count is found to be 100 cells/μL and his viral load is 250,000 copies/mL.

A. Why did the provider do an HIV test after the man was diagnosed with PCP?
B. Is there a way to prevent PCP?
C. What classification does this man fall into based on his $CD4^+$ count and symptomatology, and why?

REFERENCES

1. Abbas A.K., Lichtman A.H. (2003). *Cellular and molecular immunology* (5th ed., pp. 369–390, 453–464). Philadelphia: W.B. Saunders.
2. Kumar V., Abbas A.K., Fautso N., et al. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 183–249). Philadelphia: Saunders Elsevier.
3. Warren J.S., Bennett D.P., Pomerantz R.J. (2008). Immunopathology. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 99–131). Philadelphia: Lippincott Williams & Wilkins.
4. Kay A.B. (2001). Allergy and allergic disease (parts 1 and 2). *New England Journal of Medicine* 344, 30–37, 109–113.
5. Galli S.J. (1993). New concepts about the mast cell. *New England Journal of Medicine* 328, 257–265.
6. Benoist C., Mathias D. (2003). Mast cells in autoimmune disease. *Nature* 420, 875–878.
7. Tang A.W. (2003). A practical guide to anaphylaxis. *American Family Physician* 68, 1325–1340.
8. Lieberman P. (2006). Anaphylaxis. *Medical Clinics of North America* 90, 77–95.
9. Lieberman P., Kemp S.F., Oppenheimer J., et al. (Chief Editors, Joint Task Force on Practice Parameters, Joint Counsel of Allergy, Asthma and Immunology). (2005). The diagnosis and management of anaphylaxis: An updated practice parameter. *Journal of Allergy and Clinical Immunology* 115(3 Suppl), S483–S523.
10. Quillen D.M., Feller D.B. (2006). Diagnosis of rhinitis: Allergic vs. nonallergic. *American Family Physician* 73, 1583–1590.
11. Greiner A.N. (2006). Allergic rhinitis: Impact of the disease and consideration for management. *Medical Clinics of North America* 90, 17–38.
12. Sampson H.A. (2004). Update on food allergy. *Journal of Allergy and Clinical Immunology* 113, 805–819.
13. Sampson H.A. (2002). Peanut allergy. *New England Journal of Medicine* 346, 1294–1299.
14. Keet C.A., Wood R.A. (2007). Food allergy and anaphylaxis. *Immunology and Allergy Clinics of North America* 27, 193–212.
15. Mark B.J., Slavin R.G. (2006). Allergic contact dermatitis. *Medical Clinics of North America* 90, 169–185.
16. Selman M. (2004). Hypersensitivity pneumonitis: A multifaceted deceiving disorder. *Clinical Chest Medicine* 25, 531–547.
17. Gilliam A.C. (2004). Update on graft versus host disease. *Journal of Investigative Dermatology* 123, 251–257.
18. Couriel D., Caldera H., Champlin R.E., et al. (2004). Acute graft-versus-host disease: Pathophysiology, clinical manifestations, and management. *Cancer* 101, 1936–1946.
19. Crawford J.M. (2005). The liver and biliary tract. In Kumar V., Abbas A.K., Fausto N. (Eds.), *Robbins and Cotran pathologic basis of disease* (7th ed., pp. 919–920). Philadelphia: Elsevier Saunders.
20. Kamradt T., Mitchison N.A. (2001). Advances in immunology: Tolerance and autoimmunity. *New England Journal of Medicine* 344, 655–664.
21. Davidson A., Diamond B. (2001). Autoimmune disease. *New England Journal of Medicine* 345, 340–350.
22. Rioux J.D., Abbas A.K. (2005). Paths to understanding the genetic basis of autoimmune disease. *Nature* 435, 584–589.
23. Goodnow C.C., Sprent J., de St Groth B.F., et al. (2005). Cellular and genetic mechanisms of self tolerance and autoimmunity. *Nature* 435, 590–597.
24. Navratil J.S., Sabatine J.M., Ahearn J.M. (2004). Apoptosis and immune responses to self. *Rheumatic Disease Clinics of North America* 30, 193–212.
25. Jiang H., Chess L. (2006). Regulation of immune responses by T cells. *New England Journal of Medicine* 354, 166–176.
26. Kronberg M., Rudensky A. (2005). Regulation of immunity by self-reactive T cells. *Nature* 435, 598–604.
27. Zandman-Goddard G., Peeva E., Shoenfeld Y. (2007). Gender and autoimmunity. *Autoimmunity Review* 6, 366–372.
28. Cutolo M., Sulli A., Seriolo S., et al. (1995). Estrogens, the immune response and autoimmunity. *Clinical and Experimental Rheumatology* 13, 217–226.
29. Fujinami R.S., von Herrath M.G., Christen U., et al. (2006). Molecular mimicry, bystander activation, or viral persistence: Infections and autoimmune disease. *Clinical Microbiology Reviews* 19, 80–94.
30. Anders H.-J., Zecher D., Pawar R.D., et al. (2005). Molecular mechanisms of autoimmunity triggered by microbial infection. *Arthritis Research & Therapy* 7, 215–224.
31. Llewelyn M., Cohen J. (2001). Superantigen antagonist peptides. *Critical Care* 5, 53–55.
32. Verbsky J.W., Grossman W.J. (2006). Cellular and genetic basis of primary immune deficiencies. *Pediatric Clinics of North America* 53, 649–684.
33. Bonilla F.A., Geha R.S. (2006). Update on primary immunodeficiency diseases. *Journal of Allergy and Clinical Immunology* 117(2 Suppl), S435–S441.
34. Buckley R.H. (2000). Primary immunodeficiency diseases due to defects in lymphocytes. *New England Journal of Medicine* 343, 1313–1324.
35. Buckley R. (2004). T-, B-, and NK-cell systems. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 683–700). Philadelphia: Elsevier Saunders.
36. The Jeffrey Modell Foundation Medical Advisory Board. (2008). *Ten warning signs of primary immunodeficiency.* [Online] Available: www.info4pi.org/index.cfm?CFID=11982666&CFTOKEN=43062451. Accessed March 5, 2008.
37. Sorensen R.U., Moore C. (2000). Antibody deficiency syndromes. *Pediatric Clinics of North America* 47, 1225–1252.
38. Rose M.E., Lang D.M. (2006). Evaluating and managing hypogammaglobulinemia. *Cleveland Clinic Journal of Medicine* 73, 133–144.
39. Elder M.E. (2000). T-cell immunodeficiencies. *Pediatric Clinics of North America* 47, 1253–1274.
40. Buckley R.H. (2002). Primary cellular immunodeficiency. *Journal of Allergy and Clinical Immunology* 109, 747–757.
41. Buckley R.H. (2004). Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. *Annual Review of Immunology* 22, 625–655.
42. Rudd C.E. (2006). Disabled receptor signaling and new primary immunodeficiency disorders. *New England Journal of Medicine* 354, 1874–1877.
43. Ochs H.D., Thrasher A.J. (2006). The Wiskott-Aldrich syndrome. *Journal of Allergy and Clinical Immunology* 117, 725–738.
44. UNAIDS. (2008). *2008 Report on global AIDS epidemic, August 2008.* [Online] Available: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp. Accessed January 30, 2009.

45. Karim S.S.A., Karim Q.A., Gouuws E., et al. (2007). Global epidemiology of HIV-AIDS. *Infectious Disease Clinics of North America* 21, 1–17.
46. Zetola N.M., Pilcher C.D. (2007). Diagnosis and management of acute HIV infection. *Infectious Disease Clinics of North America* 21, 19–48.
47. Gershon R.R.M., Vlahov D., Nelson K.E. (1990). The risk of transmission of HIV-1 through non-percutaneous, non-sexual modes: A review. *AIDS* 4, 645–650.
48. Stramer S.L., Glynn S.A., Kleinman S.H., et al. (2004). Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. *New England Journal of Medicine* 351, 760–768.
49. Centers for Disease Control and Prevention. (2002). *Preventing occupational HIV transmission to healthcare personnel.* [Online] Available: http://www.cdc.gov/hiv/resources/factsheets/PDF/hcwprev.pdf. Accessed February 2, 2009.
50. Brenner B.G., Roger M., Routy J.P., et al. (2007). Amplified transmission in early HIV infection. *Journal of Infectious Disease* 195, 951–959.
51. Trecarichi E.M., Tumbarello M., de Gaetano Donati K., et al. (2006). Partial protective effect of CCR5-delta 32 heterozygosity in a cohort of heterosexual Italian HIV-1 exposed uninfected individuals. *AIDS Research and Therapy* 3, 22.
52. Centers for Disease Control and Prevention. (1992). 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report* 41(RR-17), 1–23.
53. Casaa C., Solomba S., Rauch A., et al. (2010). Host and viral genetic correlates of clinical definitions of HIV-1 progression. *PLos One 5*, 6, e11079.
54. Schneider E., Whitmore S., Glynn M.K., et al. (2008). Revised surveillance case definitions for HIV infections among adults, adolescents, and children aged <18 months and for children aged 18 months to <13 years–United States, 2008. *MMWR 57*, RR10, 1–8.
55. Hecht F.M., Wang L., Collier A. (2006). A multicenter observational study of potential benefits of initiating combination antiretroviral therapy during acute infection. *Journal of Infectious Disease* 194, 725–733.
56. Rodriguez B., Sethi A.K., Cheruvu V.K. (2006). Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection. *Journal of the American Medical Association* 296, 1498–1506.
57. Kaplan J.E., Hanson D., Dworkin M.S., et al. (2000). Epidemiology of HIV associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clinical Infectious Diseases* 30(Suppl 1), S5–S14.
58. UNAIDS. (2006). *Frequently asked questions about tuberculosis.* [Online] Available: http://data.unaids.org/pub/factsheet/2006/tb_hiv_qa.pdf. Accessed February 18, 2009.
59. Wilcox C.M. (2004). Gastrointestinal manifestations of AIDS. *Nutrition in Clinical Practice* 19, 356–364.
60. Antinori A., Arendt G., Becker J.T. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 69, 1789–1799.
61. Dedicoat M., Livesley N. (2006). Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). *Cochrane Database of Systematic Reviews,* July 19, 3, CD005420.
62. Berger J.R., Houff S. (2006). Progressive multifocal leukoencephalopathy: Lessons from AIDS and natalizumab. *Neurological Research* 28, 299–305.
63. Silverberg M.J., Abrams D.I. (2007). AIDS-defining and non-AIDS-defining malignancies: Cancer occurrence in the antiretroviral therapy era. *Current Opinion in Oncology* 19, 446–451.
64. Antman K., Chang Y. (2000). Kaposi's sarcoma. *New England Journal of Medicine* 342, 1027–1038.
65. De Vuyst H., Franceschi S. (2007). Human papillomavirus vaccines in HIV-positive men and women. *Current Opinion in Oncology* 19, 470–475.
66. Polsky B., Kotler D., Steinhart C. (2004). Treatment guidelines for HIV-associated wasting. *HIV Clinical Trials* 5, 50–61.
67. Umeh O.C., Currier J.S. (2005). Lipids, metabolic syndrome, and risk factors for future cardiovascular disease among HIV-infected patients. *Current HIV/AIDS Reports* 2, 132–139.
68. Brown T.T., Cole S.R., Li X., et al. (2005). Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Archives of Internal Medicine* 165, 1179–1184.
69. Tershakovec A.M., Frank I., Rader D. (2004). HIV-related lipodystrophy and related factors. *Atherosclerosis* 174, 1–10.
70. Mulligan K., Parker R.A., Komarow L., et al. (2006). Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. *Journal of Acquired Immune Deficiency Syndromes* 41, 590–597.
71. Grinspoon S., Carr A. (2005). Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *New England Journal of Medicine* 352, 48–62.
72. McComsey G., Lonergan J.T. (2004). Mitochondrial dysfunction: Patient monitoring and toxicity management. *Journal of Acquired Immune Deficiency Syndromes* 37(Suppl 1), S30–S35.
73. Aberg J.A., Kaplan J.E., Libman H., et al. (2009). Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clinics of Infectious Disease 49*(5), 651–681.
74. Delaney K.P., Branson B.M., Uniyal A., et al. (2006). Performance of an oral rapid HIV-1/2 test experience with four CDC studies. *AIDS* 20, 1655–1660.
75. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1–161. [Online] http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 9, 2010.
76. Maplanka C. (2007). AIDS: Is there an answer to the global pandemic? The immune system in HIV infection and control. *Viral Immunology* 20, 331–342.
77. McIntyre J. (2008). Managing pregnant patients. In Dolin R., Masur H., Saag M. (Eds.), *AIDS therapy* (3rd ed., pp. 595–597). London: Churchill Livingston.
78. Yogev R., Chadwick E.G. (2007). Acquired immunodeficiency syndrome (human immunodeficiency virus). In Behrman R.E., Kliegman R.M., Jenson H.B., et al., eds. *Nelson textbook of pediatrics* (18th ed., pp. 1427–1443). Philadelphia: Saunders Elsevier.
79. Connor E.M., Sperling R.S., Gelber R., et al. (1994). Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 33, 1173–1180.
80. Public Health Service Task Force. (2008). Recommendations for use of antiviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. [Online] Available: http://AIDSinfo.nih.gov. Accessed February 18, 2009.
81. Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association of Infectious Diseases Society of America, the Pediatric Infectious Disease Society, and the American Academy of Pediatrics. (2008). *Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children.* [Online] Available: http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf. Accessed February 18, 2009.

UNIT 5

Circulatory Function

Organization of the Circulatory System
- *Pulmonary and Systemic Circulations*
- *Volume and Pressure Distribution*

Principles of Blood Flow
- *Pressure, Resistance, and Flow*
  - Laminar Versus Turbulent Flow
- *Wall Tension, Radius, and Pressure*
- *Distensibility and Compliance*

The Heart as a Pump
- *Functional Anatomy of the Heart*
  - Pericardium
  - Myocardium
  - Endocardium
  - Heart Valves and Fibrous Skeleton
- *Cardiac Conduction System*
  - Action Potentials
  - Absolute and Relative Refractory Periods
  - Arrhythmias and Conduction Disorders
  - Electrocardiography
- *Cardiac Cycle*
  - Ventricular Systole and Diastole
  - Atrial Filling and Contraction
- *Regulation of Cardiac Performance*
  - Preload
  - Afterload
  - Cardiac Contractility
  - Heart Rate

The Systemic Circulation and Control of Blood Flow
- *Blood Vessels*
  - Vascular Smooth Muscle
- *Arterial System*
  - Arterial Pressure Pulsations
- *The Venous System*
- *The Microcirculation and the Lymphatic System*
  - Structure of the Microcirculation and Capillary System
  - Lymphatic System
- *Local and Humoral Control of Blood Flow*
  - Autoregulation of Blood Flow
  - Endothelial Control of Blood Flow
  - Humoral Control of the Circulation
- *Collateral Circulation*

Neural Control of Circulatory Function
- *Autonomic Nervous System Regulation*
  - Autonomic Regulation of Vascular Function
  - Autonomic Neurotransmitters
- *Central Nervous System Responses*

Chapter 17

Control of Cardiovascular Function

The main function of the *circulatory system*, which consists of the heart and blood vessels, is transport. The circulatory system delivers oxygen and nutrients needed for metabolic processes to the tissues, carries waste products from cellular metabolism to the kidneys and other excretory organs for elimination, and circulates electrolytes and hormones needed to regulate body function. This process of nutrient delivery is carried out with exquisite precision so that the blood flow to each tissue of the body is exactly matched to tissue need.

Organization of the Circulatory System

Pulmonary and Systemic Circulations

The circulatory system can be divided into two parts: the *pulmonary circulation*, which moves blood through the lungs and creates a link with the gas exchange function of the respiratory system, and the *systemic circulation*, which moves blood throughout all the other tissues of the body (Fig. 17-1). The blood that is in the heart and pulmonary circulation is sometimes referred to as the *central circulation* and that outside the central circulation as the *peripheral circulation*.

The pulmonary circulation consists of the right side of the heart, the pulmonary arteries, the pulmonary capillaries, and the pulmonary veins. The large pulmonary vessels are unique in that the pulmonary artery is the

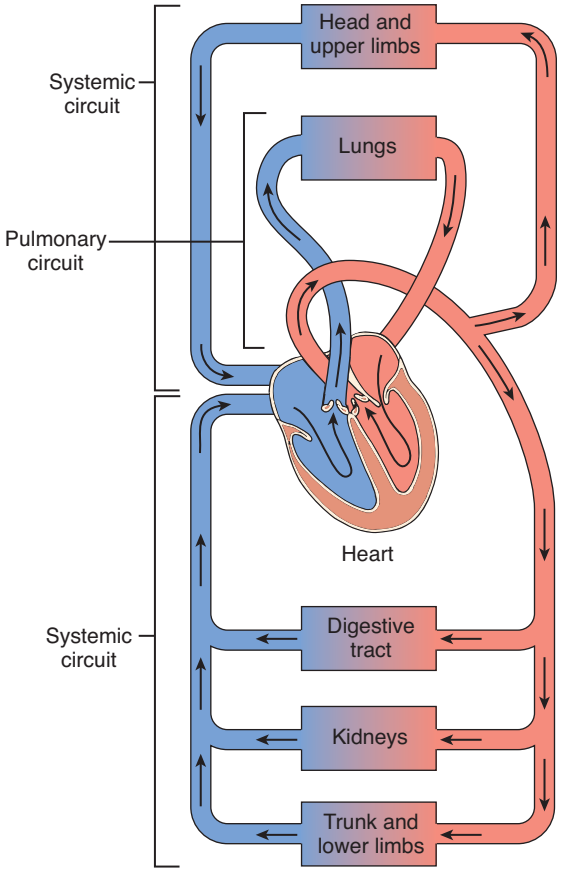


FIGURE 17-1. Systemic and pulmonary circulations. The right side of the heart pumps blood to the lungs, and the left side of the heart pumps blood to the systemic circulation.

only artery that carries deoxygenated venous blood and the pulmonary veins are the only veins that carry oxygenated arterial blood. The systemic circulation consists of the left side of the heart, the aorta and its branches, the capillaries that supply the brain and peripheral tissues, and the systemic venous system and the vena cava. The veins from the lower portion of the body merge to form the inferior vena cava and those from the head and upper extremities merge to form the superior vena cava, both of which empty into the right heart.

Although the pulmonary and systemic circulations function similarly, they have some important differences. The pulmonary circulation is the smaller of the two and functions with a much lower pressure. Because the pulmonary circulation is located in the chest near the heart, it functions as a low-pressure system with a mean arterial pressure of approximately 12 mm Hg. The low pressure of the pulmonary circulation allows blood to move through the lungs more slowly, which is important for gas exchange. Because the systemic circulation must transport blood to distant parts of the body, often against the effects of gravity, it functions as a high-pressure system, with a mean arterial pressure of 90 to 100 mm Hg.

The heart, which propels blood through the circulatory system, consists of two pumps in series—the right heart, which propels blood through the gas exchange vessels in the lungs, and the left heart, which propels blood through the vessels that supply all the other tissues in the body. Both sides of the heart are further divided into two chambers, an *atrium* and a *ventricle*. The atria function as collection chambers for blood returning to the heart and as auxiliary pumps that assist in filling the ventricles. The ventricles are the main pumping chambers of the heart. The right ventricle pumps blood through the pulmonary artery to the lungs and the left ventricle pumps blood through the aorta into the systemic circulation. The ventricular chambers of the right and left heart have inlet valves and outlet valves that act reciprocally (i.e., one set of valves is open while the other is closed) to control the direction of blood flow through the cardiac chambers and into the arteries.

Because it is a closed system, the effective function of the circulatory system requires that both sides of the heart must pump the same amount of blood over time. If the output of the left heart were to fall below that of the right heart, blood would accumulate in the pulmonary circulation. Likewise, if the right heart were to pump less effectively than the left heart, blood would accumulate in the systemic circulation. However, the left and right heart seldom eject exactly the same amount of blood with each beat. This is because blood return to the heart is affected by activities of daily living such as taking a deep breath or moving from the seated to standing position. These beat-by-beat variations in cardiac output are accommodated by the large storage capabilities of the venous system that allow for temporary changes in blood volume. The accumulation of blood occurs only when the storage capacity of the venous system has been exceeded.

Functional Organization of the Circulatory System

- The circulatory system consists of the heart, which pumps blood; the arterial system, which distributes oxygenated blood to the tissues; the venous system, which collects deoxygenated blood from the tissues and returns it to the heart; and the capillaries, where exchange of gases, nutrients, and wastes takes place.
- The circulatory system is divided into two parts: the low-pressure pulmonary circulation, linking circulation and gas exchange in the lungs, and the high-pressure systemic circulation, providing oxygen and nutrients to the tissues.
- Blood flows down a pressure gradient from the high-pressure arterial circulation to the low-pressure venous circulation.
- The circulation is a closed system, so the output of the right and left heart must be equal over time for effective functioning of the circulation.

Volume and Pressure Distribution

Blood flow in the circulatory system depends on a blood volume that is sufficient to fill the blood vessels and a pressure difference across the system that provides the force that is needed to move blood forward. As shown in Figure 17-2, approximately 4% of the blood at any given time is in the left heart, 16% is in the arteries and arterioles, 4% is in the capillaries, 64% is in the venules and veins, and 4% is in the right heart. The arteries and arterioles, which have thick, elastic walls and function as a distribution system, have the highest pressure. The capillaries are small, thin-walled vessels that link the arterial and venous sides of the circulation. They serve as an exchange system where transfer of gases, nutrients, and wastes take place. Because of their small size and large surface area, the capillaries contain the smallest amount of blood. The venules and veins, which contain the largest amount of blood, are thin-walled, distensible vessels that function as a reservoir to collect blood from the capillaries and return it to the right heart.

Blood moves from the arterial to the venous side of the circulation along a pressure gradient, moving from an area of higher pressure to one of lower pressure. The pressure distribution in the different parts of the circulation is almost an inverse of the volume distribution (see Fig. 17-2). The pressure in the arterial side of the circulation, which contains only approximately one sixth of the blood volume, is much greater than the pressure on the venous side of the circulation, which contains approximately two thirds of the blood. This pressure and volume distribution is due in large part to the structure and relative elasticity of the arteries and veins. It is the pressure difference between the arterial and venous sides of the circulation (approximately 84 mm Hg) that provides the driving force for flow of blood in the systemic circulation. The pulmonary circulation has a similar arterial–venous pressure difference, albeit of a lesser magnitude, that facilitates blood flow.

Because the pulmonary and systemic circulations are connected and function as a closed system, blood can be shifted from one circulation to the other. In the pulmonary circulation, the blood volume (approximately 450 mL in the adult) can vary from as low as 50% of normal to as high as 200% of normal. An increase in intrathoracic pressure, such as occurs when exhaling against a closed glottis, impedes venous return to the right heart. This can produce a transient shift from the central to the systemic circulation of as much as 250 mL of blood as blood backs up in the vena cava and large veins. Body position also affects the distribution of blood volume. In the recumbent position, approximately 25% to 30% of the total blood volume is in the central circulation. On standing, this blood is rapidly displaced to the lower part of the body because of the forces of gravity. Because the volume of the systemic circulation is approximately seven times that of the pulmonary circulation, a shift of blood from one system to the other has a much greater effect in the pulmonary than in the systemic circulation.

In summary, the circulatory system functions as a transport system that circulates nutrients and other materials to the tissues and removes waste products. The heart pumps blood throughout the system, and the blood vessels serve as tubes through which blood flows. The arterial system carries blood from the heart to the tissues and the veins carry it back to the heart. The circulatory system can be divided into two parts: the pulmonary circulation and the systemic circulation. The systemic circulation, which is served by the left heart, provides blood flow for all the tissues except the lungs, which are served by the right heart and the pulmonary circulation. Blood moves throughout the circulation along a pressure gradient, moving from the high-pressure

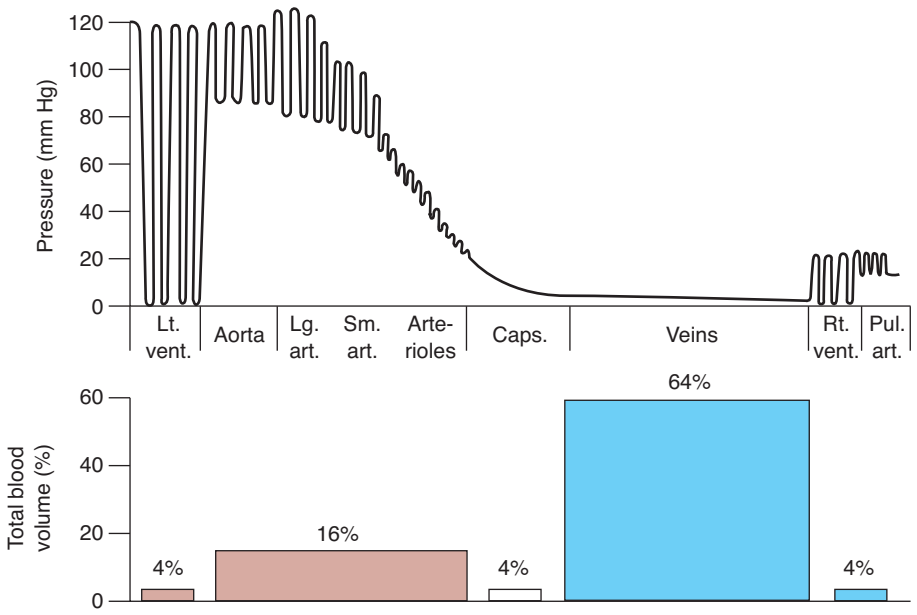


FIGURE 17-2. Pressure and volume distribution in the systemic circulation. The graphs show the inverse relation between internal pressure and volume in different portions of the circulatory system. (From Smith J.J., Kampine J.P. [1990]. *Circulatory physiology: The essentials* [3rd ed.]. Baltimore: Williams & Wilkins.)

arterial system to the low-pressure venous system. In the circulatory system, pressure is inversely related to volume. The pressure on the arterial side of the circulation, which contains only approximately one sixth of the blood volume, is much greater than the pressure on the venous side of the circulation, which contains approximately two thirds of the blood.

Principles of Blood Flow

The term *hemodynamics* refers to the principles that govern blood flow in the circulatory system. These basic principles of physics are the same as those applied to the movement of fluid in general. The concepts of flow, pressure, and resistance as applied to blood flow in the cardiovascular system will be used in subsequent chapters to describe the hemodynamic changes that occur with disorders of the cardiovascular system.

Pressure, Resistance, and Flow

The most important factors governing the flow of blood in the circulatory system are *pressure, resistance,* and *flow.* Blood flow, which is determined by the pressure difference (ΔP) between the two ends of a vessel or group of vessels and the resistance (R) that blood must overcome as it moves through the vessel or vessels, can be expressed by the equation flow = $\Delta P/R$. In the circulatory system, blood flow is represented by the cardiac output (CO). Resistance is the opposition to flow caused by friction between the moving blood components and the stationary vessel wall. In the peripheral circulation, the collective resistance of all the vessels in that part of the circulation is referred to as the *peripheral vascular resistance* (PVR) or, sometimes, as the *systemic vascular resistance.*

The blood vessels and the blood itself constitute resistance to flow. A helpful equation for understanding the relationship between resistance, vessel radius (r), vessel length (L), and blood viscosity (η) that affects blood flow was derived by the French physician Poiseuille more than a century ago. The equation Flow = $\Delta P \times \pi \times r^4/8 \times L \times$ viscosity expands the previous equation, Flow = $\Delta P/R$, by relating flow to several additional determinants of resistance—vessel radius and blood viscosity. The length of vessels does not usually change and 8 is a constant that does not change. Because flow is directly related to the fourth power of the radius, small changes in vessel radius can produce large changes in flow to an organ or tissue. For example, if the pressure remains constant, the rate of flow is 16 times greater in a vessel with a radius of 2 mm ($2 \times 2 \times 2 \times 2$) than in a vessel with a radius of 1 mm. *Viscosity* generates resistance to flow by producing friction between the molecules of a liquid. The viscosity of a liquid is largely related to its thickness or number particles that it contains. Unlike water that flows through plumbing pipes, blood is a nonhomogeneous liquid. It contains blood cells, platelets, fat globules, and plasma proteins that increase its viscosity. The red blood cells, which constitute 40% to 45% of the formed elements of the blood, largely determine the viscosity of the blood. Under special conditions, temperature may affect viscosity. There is a 2% rise in viscosity for each 1°C decrease in body temperature, a fact that helps explain the sluggish blood flow seen in persons with hypothermia.

Flow is a volume measurement (milliliters per second); it is determined by the cross-sectional area of a vessel and the velocity of flow. *Velocity* is a distance measurement; it refers to the speed or linear movement per unit time of blood as it flows through a vessel. When the flow through a given segment of the circulatory system is constant—as it must be for continuous flow—the velocity is inversely proportional to the cross-sectional area of the vessel (i.e., the smaller the cross-sectional area, the greater is the velocity of flow). This phenomenon can be compared with cars moving from a two-lane to a single-lane section of a highway. To keep traffic moving at its original pace, cars would have to double their speed in the single-lane section of the highway. So it is with flow in the circulatory system.

The linear velocity of blood flow in the circulatory system varies widely from 30 to 35 cm/second in the aorta to 0.2 to 0.3 mm/second in the capillaries. This is because even though each individual capillary is very small, the total cross-sectional area of all the systemic capillaries greatly exceeds the cross-sectional area of other parts of the circulation. As a result of this large surface area, the slower movement of blood allows ample time for exchange of nutrients, gases, and metabolites between the tissues and the blood.

Laminar Versus Turbulent Flow

Ideally, blood flow should be *laminar* or *streamlined,* with its components arranged in layers so that the plasma is adjacent to the smooth, slippery endothelial surface of the blood vessel, and the blood elements, including the platelets, are in the center or *axis* of the bloodstream. This arrangement reduces friction by allowing the blood layers to slide smoothly over one another, with the axial layer having the most rapid rate of flow. Under certain conditions, however, blood flow switches from laminar to turbulent flow. In turbulent flow, the laminar stream is disrupted and the flow becomes mixed, moving radially (crosswise) and axially (lengthwise). Because energy is used in propelling blood both radially and axially, more energy (pressure) is required to drive turbulent flow than laminar flow.

Turbulent flow can be caused by a number of factors, including high velocity of flow, change in vessel diameter, and low blood viscosity. The tendency for turbulence to occur is increased in direct proportion to the velocity of flow. Low blood viscosity allows the blood to move faster and accounts for the transient occurrence of heart murmurs in some persons who are severely anemic. Turbulence is often accompanied by vibrations of the blood and surrounding structures. Some of these vibrations are in the audible range and can be heard using a stethoscope. For example, a heart murmur results from turbulent flow

through a diseased heart valve. Turbulent flow may also predispose to clot formation as platelets and other coagulation factors come in contact with the endothelial lining of the vessel.

Wall Tension, Radius, and Pressure

In a blood vessel, *wall tension* is the force in the vessel wall that opposes the distending pressure inside the vessel. The French astronomer and mathematician Pierre de Laplace described the relationship between wall tension, pressure, and the radius of a vessel or sphere more than 200 years ago. This relationship, which has come to be known as the *law of Laplace*, can be expressed by the equation $P = T/r$, in which T is the wall tension, P is the intraluminal pressure, and r is the vessel radius (Fig. 17-3A). Accordingly, the internal pressure expands the vessel until it is exactly balanced by the tension in the vessel wall. The smaller the radius, the greater is the pressure needed to balance the wall tension. The law of Laplace can also be used to express the effect of the vessel radius on wall tension ($T = P \times r$). This correlation can be compared with a partially inflated balloon (see Fig. 17-3B). Because the pressure is equal throughout, the tension in the part of the balloon with the smaller radius is less than the tension in the section with the larger radius. The same holds true for an arterial aneurysm in which the tension and risk of rupture increase as the aneurysm grows in size (see Chapter 18).

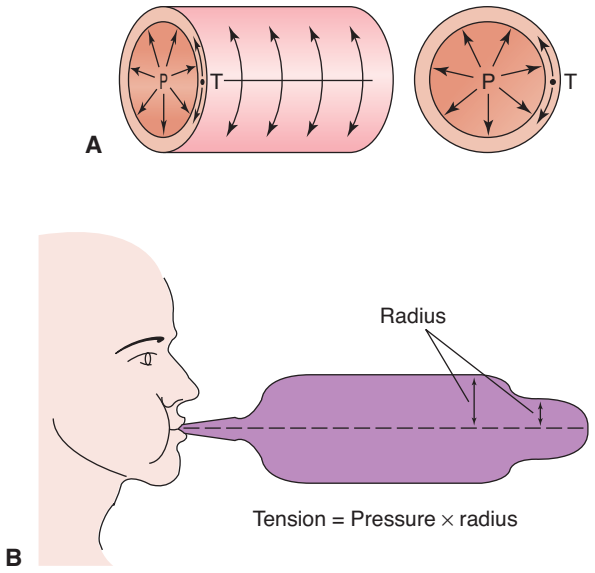


FIGURE 17-3. The law of LaPlace relates pressure (P), tension (T), and radius (r) to a cylindrical blood vessel. **(A)** The pressure expanding the vessel is equal to the wall tension divided by the vessel radius. **(B)** Effect of the radius on tension in a cylindrical balloon. In a balloon, the tension in the wall is proportional to the radius because the pressure is the same everywhere inside the balloon. The tension is lower in the portion of the balloon with the smaller radius. (From Rhoades R.A., Tanner G.A. [1996]. *Medical physiology* [p. 627]. Boston: Little, Brown.)

The law of Laplace was later expanded to include wall thickness ($T = P \times$ radius/wall thickness). Wall tension is inversely related to wall thickness, such that the thicker the vessel wall, the lower is the tension, and vice versa. In hypertension, arterial vessel walls hypertrophy and become thicker, thereby reducing the tension and minimizing wall stress. The law of Laplace can also be applied to the pressure required to maintain the patency of small blood vessels. Provided that the thickness of a vessel wall remains constant, it takes more pressure to overcome wall tension and keep a vessel open as its radius decreases in size. The *critical closing pressure* refers to the point at which vessels collapse so that blood can no longer flow through them. For example, in circulatory shock there is a decrease in blood volume and vessel radii, along with a drop in blood pressure. As a result, many of the small vessels collapse as blood pressure drops to the point where it can no longer overcome the wall tension. The collapse of peripheral veins often makes it difficult to insert venous lines that are needed for fluid and blood replacement.

Distensibility and Compliance

Distensibility refers to the ability of a blood vessel to be stretched and accommodate an increased volume of blood. It is normally expressed as the fractional increase in volume for each millimeter of mercury increase in pressure. The most distensible of all vessels are the veins, which can increase their volume with only slight changes in pressure, allowing them to function as a reservoir for storing large quantities of blood that can be returned to the circulation when it is needed. Because of their thicker muscular walls, arteries are less distensible than veins. *Compliance* refers to the *total quantity* of blood that can be stored in a given portion of the circulation for each millimeter mercury rise in pressure. The compliance of a vein is approximately 24 times that of its corresponding artery, because it is eight times as distensible and has a volume three times as great.

In summary, the most important factors governing the flow of blood in the circulatory system are pressure, resistance, and flow—factors that are influenced by vessel length, radius, cross-sectional area, wall tension, and blood viscosity. The rate of flow is directly related to the pressure difference between the two ends of the vessel and the vessel radius and inversely related to vessel length and blood viscosity. The cross-sectional area of a vessel influences the velocity of flow; as the cross-sectional area decreases, the velocity is increased, and vice versa. Laminar blood flow is flow in which there is layering of blood components in the center of the bloodstream. This reduces frictional forces and prevents clotting factors from coming in contact with the vessel

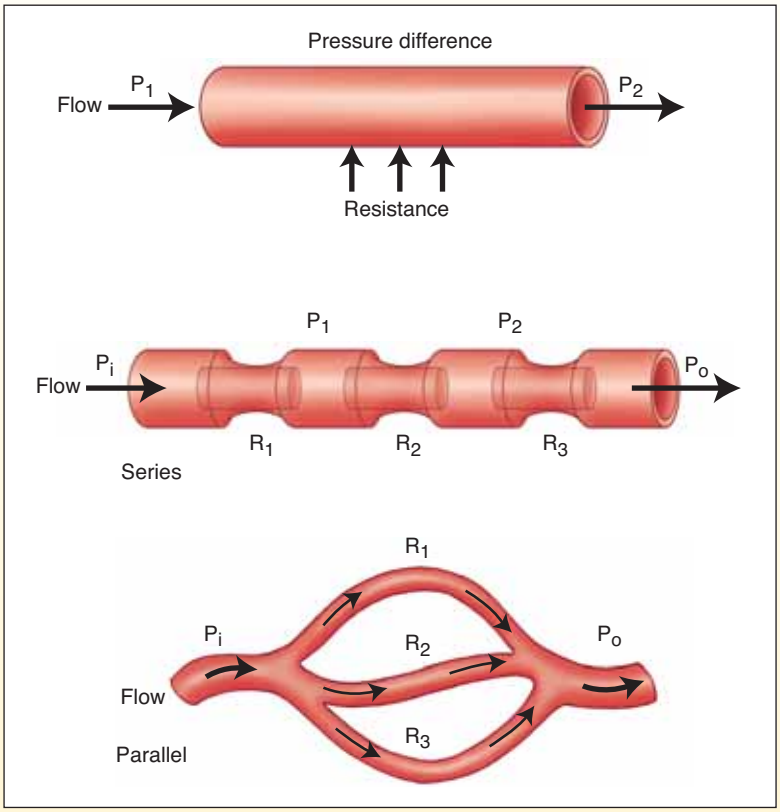
UNDERSTANDING → Hemodynamics of Blood Flow

The term *hemodynamics* is used to describe factors such as (1) pressure and resistance, (2) vessel radius, (3) cross-sectional area and velocity of flow, and (4) laminar versus turbulent flow that affect blood flow through the blood vessels in the body.

1

Pressure, Resistance, and Flow. The flow of fluid through a tube, such as blood through a blood vessel, is directly related to a pressure difference ($P_1 - P_2$) between the two ends of the tube and inversely proportional to the resistance (R) that the fluid encounters as it moves through the tube.

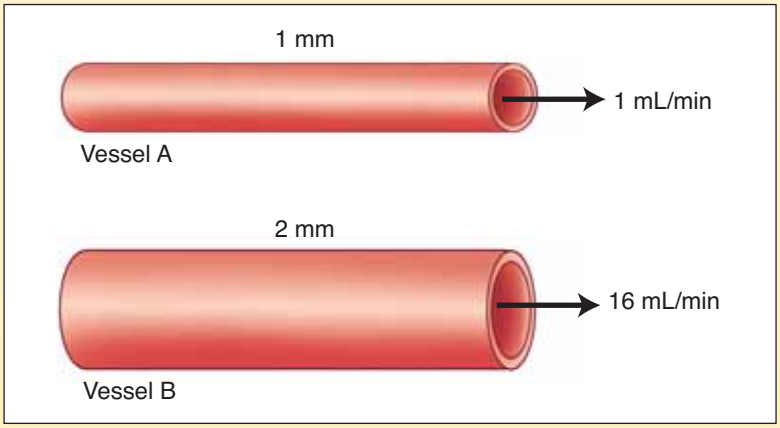
The resistance to flow, in peripheral resistance units (PRUs), is determined by the blood viscosity, vessel radius, and whether the vessels are aligned in series or in parallel. In vessels aligned in series, blood travels sequentially from one vessel to another such that the resistance becomes additive (e.g., 2 + 2 + 2 = 6 PRU). In vessels aligned in parallel, such as capillaries, the blood is not confined to a single channel but can travel through each of several parallel channels such that the resistance becomes the reciprocal of the total resistance (i.e., 1/R). As a result, there is no loss of pressure, and the total resistance (e.g., 1/2 + 1/2 + 1/2 = 3/2 PRU) is less than the resistance of any of the channels.



Pi, pressure in; Po, pressure out.

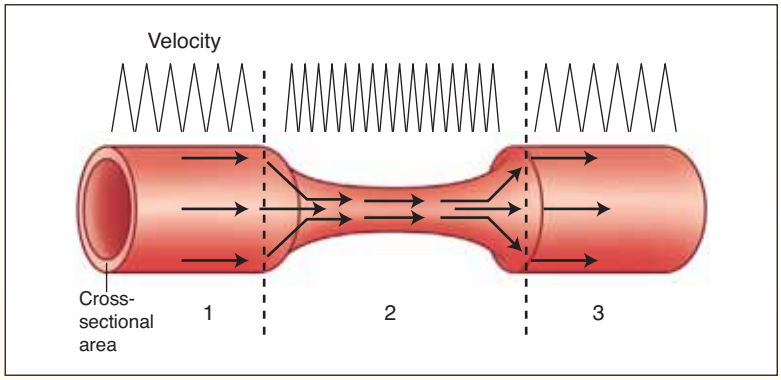
2

Vessel Radius. In addition to pressure and resistance, the rate of blood flow through a vessel is affected by the fourth power of its radius (the radius multiplied by itself four times). Thus, blood flow in vessel B with a radius of 2 mm will be 16 times greater than in vessel A with a radius of 1 mm.



3

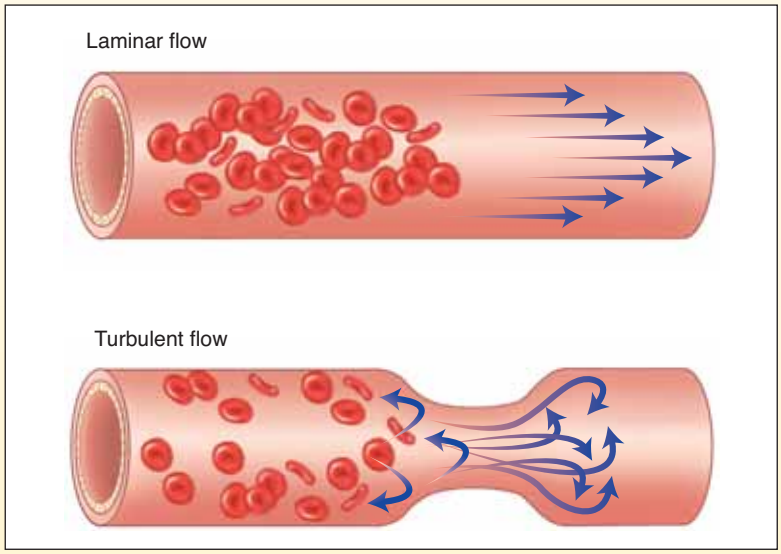
Cross-Sectional Area and Velocity of Flow. The velocity or rate of forward movement of the blood is affected by the cross-sectional area of a blood vessel. As the cross-sectional area of a vessel increases (sections 1 and 3), blood must flow laterally as well as forward to fill the increased area. As a result, the mean forward velocity decreases. In contrast, when the cross-sectional area is decreased (section 2), the lateral flow decreases and the mean forward velocity is increased.



4

Laminar and Turbulent Flow. Blood flow is normally laminar, with platelets and blood cells remaining in the center or axis of the bloodstream. Laminar blood flow can be described as layered flow in which a thin layer of plasma adheres to the vessel wall, while the inner layers of blood cells and platelets shear against this motionless layer. This allows each layer to move at a slightly faster velocity, with the greatest velocity occurring in the central part of the bloodstream.

Turbulent blood flow is flow in which the blood elements do not remain confined to a definite lamina or layer, but develop vortices (i.e., a whirlpool effect) that push blood cells and platelets against the wall of the vessel. More pressure is required to force a given flow of blood through the same vessel (or heart valve) when the flow is turbulent rather than laminar. Turbulence can result from an increase in velocity of flow, a decrease in vessel diameter, or low blood viscosity. Turbulence is usually accompanied by vibrations of the fluid and surrounding structures. Some of these vibrations in the cardiovascular system are in the audible frequency range and may be detected as murmurs or bruits.



wall. In contrast to laminar flow, turbulent flow is disordered flow, in which the blood moves crosswise and lengthwise in blood vessels. The relation between wall tension, transmural pressure, and radius is described by the law of Laplace, which states that the pressure needed to overcome wall tension becomes greater as the radius decreases. Wall tension is also affected by wall thickness; it increases as the wall becomes thinner and decreases as the wall becomes thicker. Compliance, which reflects the distensibility of blood vessels, refers to the total quantity of blood that can be stored in a given part of the circulatory system for each millimeter mercury change in pressure.

The Heart as a Pump

The heart is a four-chambered muscular pump approximately the size of a fist that beats an average of 70 times each minute, 24 hours each day, 365 days each year for a lifetime. In 1 day, this pump moves more than 1800 gallons of blood throughout the body, and the work performed by the heart over a lifetime would lift 30 tons to a height of 30,000 ft.

Functional Anatomy of the Heart

The heart, which is enclosed in a loose-fitting sac called the *pericardium*, is located between the lungs in the mediastinal space of the intrathoracic cavity. It is located posterior to the sternum and anterior to the vertebral column and extends about 5 inches from the second to fifth vertebrae (Fig. 17-4A). The heart is suspended by the great vessels, with its broader side (i.e., base) facing upward and its tip (i.e., apex) pointing downward, forward, and to the left. The heart is positioned obliquely, so that the right side of the heart is almost fully in front of the left side of the heart, with only a small portion of the lateral left ventricle on the frontal plane of the heart (Fig. 17-4B). When the hand is placed on the thorax, the main impact of the heart's contraction is felt against the chest wall at a point between the fifth and sixth ribs, a little below the nipple and approximately 3 inches to the left of the midline. This is called the *point of maximum impulse*.

The wall of the heart is composed of an outer epicardium, which lines the pericardial cavity; the myocardium or muscle layer; and the smooth endocardium, which lines the chambers of the heart (Fig. 17-5). A fibrous skeleton supports the valvular structures of the heart. The interatrial and interventricular septa divide the heart into a right and a left pump, each composed of two muscular chambers: a thin-walled atrium, which serves as a reservoir for blood coming into the heart, and a thick-walled ventricle, which pumps blood out of the heart. The increased thickness of the left ventricular wall compared to the right ventricle (Fig. 17-4C) results from the additional work this ventricle is required to perform.

The Heart

- The heart is a four-chambered pump consisting of two atria (the right atrium, which receives blood returning to the heart from the systemic circulation, and the left atrium, which receives oxygenated blood from the lungs) and two ventricles (a right ventricle, which pumps blood to the lungs, and a left ventricle, which pumps blood into the systemic circulation).
- Heart valves control the direction of blood flow from the atria to the ventricles (the atrioventricular valves), from the right side of the heart to the lungs (pulmonic valve), and from the left side of the heart to the systemic circulation (aortic valve).
- The myocardium, or muscle layer of the atria and ventricles, produces the pumping action of the heart. Intercalated disks between cardiac muscle cells contain gap junctions that allow for immediate communication of electrical signals from one cell to another so the cardiac muscle acts as a single unit, or syncytium.
- The cardiac cycle is divided into two major periods: systole, when the ventricles are contracting, and diastole, when the ventricles are relaxed and filling.
- The cardiac output or amount of blood that the heart pumps each minute is determined by the amount of blood pumped with each beat (stroke volume) and the number of times the heart beats each minute (heart rate). Cardiac reserve refers to the maximum percentage of increase in cardiac output that can be achieved above the normal resting level.
- The work of the heart is determined by the volume of blood it pumps out (preload) and the pressure that it must generate to pump the blood out of the heart (afterload).

Pericardium

The pericardium forms a fibrous covering around the heart, holding it in a fixed position in the thorax and providing physical protection and a barrier to infection. The pericardium consists of a tough outer fibrous layer and a thin inner serous layer. The outer fibrous layer is attached to the great vessels that enter and leave the heart, the sternum, and the diaphragm. The fibrous pericardium is highly resistant to distention; it prevents acute dilatation of the heart chambers and exerts a restraining effect on the left ventricle. The inner serous layer consists

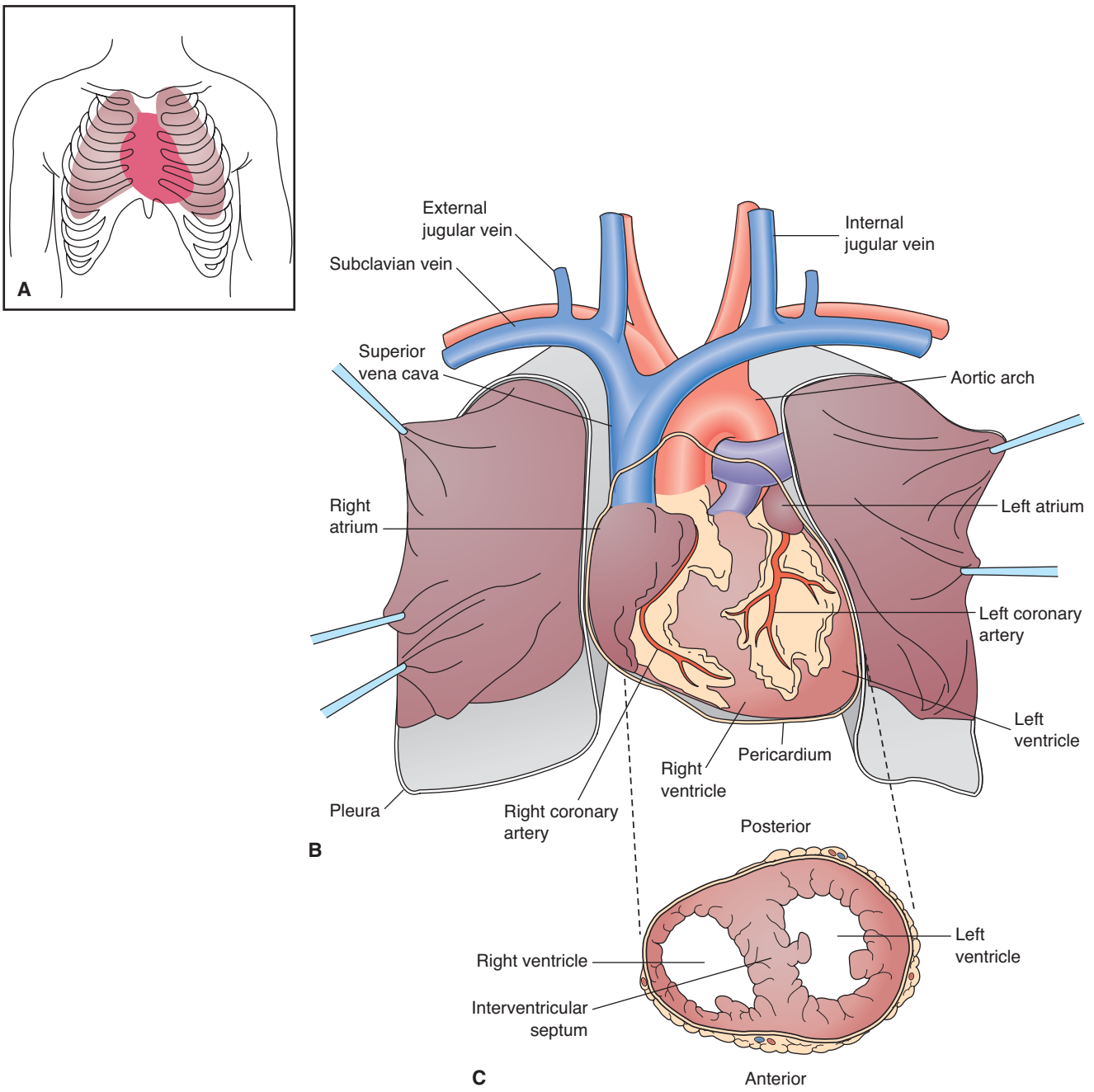


FIGURE 17-4. **(A)** The heart in relation to the sternum, ribs, and lungs. **(B)** Anterior view of the heart and great vessels (note that the lungs, which normally fold over part of the heart's anterior, have been pulled back). **(C)** Cross-section of the heart showing the increased thickness of the left ventricle compared to the right.

of a visceral layer and a parietal layer. The visceral layer, also known as the visceral pericardium or *epicardium*, covers the entire heart and great vessels and then folds over to form the parietal layer that lines the fibrous pericardium (see Fig. 17-5). Between the visceral and parietal layers is the *pericardial cavity*, a potential space that contains 30 to 50 mL of serous fluid. This fluid acts as a lubricant to minimize friction as the heart contracts and relaxes.

Myocardium

The myocardium, or muscular portion of the heart, forms the walls of the atria and ventricles. Cardiac muscle cells, like skeletal muscle, are striated and composed of *sarcomeres* that contain actin and myosin filaments (see Chapter 1). They are smaller and more compact than skeletal muscle cells and contain many large mitochondria, reflecting their continuous energy needs.

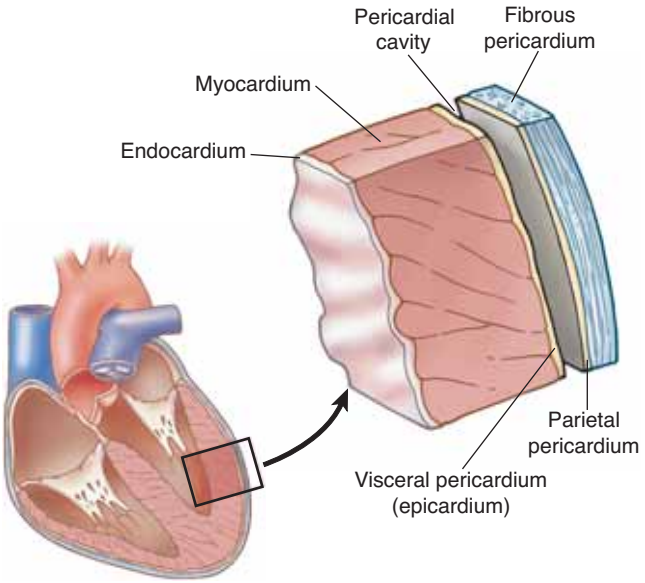


FIGURE 17-5. Layers of the heart, showing the visceral pericardium, the pericardial cavity, and the parietal pericardium.

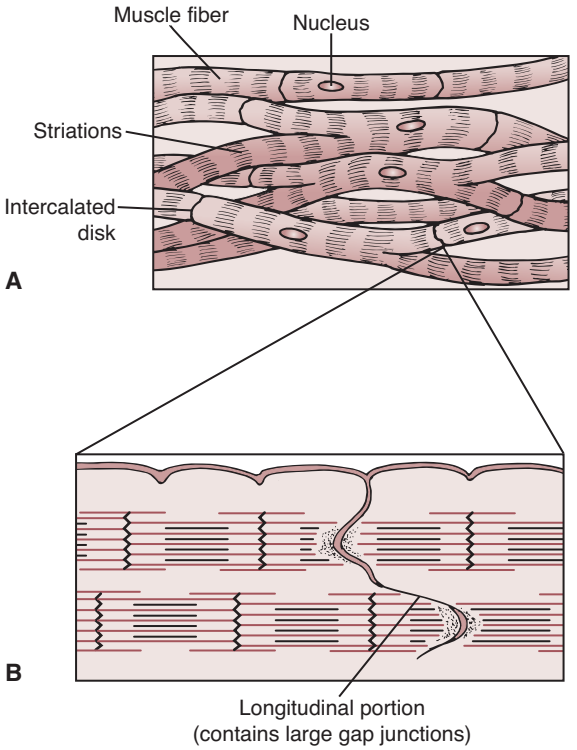


FIGURE 17-6. **(A)** Cardiac muscle fibers showing their branching structure. **(B)** Area indicated where cell junctions lie in the intercalated disks.

The contractile properties of cardiac muscle are similar to those of skeletal muscle, except the contractions are involuntary and the duration of contraction is much longer. Unlike the orderly longitudinal arrangement of skeletal muscle fibers, cardiac muscle cells are arranged as an interconnecting latticework, with their fibers dividing, recombining, and then dividing again (Fig. 17-6A). The fibers are separated from neighboring cardiac muscle cells by dense structures called *intercalated disks*. The intercalated disks, which are unique to cardiac muscle, contain gap junctions that serve as low-resistance pathways for passage of ions and electrical impulses from one cardiac cell to another (Fig. 17-6B). Thus, the myocardium behaves as a single unit, or *syncytium*, rather than as a group of isolated units, as does skeletal muscle. When one myocardial cell becomes excited, the impulse travels rapidly so the heart can beat as a unit.

As in skeletal muscle, cardiac muscle contains actin and myosin filaments, which interact and slide along one another during muscle contraction. A number of important proteins regulate actin–myosin binding. These include tropomyosin and the troponin complex (see Chapter 1, Fig. 1-19). The troponin complex consists of three subunits (troponin T, troponin I, and troponin C) that regulate calcium-mediated contraction in striated muscle. In clinical practice, the serum levels of specific cardiac forms of troponin T and troponin I are used in the diagnosis of myocardial infarction (see Chapter 19).

Although cardiac muscle cells require calcium for contraction, they have a less well-defined sarcoplasmic reticulum for storing calcium than skeletal muscle cells. Thus, cardiac muscle relies more heavily than skeletal muscle on an influx of extracellular calcium ions for contraction. The cardiac glycosides (e.g., digoxin) are inotropic drugs that increase cardiac contractility by increasing the free intracellular calcium concentration in cardiac muscle.

Endocardium

The endocardium is a thin, three-layered membrane that lines the heart and covers the valves. The innermost layer, which lines the heart chambers, consists of smooth endothelial cells supported by a thin layer of connective tissue. The endothelial lining of the endocardium is continuous with the lining of the blood vessels that enter and leave the heart. The middle layer consists of dense connective tissue with elastic fibers. The outer layer, which is composed of irregularly arranged connective tissue cells, contains blood vessels and branches of the conduction system and is continuous with the myocardium.

Heart Valves and Fibrous Skeleton

An important structural feature of the heart is its fibrous skeleton, which consists of four interconnecting valve rings and surrounding connective tissue (Fig. 17-7). The fibrous skeleton separates the atria and ventricles and forms a rigid support for attachment of the valves and insertion of the cardiac muscle. The tops of the valve rings are attached to the muscle tissue of the atria, pulmonary trunks, and aorta. The bottoms are attached to the ventricular walls. For the heart to function effectively, blood must flow in one direction only, moving forward through the chambers of the right heart to the lungs and then through the chambers of the left heart to the systemic circulation. This unidirectional flow is provided by the heart's paired atrioventricular (i.e., tricuspid and mitral)

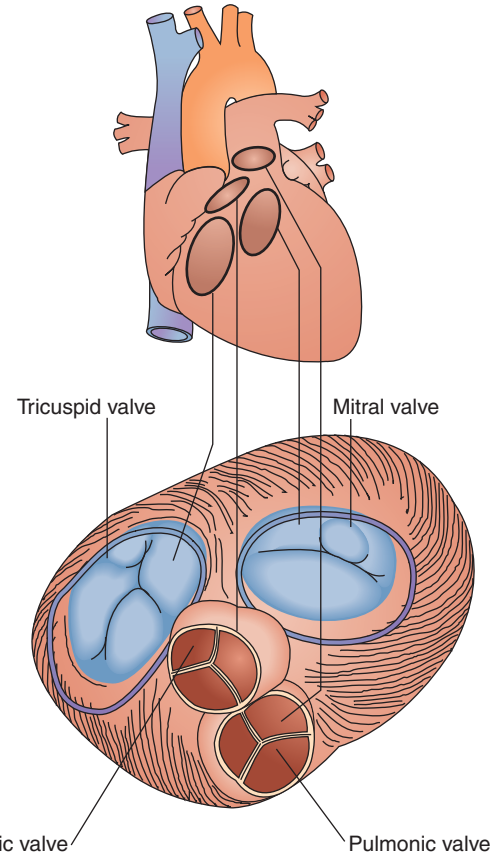


FIGURE 17-7. Fibrous skeleton of the heart, which forms the four interconnecting valve rings and support for attachment of the valves and insertion of cardiac muscle.

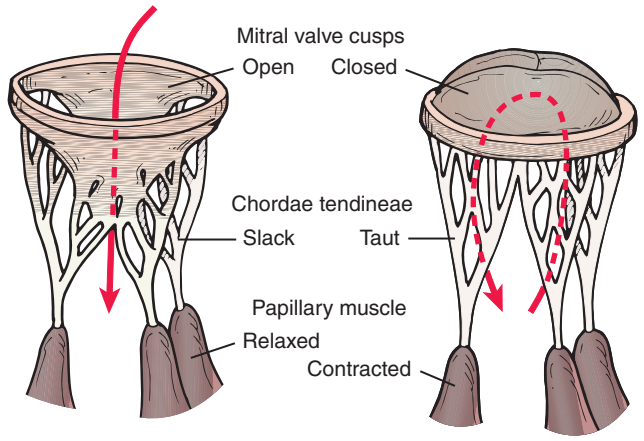


FIGURE 17-9. The mitral atrioventricular valve showing the papillary muscles and chordae tendineae. **(A)** The open mitral valve with relaxed papillary muscles and slack chordae tendineae. **(B)** The closed mitral valve with contracted papillary muscles and taut chordae tendineae that prevent the valve cusps from everting into the atria.

valves and two semilunar (i.e., pulmonic and aortic) valves (Fig. 17-8).

The atrioventricular (AV) valves control the flow of blood between the atria and the ventricles (Fig. 17-9). The thin edges of the AV valves form cusps, two on the left side of the heart (i.e., *bicuspid* or *mitral valve*) and three on the right side (i.e., *tricuspid valve*). The AV valves are supported by the papillary muscles, which

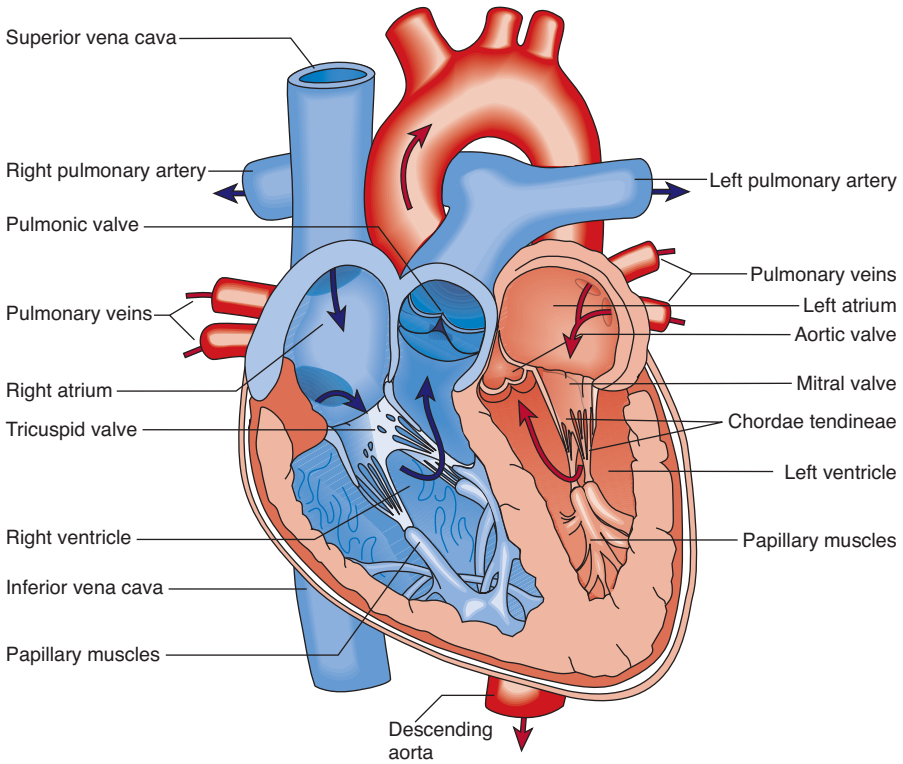


FIGURE 17-8. Valvular structures of the heart. The atrioventricular valves are in an open position, and the semilunar valves are closed. There are no valves to control the flow of blood at the inflow channels (i.e., vena cava and pulmonary veins) to the heart.

project from the wall of the ventricles, and the chordae tendineae, which attach to the valve. Contraction of the papillary muscles at the onset of systole ensures closure by producing tension on the leaflets of the AV valves before the full force of ventricular contraction pushes against them. The chordae tendineae are cordlike structures that support the AV valves and prevent them from everting into the atria during systole.

The *aortic* and *pulmonic* valves control the movement of blood out of the ventricles. The pulmonic valve, which is located between the right ventricle and the pulmonary artery, controls the flow of blood into the pulmonary circulation, and the aortic valve, located between the left ventricle and the aorta, controls the flow of blood into the systemic circulation. Because their flaps are shaped like half-moons, they are often referred to as the *semilunar* valves. The semilunar valves have three cuplike cusps that are attached to the valve rings (Fig. 17-10B). These cuplike structures collect the *retrograde*, or backward, flow of blood that occurs toward the end of systole, enhancing closure. For the development of a perfect seal along the free edges of the semilunar valves, each valve cusp must have a triangular shape, which is facilitated by a nodular thickening at the apex of each leaflet (Fig. 17-10A). Behind the semilunar valves are the *sinuses of Valsalva*. In these sinuses, eddy currents develop that tend to keep the valve cusps away from the vessel walls. The openings for the coronary arteries are located behind the right and left cusps, respectively, of the aortic valve. Were it not for the presence of the sinuses of Valsalva and the eddy currents, the coronary artery openings would be blocked by the valve cusps.

There are no valves at the atrial sites (i.e., venae cavae and pulmonary veins) where blood enters the heart (see Fig. 17-8). This means that excess blood is pushed back into the veins when the atria become distended. For example, the jugular veins typically become prominent in severe right-sided heart failure, whereas normally they are flat or collapsed. Likewise, the pulmonary venous system becomes congested when outflow from the left atrium is impeded.

Cardiac Conduction System

Heart muscle is unique among other muscles in that it is capable of generating and rapidly conducting its own action potentials (i.e., electrical impulses). These action potentials result in excitation of muscle fibers throughout the myocardium. Impulse formation and conduction result in weak electrical currents that spread through the entire body. An electrocardiogram (ECG) or recording of the electrical activity of the heart can be obtained when electrodes are applied to various positions on the body and connected to an electrocardiograph monitor or recorder.

In certain areas of the heart, the myocardial cells have been modified to form the specialized cells of the conduction system (Fig. 17-11). Although most myocardial cells are capable of initiating and conducting impulses, it is this specialized conduction system that maintains the pumping efficiency of the heart. Specialized pacemaker cells generate impulses at a faster rate than do other types of heart tissue, and the conduction tissue transmits impulses at a faster rate than do other types of heart tissue. Because of these properties, the conduction system usually controls the rhythm of the heart.

The conduction system consists of the sinoatrial (SA) node, where the rhythmic impulse is generated; the internodal pathways, which conduct the impulse from the SA node to the AV node; the AV node, in which the impulse from the atria is delayed before passing to the ventricles; the AV bundle, which conducts the impulse from the atria to the ventricles; and the left and right bundles of the Purkinje system, which conduct the impulses to all parts of the ventricles.

The *SA node* has the fastest intrinsic rate of firing (60 to 100 beats per minute) and is normally the pacemaker of the heart. The heart essentially has two conduction

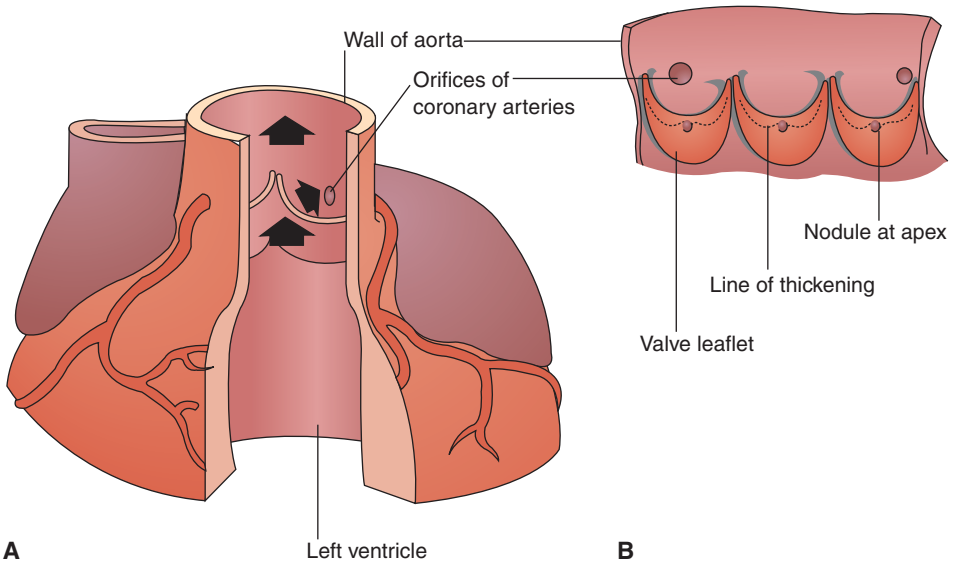


FIGURE 17-10. Diagram of the aortic valve. **(A)** The position of the aorta at the base of the ascending aorta is indicated. **(B)** The appearance of the three leaflets of the aortic valve when the aorta is cut open and spread out, flat. (Cormack D.H. [1987]. *Ham's histology* [9th ed.]. Philadelphia: J.B. Lippincott.)

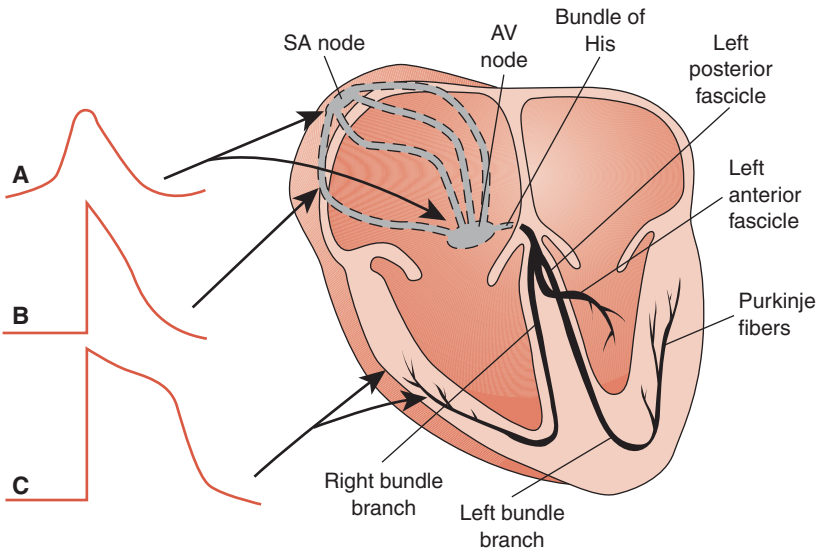


FIGURE 17-11. Conduction system of the heart and action potentials. **(A)** Action potential of sinoatrial (SA) and atrioventricular (AV) nodes. **(B)** Atrial muscle action potential. **(C)** Action potential of ventricular muscle and Purkinje fibers.

systems: one that controls atrial activity and one that controls ventricular activity. The AV junction connects the two systems and normally provides for a one-way conduction between the atria and ventricles. Within the AV node, atrial fibers connect with very small junctional fibers of the node itself. Because of these connections, the zone surrounding and including the AV node and the adjacent atrial and ventricular conduction pathways is often referred to as the *AV junctional area*. The velocity of conduction through these fibers is very slow (approximately one-half that of normal cardiac muscle), which greatly delays transmission of the impulse into the AV node. A further delay occurs as the impulse travels through the AV node into the transitional fibers and into the AV bundle, also known as the *bundle of His*. This delay provides a mechanical advantage whereby the atria complete their ejection of blood before ventricular contraction begins. Under normal circumstances, the AV junction provides the only connection between the two conduction systems. The atria and ventricles would beat independently of each other if the transmission of impulses through the AV node were blocked.

The Purkinje system, which supplies the ventricles, has large specialized fibers that allow for rapid conduction and almost instantaneous excitation of both the right and left ventricles. This rapid rate of conduction is necessary for the swift and efficient ejection of blood from the heart. Fibers of the Purkinje system originate in the AV node and then travel downward in the AV bundle into the ventricular septum, where they divide to form the *right* and *left bundle branches* that lie beneath endocardium on the two respective sides of the ventricular septum. The main trunk of the left bundle branch extends for approximately 1 to 2 cm before fanning out as it enters the septal area and divides further into two segments: the *left posterior* and *anterior fascicles*.

The AV nodal fibers, when not stimulated, discharge at an intrinsic rate of 45 to 50 times a minute, and the Purkinje fibers discharge 15 to 40 times per minute. Although the AV node and Purkinje system have the ability to control the rhythm of the heart, they do not normally do so because the discharge rate of the SA node is considerably faster. Each time the SA node discharges, its impulses are conducted into the AV junctional and Purkinje fibers, causing them to fire. The AV node can assume the pacemaker function of the heart, should the SA node fail to discharge, and the Purkinje system can assume the pacemaker function of the ventricles, should the AV junction fail to conduct impulses from the atria to the ventricles. Under these circumstances, the heart rate reflects the intrinsic firing rate of the prevailing structures.

Action Potentials

An action potential represents the sequential change in electrical potential that occurs across a cell membrane when excitation occurs (see Chapter 4, Understanding Membrane Potentials). Action potentials can be divided into three parts: the *resting* or *unexcited* state during which the membrane is polarized (positive on the outside and negative on the inside of the membrane), *depolarization* or change in the direction of polarity (positive on the inside and negative on the outside), and *repolarization* or reestablishment of polarity of the resting membrane potential. The sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) ions are the major charge carriers in cardiac muscle cells. Disorders of the ion channels along with disruption in the flow of these current-carrying ions are increasingly being linked to the generation of cardiac arrhythmias and conduction disorders.

The action potential of cardiac muscle is divided into five phases: *phase 0*—the upstroke or rapid depolarization; *phase 1*—early repolarization; *phase 2*—the plateau; *phase 3*—rapid repolarization; and *phase 4*—the resting membrane potential (Fig. 17-12A). Cardiac muscle has three types of membrane ion channels that contribute to the voltage changes that occur during these phases of the action potential. They are the (1) fast sodium channels, (2) slow

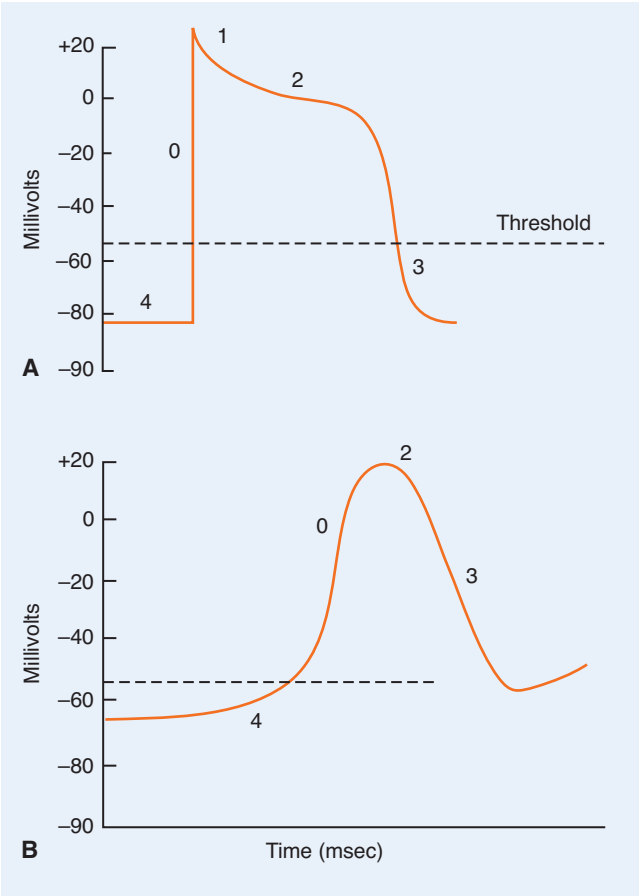


FIGURE 17-12. Phases in an action potential recorded from **(A)** a fast response in a cardiac muscle cell and **(B)** a slow response recorded in the sinoatrial and atrioventricular nodes. The phases of the action potential are identified by numbers: phase 4, resting membrane potential; phase 0, depolarization; phase 1, brief period of repolarization; phase 2, plateau; phase 3, repolarization. The slow response is characterized by a slow, spontaneous rise in the phase 4 membrane potential to threshold levels; it has a lesser amplitude and shorter duration than the fast response. Increased automaticity (B) occurs when the rate of phase 4 depolarization is increased.

calcium-sodium channels, and (3) potassium channels. During *phase 0* in atrial and ventricular muscle and in the Purkinje system, opening of the fast sodium channels for a few ten-thousandths of a second is responsible for the spikelike onset of the action potential. The point at which the sodium gates open is called the *depolarization threshold*. When the cell has reached this threshold, a rapid influx of sodium ions to the interior of the membrane causes the membrane potential to shift from a resting membrane potential of approximately −90 mV to +20 mV.

Phase 1 occurs at the peak of the action potential and signifies inactivation of the fast sodium channels with an abrupt decrease in sodium permeability. *Phase 2* represents the plateau of the action potential. It is caused primarily by the slower opening of the calcium channels, which lasts for a few tenths of a second. Calcium ions entering the muscle during this phase of the action potential play a key role in the contractile process of the cardiac muscle fibers. These unique features of the phase 2 plateau cause the action potential of cardiac muscle to last 3 to 15 times longer than that of skeletal muscle and cause a corresponding increased period of contraction.

Phase 3 reflects final rapid repolarization and begins with the down-slope of the action potential. During the phase 3 repolarization period, the slow channels close and the influx of calcium and sodium ceases. There is a sharp rise in potassium permeability, contributing to the rapid outward movement of potassium during this phase and facilitating the reestablishment of the resting membrane potential (−90 mV). At the conclusion of phase 3, distribution of sodium and potassium returns to the normal resting state. *Phase 4* is the resting membrane potential. During phase 4, the sodium-potassium pump is activated, transporting sodium out of the cell and moving potassium back into the cell.

There are two main types of action potentials in the heart—the slow response and the fast response. The *slow response,* which is initiated by the slow calcium channels, is found in the SA node, which is the natural pacemaker of the heart, and the conduction fibers of the AV node (see Fig. 17-12B). The *fast response,* which is characterized by the opening of the fast sodium channels, occurs in the normal myocardial cells of the atria, the ventricles, and the Purkinje fibers (Fig. 17-12A). The fast-response cardiac cells do not normally initiate cardiac action potentials. Instead, these impulses originate in the specialized slow-response cells of the SA node and are conducted to the fast-response myocardial cells in the atria and ventricles, where they effect a change in membrane potential to the threshold level. On reaching threshold, the voltage-dependent sodium channels open to initiate the rapid upstroke of the phase 1 action potential. The amplitude and the rate of rise of phase 1 are important to the conduction velocity of the fast response.

The hallmark of the pacemaker cells in the SA and AV nodes is a spontaneous phase 4 depolarization. The membrane permeability of these cells allows a slow inward leak of current to occur through the slow channels during phase 4. This leak continues until the threshold for firing is reached, at which point the cell spontaneously depolarizes. The rate of pacemaker cell discharge varies with the resting membrane potential and the slope of phase 4 depolarization (see Fig. 17-12B). Catecholamines (i.e., epinephrine and norepinephrine) increase the heart rate by increasing the slope or rate of phase 4 depolarization. Acetylcholine, which is released during vagal stimulation of the heart, slows the heart rate by decreasing the slope of phase 4.

Absolute and Relative Refractory Periods

There is a period in the action potential curve during which no stimuli can generate another action potential (Fig. 17-13). This period, which is known as the *absolute refractory period,* includes phases 0, 1, 2 and part of phase 3. During this time, the cell cannot depolarize again under any circumstances. In skeletal muscle, the refractory period is very short compared with the duration of muscle contraction, such that a second contraction can

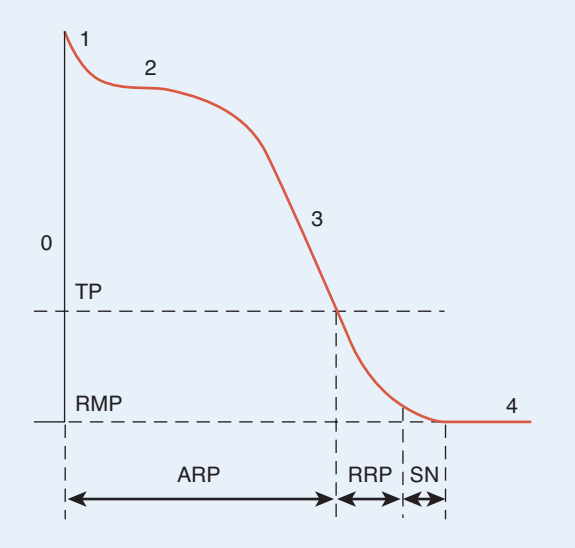


FIGURE 17-13. Diagram of an action potential of a ventricular muscle cell, showing the threshold potential (TP), resting membrane potential (RMP), absolute refractory period (ARP), relative refractory period (RRP), and supernormal (SN) period.

be initiated before the first is over, resulting in a summated tetanized contraction. In cardiac muscle, the absolute refractory period is almost as long as the contraction and a second contraction cannot be stimulated until the first is over. The longer length of the absolute refractory period of cardiac muscle is important in maintaining the alternating contraction and relaxation that are essential to the pumping action of the heart and for the prevention of fatal arrhythmias. When repolarization has returned the membrane potential to a level below the threshold potential, but not to the resting membrane potential, the cell is capable of responding to a greater than normal stimulus. This part of the action potential is referred to as the *relative refractory period*. After the relative refractory period there is a short period, called the *supernormal excitatory period*, during which a weak stimulus can evoke a response. It is during this period that many cardiac arrhythmias develop.

Arrhythmias and Conduction Disorders

Arrhythmias represent disorders of cardiac rhythm. Cardiac arrhythmias are commonly divided into two categories: supraventricular and ventricular arrhythmias. The supraventricular arrhythmias include those that are generated in the SA node, atria, AV node, and junctional tissues. The ventricular arrhythmias include those that are generated in the ventricular conduction system and the ventricular muscle. Because the ventricles are the pumping chambers of the heart, ventricular arrhythmias (e.g., ventricular tachycardia and fibrillation) are the most serious in terms of immediate life-threatening events.

Disorders of cardiac rhythm can range from an excessively rapid heart rate (tachyarrhythmias) to an extremely slow heart rate (bradyarrhythmias). Conduction disorders disrupt the flow of impulses through the conduction system of the heart. *Heart block* occurs when the conduction of impulses is blocked, often in the AV junction. Under normal conditions, the AV junction provides the only connection for transmission of impulses between the atrial and ventricular conduction systems; in complete heart block, the atria and ventricles beat independently of each other. The most serious effect of some forms of AV block is a slowing of heart rate to the extent that circulation to the brain is compromised. An *ectopic pacemaker* is an excitable focus outside the normally functioning SA node. A *premature ventricular complex* (PVC) occurs when an ectopic pacemaker initiates a beat. The occurrence of frequent PVCs in the diseased heart predisposes one to the development of other, more serious arrhythmias, including ventricular tachycardia and ventricular fibrillation.

Fibrillation is the result of disorganized current flow within the atria (atrial fibrillation) or ventricle (ventricular fibrillation). Fibrillation interrupts the normal contraction of the atria or ventricles. In ventricular fibrillation, the ventricle quivers but does not contract. When the ventricle does not contract, there is no cardiac output, and there are no palpable or audible pulses. Ventricular fibrillation is a fatal event unless treated with immediate defibrillation.

Electrocardiography

The ECG is a recording of the electrical activity of the heart. The electrical currents generated by the heart spread through the body to the skin, where they can be sensed by appropriately placed electrodes, amplified, and viewed on an oscilloscope or chart recorder. Figure 17-14 depicts the electrical activity of the conduction system on an ECG tracing. The deflection points of an ECG are designated by the letters P, Q, R, S, and T. SA node depolarization does have sufficient current to be revealed on the ECG. The P wave represents the atrial depolarization, the QRS complex (i.e., beginning of the Q wave to the end of the S wave) depicts ventricular depolarization, and the T wave portrays ventricular repolarization. The isoelectric or zero line between the P wave and the Q wave represents depolarization of the AV node, bundle branches, and Purkinje system (see Fig. 17-14). Atrial repolarization occurs during ventricular depolarization and is hidden in the QRS complex.

On the horizontal axis of the ECG, the unit of measurement is time in seconds, and on the vertical axis the unit of measurement is the amplitude of the impulse in millivolts (mV). The vertical lines are time calibration lines, with five 0.04-second vertical lines representing 0.20 seconds (Fig. 17-14). The horizontal lines are arranged so that five lines of upward or downward deflection in the ECG tracing represent 0.50 mV.

The ECG records the potential difference in charge between two electrodes as the depolarization and repolarization waves move through the heart and are conducted to the skin surface. The shape of the recorder tracing is determined by the direction in which the impulse spreads through the heart muscle in relation to

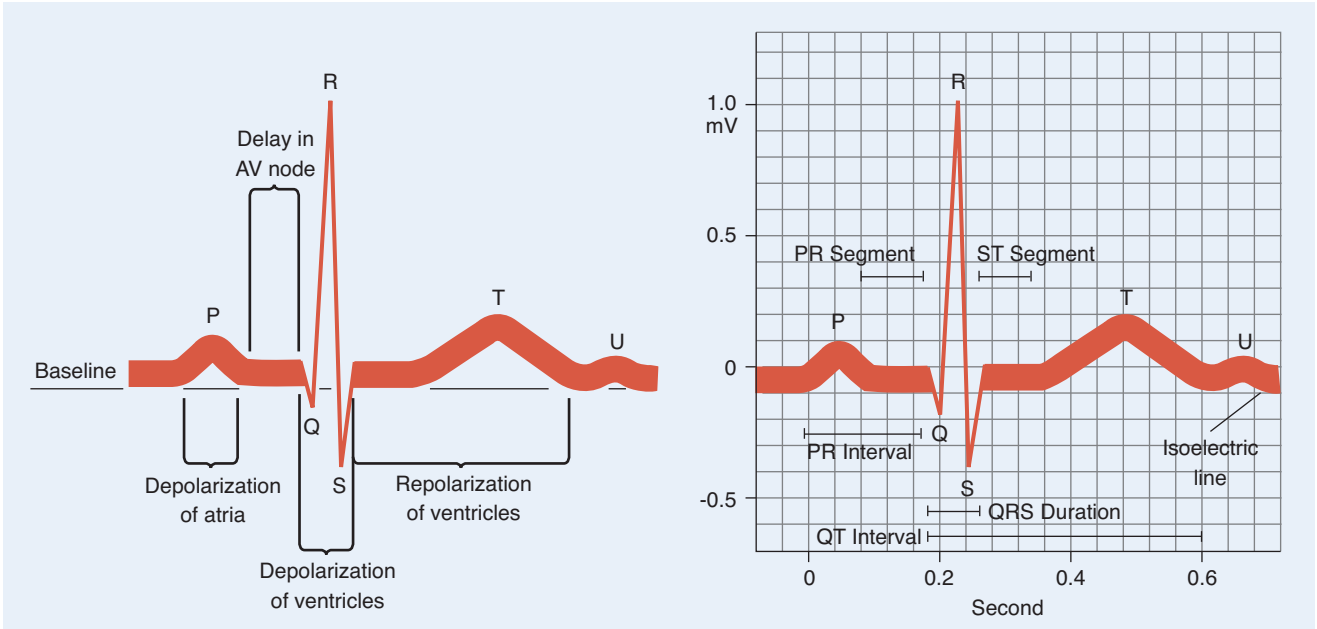


FIGURE 17-14. Diagram of the electrocardiogram (lead II) and representative depolarization and repolarization of the atria and ventricles. The P wave represents atrial depolarization, the QRS complex ventricular depolarization, and the T wave ventricular repolarization. Atrial repolarization occurs during ventricular depolarization and is hidden under the QRS complex. AV, atrioventricular.

electrode placement. A depolarization wave that moves toward the recording electrode registers as a positive, or upward, deflection. Conversely, if the impulse moves away from the recording electrode, the deflection is downward, or negative. When there is no flow of charge between electrodes, the potential is zero, and a straight line is recorded at the baseline of the chart.

Conventionally, 12 leads or electrodes are used for recording a diagnostic ECG, each providing a unique view of the electrical forces of the heart from a different position on the body's surface. Six limb leads view the electrical forces as they pass through the heart on the frontal or vertical plane. The electrodes for the limb leads are attached to the four extremities or representative areas on the body near the shoulders and lower chest or abdomen. Chest electrodes provide a view of the electrical forces as they pass through the heart on the horizontal plane. They are moved to different positions on the chest, including the right and left sternal borders and the left anterior surface. When indicated, additional electrodes may be applied to other areas of the body, such as the posterior or right anterior chest.

Cardiac Cycle

The term *cardiac cycle* is used to describe the rhythmic pumping action of the heart. The cardiac cycle is divided into two parts: *systole,* the period during which the ventricles are contracting, and *diastole,* the period during which the ventricles are relaxed and filling with blood. Simultaneous changes occur in atrial pressure, ventricular pressure, aortic or pulmonary artery pressure, ventricular volume, the ECG, and heart sounds during the cardiac cycle (Fig. 17-15).

Ventricular Systole and Diastole

Ventricular systole is divided into two periods: the isovolumetric contraction period and the ejection period. The *isovolumetric contraction period,* which begins with the closure of the AV valves and occurrence of the first heart sound, heralds the onset of systole. Immediately after closure of the AV valves, there is an additional 0.02 to 0.03 second during which the semilunar outlet (pulmonic and aortic) valves remain closed. During this period, the ventricular volume remains the same while the ventricles contract, producing an abrupt increase in pressure. The ventricles continue to contract until left ventricular pressure is slightly higher than aortic pressure, and right ventricular pressure is higher than pulmonary artery pressure. At this point, the semilunar valves open, signaling the onset of the *ejection period.* Approximately 60% of the stroke volume is ejected during the first quarter of systole, and the remaining 40% is ejected during the next two quarters of systole. Little blood is ejected from the heart during the last quarter of systole, although the ventricles remain contracted. At the end of systole, the ventricles relax, causing a precipitous fall in intraventricular pressures. As this occurs, blood from the large arteries flows back toward the ventricles, causing the aortic and pulmonic valves to snap shut—an event that is marked by the second heart sound.

The aortic pressure reflects changes in the ejection of blood from the left ventricle. There is a rise in pressure and stretching of the elastic fibers in the aorta as blood is ejected into the aorta at the onset of the ejection period. The aortic pressure continues to rise and then begins to fall during the last quarter of systole as blood flows out of the aorta into the peripheral vessels. The incisura, or notch, in the aortic pressure tracing represents closure of

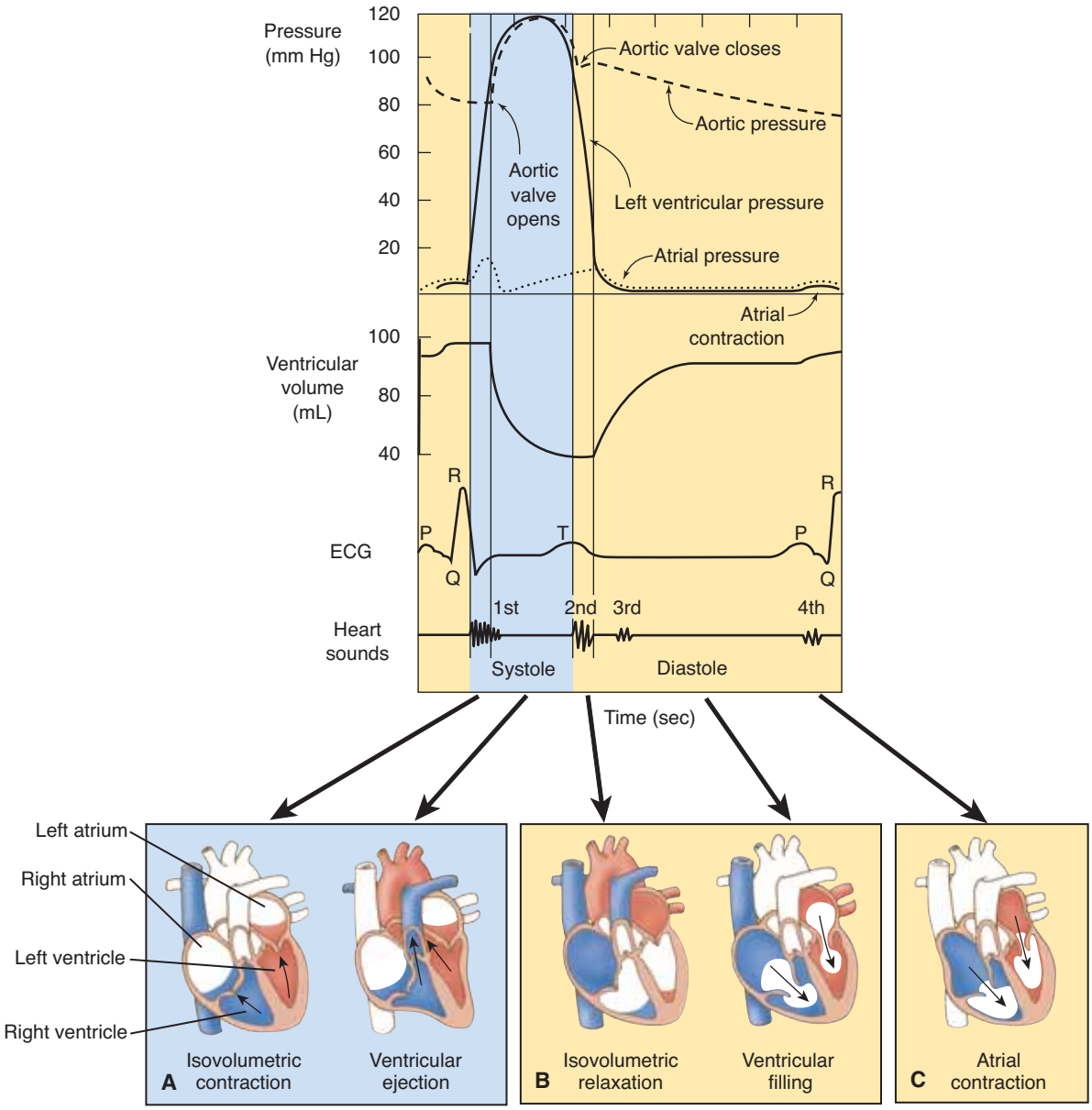


FIGURE 17-15. (*Top*) Events in the left side of the heart, showing changes in aortic pressure, left ventricular pressure, atrial pressure, left ventricular volume, the electrocardiogram (ECG), and heart sounds during the cardiac cycle. (*Bottom*) Position of the atrioventricular valves during **(A)** the isovolumetric contraction and ejection phases of ventricular systole, **(B)** the isovolumetric relaxation and ventricular filling phases during early diastole, and **(C)** atrial contraction.

the aortic valve. The aorta is highly elastic and as such stretches during systole to accommodate the blood that is being ejected from the left heart during systole. During diastole, recoil of the elastic fibers in the aorta serves to maintain the arterial pressure.

Diastole is marked by ventricular relaxation and filling. After closure of the semilunar valves, the ventricles continue to relax for another 0.03 to 0.06 second. During this time, which is called the *isovolumetric relaxation period*, ventricular volume remains the same but ventricular pressure drops until it becomes less than atrial pressure. As this occurs, the AV valves open, and the blood that has been accumulating in the atria during systole flows into the ventricles. Most of ventricular filling occurs during the first third of diastole, which is called the *rapid filling period*. During the middle third of diastole, inflow into the ventricles is almost at a standstill. The last third of diastole is marked by atrial contraction, which gives an additional thrust to ventricular filling. When audible, the third heart sound is heard at the end the rapid filling period due to vibrations that are caused by the abrupt cessation of ventricular distention and by the deceleration of blood entering the ventricles. A third heart sound is sometimes heard in children with thin chest walls and in persons with a distended or noncompliant ventricle. A fourth heart sound, when present, occurs during the last third of diastole as the atria contract.

During diastole, the ventricles increase their volume to approximately 120 mL (i.e., the *end-diastolic volume*), and at the end of systole, approximately 50 mL of blood (i.e., the *end-systolic volume*) remains in the ventricles. The difference between the end-diastolic and end-systolic volumes (approximately 70 mL) is called the *stroke volume*. The *ejection fraction,* which is the stroke volume divided by the end-diastolic volume, represents the fraction or percentage of the diastolic volume that is ejected from the heart during systole.

Atrial Filling and Contraction

Because there are no valves between the junctions of the central veins (i.e., venae cavae and pulmonary veins) and the atria, atrial filling occurs during both systole and diastole. During normal quiet breathing, right atrial pressure usually varies between −2 and +2 mm Hg. It is this low atrial pressure that maintains the movement of blood from the systemic veins into the right atrium and from the pulmonary veins into the left atrium.

There are three main atrial pressure waves that occur during the cardiac cycle (Fig. 17-15). The first, or *c wave,* occurs as the ventricles begin to contract and their increased pressure causes the AV valves to bulge into the atria. The second, or *v wave,* occurs toward the end of systole when the AV valves are still closed and results from a slow buildup of blood in the atria. The third, or *a wave,* occurs during the last part of diastole and is caused by atrial contraction. The right atrial pressure waves are transmitted to the internal jugular veins as pulsations. These pulsations can be observed visually and may be used to assess cardiac function. For example, exaggerated a waves occur when the volume of the right atrium is increased because of impaired emptying into the right ventricle.

Right atrial pressure and filling is regulated by a balance between the ability of the right ventricle to move blood out of the right heart and the pressures that move blood from the venous circulation into the right atrium (venous return). When the heart pumps strongly, right atrial pressure is decreased and atrial filling is enhanced. Right atrial pressure is also affected by changes in intrathoracic pressure. It is decreased during inspiration when intrathoracic pressure becomes more negative, and it is increased during coughing or forced expiration when intrathoracic and right atrial pressures become more positive.

Although the main function of the atria is to store blood as it enters the heart, these chambers also act as pumps that aid in ventricular filling. Atrial contraction occurs during the last third of diastole. Atrial contraction becomes more important during periods of increased activity when the diastolic filling time is decreased because of an increase in heart rate or when heart disease impairs ventricular filling. In these two situations, the cardiac output would fall drastically were it not for the action of the atria. It has been estimated that atrial contraction can contribute as much as 30% to cardiac reserve during periods of increased need, while having little or no effect on cardiac output during rest.

Regulation of Cardiac Performance

The efficiency and work of the heart as a pump often is measured in terms of *cardiac output* or the amount of blood the heart pumps each minute. The cardiac output (CO) is the product of the *stroke volume* (SV) and the *heart rate* (HR) and can be expressed by the equation $CO = SV \times HR$. The cardiac output varies with body size and the metabolic needs of the tissues. It increases with physical activity and decreases during rest and sleep. The average cardiac output in normal adults ranges from 3.5 to 8.0 L/minute. In the highly trained athlete, this value can increase to levels as high as 32 L/minute during maximum exercise.

The *cardiac reserve* refers to the maximum percentage of increase in cardiac output that can be achieved above the normal resting level. The normal young adult has a cardiac reserve of approximately 300% to 400%. Cardiac performance is influenced by the work demands of the heart and the ability of the coronary circulation to meet its metabolic needs. The heart's ability to increase its output according to body needs mainly depends on four factors: the *preload* or ventricular filling, the *afterload* or resistance to ejection of blood from the heart, *cardiac contractility*, and the *heart rate*. Heart rate and cardiac contractility are strictly cardiac factors, meaning they originate in the heart, although they are controlled by various neural and humoral mechanisms. Preload and afterload, on the other hand, are mutually dependent on the behavior of the heart and blood vessels.

Preload

The preload represents the volume work of the heart. It is called the *preload* because it is the work or load imposed on the heart before the contraction begins. It is the amount of blood that the heart must pump with each beat and represents the volume of blood stretching the ventricular muscle fibers at the end of diastole (i.e., end-diastolic volume) and is the sum of the blood remaining in the heart at the end of systole (end-systolic volume) and the venous return to the heart.

The increased force of contraction that accompanies an increase in ventricular end-diastolic volume is referred to as the *Frank-Starling mechanism* or Starling law of the heart (Fig. 17-16). The anatomic arrangement of the actin and myosin filaments in the myocardial muscle fibers is such that the tension or force of contraction is greatest when the muscle fibers are optimally stretched just before the heart begins to contract. The maximum force of contraction and cardiac output is achieved when venous return produces an increase in left ventricular end-diastolic filling (i.e., preload) such that the muscle fibers are stretched about two and one-half times their normal resting length. When the muscle fibers are stretched to this degree, there is optimal overlap of the actin and myosin filaments needed for maximal contraction.

The Frank-Starling mechanism allows the heart to adjust its pumping ability to accommodate various levels of venous return. Cardiac output is less when decreased filling causes excessive overlap of the actin and myosin filaments or when excessive filling causes the filaments to

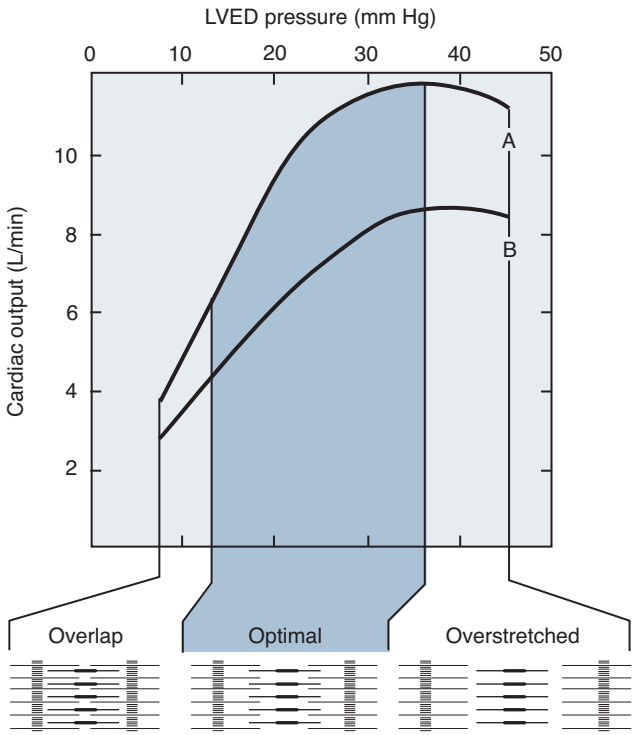


FIGURE 17-16. The Frank-Starling ventricular function curve. (*Bottom*) The effect of diastolic filling and left ventricular end-diastolic (LVED) pressure on cardiac output by means of the Frank-Starling mechanism: **(A)** decreased filling with excessive overlap of actin and myosin filaments; **(B)** maximum force of contraction when the muscle fibers are stretched about two and one-half times their resting length; and **(C)** increased filling with overstretching of muscle fiber. (*Top*) An increase in cardiac contractility produces an increase in cardiac output without a change in LVED volume and pressure.

be pulled too far apart. The Frank-Starling mechanism also plays an important role in balancing the output of two ventricles. An increase in cardiac contractility produces an increase in cardiac output without a change in preload (to be discussed).

Afterload

The afterload is the pressure or tension work of the heart. It is the pressure that the heart must generate to move blood into the aorta. It is called the *afterload* because it is the work presented to the heart after the contraction has commenced. The systemic arterial blood pressure is the main source of afterload work for the left heart and the pulmonary arterial pressure is the main source of afterload work for the right heart. The afterload work of the left ventricle is also increased with narrowing (i.e., stenosis) of the aortic valve. For example, in the late stages of aortic stenosis, the left ventricle may need to generate systolic pressures as great as 300 mm Hg to move blood through the diseased valve.

Cardiac Contractility

Cardiac contractility refers to the ability of the heart to change its force of contraction without changing its resting (i.e., diastolic) length (see Fig. 17-16). The contractile state of the myocardial muscle is determined by biochemical and biophysical properties that govern the actin and myosin interactions in the myocardial cells. It is strongly influenced by the number of calcium ions that are available to participate in the contractile process.

An *inotropic* influence is one that modifies the contractile state of the myocardium independent of the Frank-Starling mechanism. For instance, sympathetic stimulation produces a positive inotropic effect by increasing the calcium that is available for interaction between the actin and myosin filaments. Hypoxia exerts a negative inotropic effect by interfering with the generation of adenosine triphosphate (ATP), which is needed for muscle contraction.

Heart Rate

The heart rate influences cardiac output and the work of the heart by determining the frequency with which the ventricle contracts and blood is ejected from the heart. Heart rate also determines the time spent in diastolic filling. Although systole and the ejection period remain fairly constant across heart rates, the time spent in diastole and filling of the ventricles becomes shorter as the heart rate increases. This leads to a decrease in stroke volume and, at high heart rates, may produce a decrease in cardiac output. One of the dangers of ventricular tachycardia is a reduction in cardiac output because the heart does not have time to fill adequately.

In summary, the heart is a four-chambered muscular pump that lies in the pericardial sac within the mediastinal space of the intrathoracic cavity. The wall of the heart is composed of an outer epicardium, which lines the pericardial cavity; a fibrous skeleton; the myocardium, or muscle layer; and the smooth endocardium, which lines the chambers of the heart. The four heart valves control the direction of blood flow.

The specialized cells of the heart's conduction system control the rhythmic contraction and relaxation of the heart. The SA node has the fastest inherent rate of impulse generation and acts as the pacemaker of the heart. Impulses from the SA node travel through the atria to the AV junctional fibers (AV node and AV bundle) and then to the ventricular Purkinje system. The AV junction provides the only connection between the atrial and ventricular conduction systems. Cardiac action potentials are controlled by two types of responses: the *fast response*, which occurs in atrial and ventricular muscle and Purkinje fibers and depends mainly on the fast sodium channels, and the *slow response*, which occurs in the SA node and the conduction fibers of the AV node and depends on activation of the slow calcium channels. The absolute refractory period, which represents the time during which a normal cardiac impulse cannot reexcite an already excited area of cardiac muscle, is important in preventing disorders of cardiac rhythm that would disrupt the normal

pumping ability of the heart. Disorders of the cardiac conduction system include arrhythmias and conduction defects. Ventricular arrhythmias are generally more serious than atrial arrhythmias because they afford the potential for disrupting the pumping ability of the heart.

The cardiac cycle describes the pumping action of the heart. It is divided into two parts: systole, during which the ventricles contract and blood is ejected from the heart, and diastole, during which the ventricles are relaxed and blood is filling the heart. The stroke volume (approximately 70 mL) represents the difference between the end-diastolic volume (approximately 120 mL) and the end-systolic volume (approximately 50 mL). Atrial contraction occurs during the last third of diastole. Although the main function of the atria is to store blood as it enters the heart, atrial contraction acts to increase cardiac output during periods of increased activity when the filling time is reduced or in disease conditions in which ventricular filling is impaired.

The heart's ability to increase its output according to body needs depends on the preload, or filling of the ventricles (i.e., end-diastolic volume); the afterload, or resistance to ejection of blood from the heart; cardiac contractility, which is determined by the interaction of the actin and myosin filaments of cardiac muscle fibers; and the heart rate, which determines the frequency with which blood is ejected from the heart. The maximum force of cardiac contraction occurs when an increase in preload stretches muscle fibers of the heart to approximately two and one-half times their resting length (i.e., Frank-Starling mechanism).

The Systemic Circulation and Control of Blood Flow

The vascular system functions in the delivery of oxygen and nutrients and removal of wastes from the tissues. It consists of arteries and arterioles, capillaries, and venules and veins. Blood vessels are dynamic structures that constrict and relax to adjust blood pressure and flow to meet the varying needs of the many different tissue types and organ systems. Structures such as the heart, brain, liver, and kidneys require a large and continuous flow to carry out their vital functions. In other tissues, such as the skin and skeletal muscle, the need for blood flow varies with the level of function. For example, there is a need for increased blood flow to the skin during fever and for increased skeletal muscle blood flow during exercise. The discussion in this chapter focuses on the blood vessels of the systemic circulation. The coronary circulation, which supplies the heart, is discussed in Chapter 19, and the cerebral circulation, which supplies the brain, is discussed in Chapter 37.

Blood Vessels

All blood vessels, except the capillaries, have walls composed of three layers, or coats, called *tunicae* (Fig. 17-17).

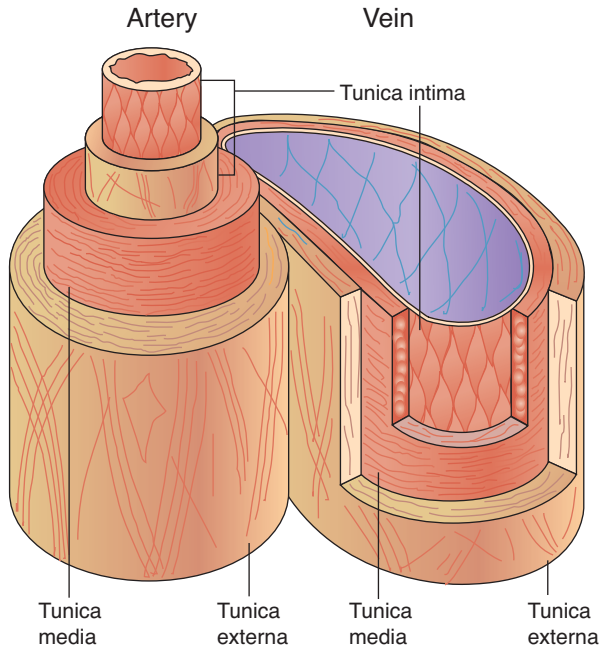


FIGURE 17-17. Medium-sized artery and vein, showing the relative thickness of the three layers.

The outermost layer of a vessel, called the *tunica externa* or *tunica adventitia*, is composed primarily of loosely woven collagen fibers that protect the blood vessel and anchor it to the surrounding structures. The middle layer, the *tunica media*, is largely a smooth muscle layer that constricts to regulate and control the diameter of the vessel. Larger arteries have an external elastic lamina that separates the tunica media from the tunica externa. The innermost layer, the *tunica intima*, consists of a single layer of flattened endothelial cells with minimal underlying subendothelial connective tissue. The endothelial layer provides a smooth and slippery inner surface for the vessel. This smooth inner lining, as long as it remains intact, prevents platelet adherence and blood clotting.

The layers of the different types of blood vessels vary with vessel function. The walls of the arterioles, which control blood pressure, have large amounts of smooth muscle. Veins are thin-walled, distensible, and collapsible vessels. Capillaries are single-cell–thick vessels designed for the exchange of gases, nutrients, and waste materials.

Vascular Smooth Muscle

Vascular smooth muscle cells, which form the predominant cellular layer in the tunica media, produce vasoconstriction or dilation of blood vessels. Smooth muscle contracts slowly and generates high forces for long periods with low energy requirements; it uses only 1/10 to 1/300 the energy of skeletal muscle. These characteristics are important in structures, such as blood vessels, that must maintain their tone day in and day out.

Compared with skeletal and cardiac muscle, smooth muscle has less–well-developed sarcoplasmic reticulum for storing intracellular calcium, and it has very few fast sodium channels. Therefore, depolarization of smooth muscle relies largely on extracellular calcium, which

enters through calcium channels in the muscle membrane. Sympathetic nervous system control of vascular smooth muscle tone occurs by way of receptor-activated opening and closing of the calcium channels. In general, α-adrenergic receptors are excitatory, in that they cause the channels to open and produce vasoconstriction, and β-adrenergic receptors are inhibitory, in that they cause the channels to close and produce vasodilation. Calcium channel–blocking drugs cause vasodilation by blocking calcium entry through the calcium channels.

Smooth muscle contraction and relaxation also occur in response to local tissue factors such as lack of oxygen, increased hydrogen ion concentrations, and excess carbon dioxide. Nitric oxide (formerly known as the *endothelial relaxing factor*) acts locally to produce smooth muscle relaxation and regulate blood flow. These factors are discussed more fully in the section on local control of blood flow.

The Vascular System and Control of Blood Flow

- The vascular system, which consists of the arterial system, the venous system, and the capillaries, functions in the delivery of oxygen and nutrients and in the removal of wastes from the tissues.
- The arterial system is a high-pressure system that delivers blood to the tissues. It relies on the intermittent ejection of blood from the left ventricle and the generation of arterial pressure pulsations or waves that move blood toward the capillaries where the exchange of gases, nutrients, and wastes occur.
- The venous system is a low-pressure system that collects blood from the capillaries. It relies on the presence of valves in the veins of the extremities to prevent retrograde flow and on the milking action of the skeletal muscles that surround the veins to return blood to the right heart.
- Local control of blood flow is regulated by mechanisms that match blood flow to the metabolic needs of the tissue. Over the short term, the tissues autoregulate flow through the synthesis of vasodilators and vasoconstrictors derived from the tissue, smooth muscle, or endothelial cells; over the long term, blood flow is regulated by creation of a collateral circulation.
- Neural control of circulatory function occurs through the sympathetic and parasympathetic nervous divisions of the autonomic nervous system. Sympathetic stimulation increases cardiac contractility and vessel tone (vascular resistance), whereas parasympathetic stimulation decreases heart rate.
- Neural control of blood flow is largely vested in the sympathetic nervous system and its control of vascular smooth muscle tone. Increased sympathetic activity generally leads to an increase in tone and vessel constriction, and decreased activity to a reduction in tone and vessel dilation.

Arterial System

The arterial system consists of the large and medium-sized arteries and the arterioles. Arteries are thick-walled vessels with large amounts of elastic fibers. The elasticity of these vessels allows them to stretch during cardiac systole, when the heart contracts and blood is ejected into the circulation, and to recoil during diastole, when the heart relaxes. The arterioles, which are predominantly smooth muscle, serve as resistance vessels for the circulatory system. They act as control valves through which blood is released as it moves into the capillaries. Changes in the activity of sympathetic fibers that innervate these vessels cause them to constrict or relax as needed to maintain blood pressure. The regulation of arterial blood pressure is discussed further in Chapter 18.

Arterial Pressure Pulsations

The delivery of blood to the tissues of the body is dependent on pressure pulsations or waves of pressure that are generated by the intermittent ejection of blood from the left ventricle into the distensible aorta and large arteries of the arterial system. The arterial pressure pulse represents the energy that is transmitted from molecule to molecule along the length of the vessel (Fig. 17-18). In

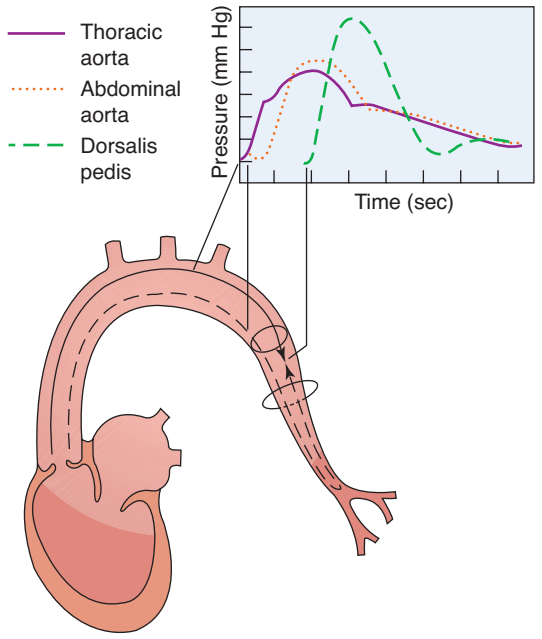


FIGURE 17-18. Amplification of the arterial pressure wave as it moves forward in the peripheral arteries. This amplification occurs as a forward-moving pressure wave merges with a backward-moving reflected pressure wave. (*Inset*) The amplitude of the pressure pulse increases in the thoracic aorta, abdominal aorta, and dorsalis pedis.

the aorta, this pressure pulse is transmitted at a velocity of 4 to 6 meters/second, which is approximately 20 times faster than the flow of blood. Therefore, the pressure pulse has no direct relation to blood flow and could occur if there was no flow at all. When taking a pulse, it is the pressure pulses that are felt, and it is the pressure pulses that produce the Korotkoff sounds heard during blood pressure measurement. The tip or maximum deflection of the pressure pulsation coincides with the systolic blood pressure, and the minimum point of deflection coincides with the diastolic pressure. The pulse pressure is the difference between systolic and diastolic pressure. If all other factors are equal, the magnitude of the pulse pressure reflects the volume of blood ejected from the left ventricle in a single beat.

Both the pressure values and the conformation of the pressure wave change as it moves though the peripheral arteries, such that pulsations in the large arteries are even greater than those in the aorta (Fig. 17-18). Consequently, the systolic and pulse pressures are higher in the large arteries than in the aorta. The increase in pulse pressure in the "downstream" arteries is due to the fact that immediately following ejection from the left ventricle, the pressure wave travels at a higher velocity than the blood itself, augmenting the downhill pressure. Furthermore, at branch points of arteries, the forward-moving pressure waves are reflected backward, which also tends to augment the pressure. With peripheral arterial disease, there is a delay in the transmission of the reflected wave so that the pulse decreases rather than increases in amplitude.

After its initial amplification, the pressure pulse becomes smaller and smaller as it moves through the smaller arteries and arterioles, until it disappears almost entirely in the capillaries. This damping of the pressure pulse is caused by the resistance and distensibility characteristics of these vessels. The increased resistance of these small vessels impedes the transmission of the pressure waves, while their distensibility is great enough so that any small change in flow does not cause a pressure change. Although the pressure pulses usually are not transmitted to the capillaries, there are situations in which this does occur. For example, injury to a finger or other area of the body often results in a throbbing sensation. In this case, extreme dilatation of the small vessels in the injured area produces a reduction in the dampening of the pressure pulse. Capillary pulsations also occur in conditions that cause exaggeration of aortic pressure pulses, such as aortic regurgitation or patent ductus arteriosus (see Chapter 19).

The Venous System

The venous system is a low-pressure system that returns blood to the heart. The venules collect blood from the capillaries, and the veins transport blood back to the right heart. Blood from the systemic veins flows into the right atrium of the heart; therefore, the pressure in the right atrium is called the *central venous pressure*. Right atrial pressure is regulated by the ability of the right ventricle to pump blood into the pulmonary circulation and the tendency of blood to flow from the peripheral veins into the right atrium. The normal right atrial pressure is about 0 mm Hg, which is equal to atmospheric pressure. It can increase to 20 to 30 mm Hg in conditions such as right heart failure or the rapid infusion of blood or intravenous fluids at a rate that greatly increases the total blood volume and causes blood to accumulate in the systemic veins and right heart.

The veins and venules are thin-walled, distensible, and collapsible vessels. The veins are capable of enlarging and storing large quantities of blood, which can be made available to the circulation as needed. Even though the veins are thin walled, they are muscular. This allows them to contract or expand to accommodate varying amounts of blood. Veins are innervated by the sympathetic nervous system. When blood is lost from the circulation, the veins constrict as a means of maintaining intravascular volume.

Valves in the veins of extremities prevent retrograde flow (Fig. 17-19), and with the help of skeletal muscles that surround and intermittently compress the leg veins in a milking manner, blood is moved forward to the heart. This pumping action is known as the *venous* or *muscle pump*. There are no valves in the abdominal or thoracic veins, and blood flow in these veins is heavily influenced by the pressure in the abdominal and thoracic cavities, respectively.

Because the venous system is a low-pressure system, blood flow must oppose the effects of gravity. In a person in the standing position, the weight of the blood in the vascular column causes an increase of 1 mm Hg in pressure for every 13.6 mm of distance below the level of the

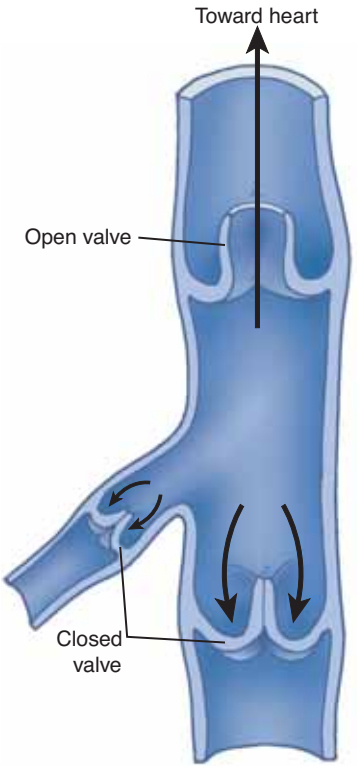


FIGURE 17-19. Portion of a femoral vein opened, to show the valves. The direction of flow is upward. Backward flow closes the valve.

heart. Were it not for the valves in the veins and the action of the skeletal muscles, the venous pressure in the feet would be about +90 mm Hg in the standing adult. Gravity has no effect on the venous pressure in a person in the recumbent position because the blood in the veins is then at the level of the heart.

The Microcirculation and the Lymphatic System

The capillaries, venules, and arterioles of the circulatory system are collectively referred to as the *microcirculation*. It is here that the exchange of gases, nutrients, and metabolites takes place between the tissues and the circulating blood. The lymphatic system represents an accessory system that removes excess fluid, proteins, and large particles from the interstitial spaces and returns them to the circulation. Because of their size, these particles cannot be reabsorbed into the capillaries. The exchange of fluid between the capillaries and the tissue spaces is discussed in Chapter 8.

Structure of the Microcirculation and Capillary System

The microcirculation of each organ is organized to serve the organ's need for blood flow. Blood enters the microcirculation through an arteriole, passes through the capillaries, and leaves by way of a small venule. The metarterioles serve as thoroughfare channels that link arterioles and capillaries (Fig. 17-20). Small cuffs of smooth muscle, the precapillary sphincters, are positioned at the arterial end of the capillary. The smooth muscle tone of the arterioles, venules, and precapillary sphincters controls blood flow through the capillary bed. Depending on venous pressure, blood flows through the capillary channels when the precapillary sphincters are open.

Blood flow through capillary channels, designed for exchange of nutrients and metabolites, is called *nutrient flow*. In some parts of the microcirculation, blood flow bypasses the capillary bed, moving through a connection called an *arteriovenous shunt,* which directly connects an arteriole and a venule. This type of blood flow is called *nonnutrient flow* because it does not allow for nutrient exchange. Nonnutrient channels are common in the skin and are important in terms of heat exchange and temperature regulation.

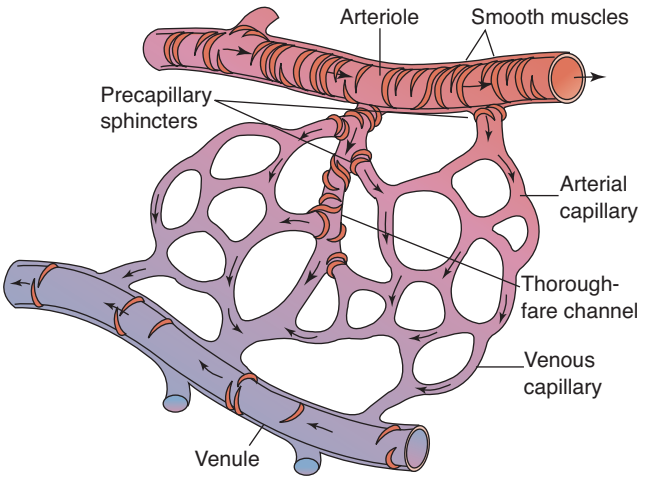


FIGURE 17-20. Capillary bed. Precapillary sphincters control the flow of blood through the capillary network. Thoroughfare channels (i.e., arteriovenous shunts) allow blood to move directly from the arteriole into the venule without moving through nutrient channels of the capillary.

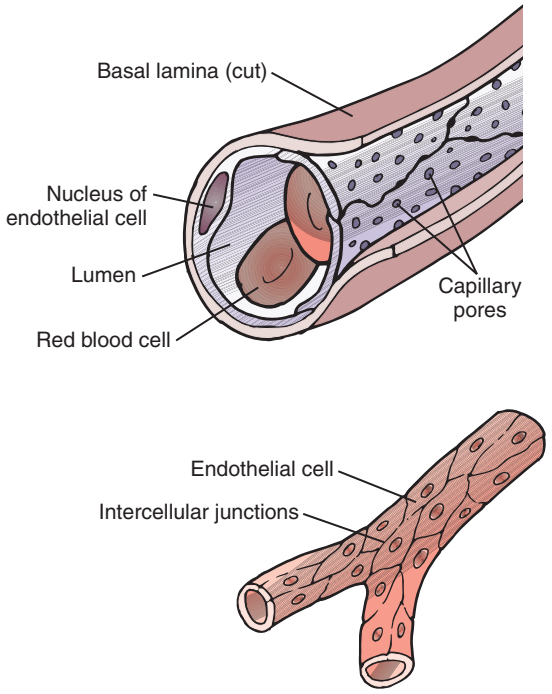


FIGURE 17-21. Endothelial cells and intercellular junctions in a section of capillary.

Structure of the Capillary Wall. Capillaries are microscopic, single-cell–thick vessels that connect the arterial and venous segments of the circulation. The capillary wall is composed of a single layer of endothelial cells surrounded by a basement membrane or basal lamina (Fig. 17-21). Intercellular junctions join the capillary endothelial cells; these are called the *capillary pores*. Lipid-soluble materials diffuse directly through the capillary cell membrane. Water and water-soluble materials leave and enter the capillary through the capillary pores. The size of the capillary pores varies with capillary function. In the brain, the endothelial cells are joined by tight junctions that form the blood-brain barrier. This prevents substances that would alter neural excitability from leaving the capillary. In organs that process blood contents, such as the liver, capillaries have large pores so that substances can pass easily through the capillary wall. In the kidneys, the glomerular capillaries have small openings called *fenestrations* that pass directly through the middle of the endothelial cells. Fenestrated capillary walls are consistent with the filtration function of the glomerulus.

Lymphatic System

The lymphatic system, commonly called the *lymphatics,* represents an accessory route through which fluid can

flow through the tissue spaces into the blood and then back to the heart. Importantly, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption into the venous system. The lymphatic system is also the main route for absorption of nutrients, particularly fats, from the gastrointestinal tract.

The lymphatic system is made up of vessels similar to those of the circulatory system. These vessels commonly travel along with an arteriole or venule or with a companion artery and vein. The terminal lymphatic vessels are made up of a single layer of connective tissue with an endothelial lining and resemble blood capillaries. The lymphatic vessels lack tight junctions and are loosely anchored to the surrounding tissues by fine filaments (Fig. 17-22). The loose junctions permit the entry of large particles, and the filaments hold the vessels open under conditions of edema, when the pressure of the surrounding tissues would otherwise cause them to collapse. The lymph capillaries drain into larger lymph vessels that ultimately empty into the right and left thoracic ducts (Fig. 17-23). The thoracic ducts empty into the circulation at the junctions of the subclavian and internal jugular veins.

Although the divisions are not as distinct as in the circulatory system, the larger lymph vessels show evidence of having intimal, medial, and adventitial layers similar to those of blood vessels. Contraction of the smooth muscle in the medial layer of the larger collecting lymph channels assists in propelling lymph fluid toward the thorax. External compression of the lymph channels by active and passive movements of body parts also aids in forward propulsion of lymph fluid. The rate of flow through the lymphatic system by way of all of the various lymph channels, approximately 120 mL/hour, is determined by the interstitial fluid pressure and the activity of lymph pumps.

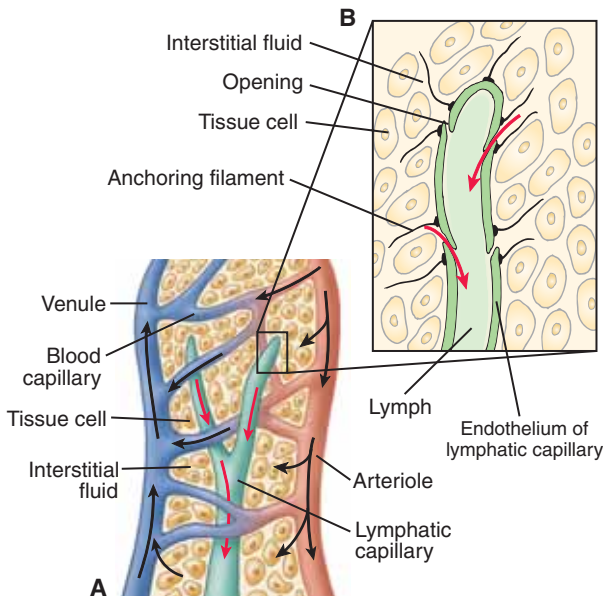


FIGURE 17-22. **(A)** Location of the lymphatic capillary. Blood from the arterial side of the capillary moves into the interstitial spaces and is reabsorbed in the venous side of the capillary bed. **(B)** Details of the lymphatic capillary with its anchoring filaments and overlapping edges that serve as valves and can be pushed open, allowing the inflow of interstitial fluids and suspended particles.

Local and Humoral Control of Blood Flow

Autoregulation of Blood Flow

Local control of blood flow is governed largely by the nutritional needs of the tissue. For example, blood flow to organs such as the heart, brain, and kidneys remains relatively constant, although blood pressure may vary over a range of 60 to 180 mm Hg. The ability of the tissues to regulate their own blood flow over a wide range of pressures is called *autoregulation*. Autoregulation of blood flow is mediated by changes in blood vessel tone due to changes in flow through the vessel or by local tissue factors, such as lack of oxygen or accumulation of tissue metabolites (i.e., potassium, lactic acid, or adenosine, which is a breakdown product of ATP). Local control is particularly important in tissues such as skeletal muscle, which has blood flow requirements that vary according to the level of activity.

Hyperemia. An increase in local blood flow is called *hyperemia*. The ability of tissues to increase blood flow in situations of increased activity, such as exercise, is called *functional hyperemia*. When the blood supply to an area has been occluded and then restored, local blood flow through the tissues increases within seconds to restore the metabolic equilibrium of the tissues. This increased flow is called *reactive hyperemia*. The transient redness seen on an arm after leaning on a hard surface is an example of reactive hyperemia. Local control mechanisms rely on a continuous flow from the main arteries; therefore, hyperemia cannot occur when the arteries that supply the capillary beds are narrowed. For example, if a major coronary artery becomes occluded, the opening of channels supplied by that vessel cannot restore blood flow.

Endothelial Control of Blood Flow

One of the important functions of the endothelial cells lining the arterioles and small arteries is the synthesis and release of factors that control vessel dilation. Of particular importance was the discovery, first reported in the early 1980s, that the intact endothelium was able to produce a factor that caused relaxation of vascular smooth muscle. This factor was originally named *endothelium-derived relaxing factor* and is now known to be *nitric oxide*. The normal endothelium maintains a continuous release of nitric oxide, which is formed from L-arginine through the action of an enzyme called *nitric oxide synthase* (Fig. 17-24). The production of nitric oxide can be stimulated by a variety of endothelial *agonists*, including acetylcholine, bradykinin, histamine, and thrombin. *Shear stress* on the endothelium resulting from an increase in blood flow or blood pressure also stimulates nitric oxide production and vessel relaxation. Nitric oxide also inhibits

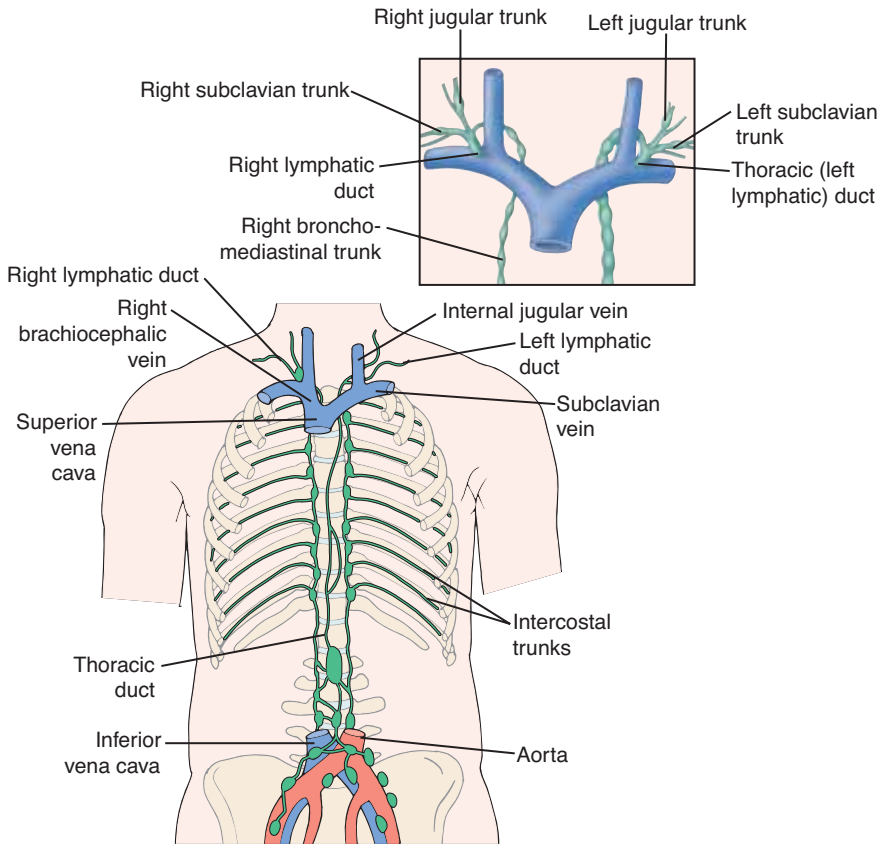


FIGURE 17-23. Lymphatic system showing the thoracic duct and position of the left and right lymphatic ducts (*inset*).

platelet aggregation and secretion of platelet contents, many of which cause vasoconstriction. The fact that nitric oxide is released into the vessel lumen (to inactivate platelets) and away from the lumen (to relax smooth muscle) suggests that it protects against both thrombosis and vasoconstriction. Nitroglycerin, a drug that is used in treatment of angina, produces its effects by releasing nitric oxide in vascular smooth muscle of the target tissues.

The endothelium also produces a number of vasoconstrictor substances, including *angiotensin II*, vasoconstrictor prostaglandins, and a family of peptides called *endothelins*. There are at least three endothelins. Endothelin-1, made by endothelial cells, is the most potent endogenous vasoconstrictor known. Receptors for endothelins also have been identified.

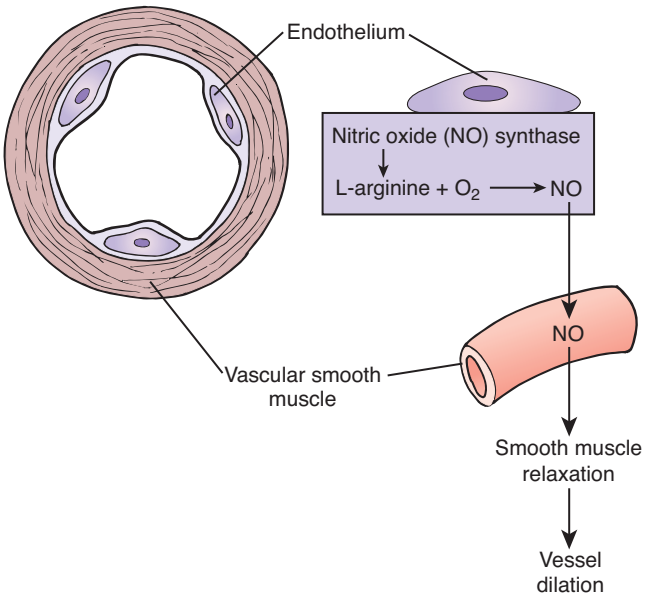


FIGURE 17-24. Function of nitric oxide in smooth muscle relaxation.

Humoral Control of the Circulation

Humoral control of blood flow involves the effect of vasodilator and vasoconstrictor substances in the blood. Some of these substances are formed by special glands and transported in the blood throughout the entire circulation. Others are formed in local tissues and aid in the local control of blood flow. Among the most important of the humoral factors are norepinephrine and epinephrine, angiotensin II, histamine, serotonin, bradykinin, and the prostaglandins.

Norepinephrine and Epinephrine. Norepinephrine is an especially powerful vasoconstrictor hormone; epinephrine is less so and in some tissues (e.g., skeletal muscle) even causes mild vasodilation. Stimulation of the sympathetic nervous system during stress or exercise causes local constriction of veins and arterioles due to the release of norepinephrine from sympathetic nerve endings. In addition, sympathetic stimulation causes the adrenal medullae to secrete both norepinephrine and

epinephrine into the blood. These hormones then circulate in the blood, causing direct sympathetic stimulation of blood vessels in all parts of the body.

Angiotensin II. Angiotensin II is another powerful vasoconstrictor substance. Angiotensin II is produced as a part of the renin-angiotensin-aldosterone system and normally acts on many of the arterioles at the same time to increase the peripheral vascular resistance, thereby increasing the arterial blood pressure (discussed in Chapter 18).

Histamine. Histamine has a powerful vasodilator effect on arterioles and has the ability to increase capillary permeability, allowing leakage of both fluid and plasma proteins into the tissues. Histamine is largely derived from mast cells in injured tissues and basophils in the blood. In certain tissues, such as skeletal muscle, the activity of the mast cells is mediated by the sympathetic nervous system; when sympathetic control is withdrawn, the mast cells release histamine.

Serotonin. Serotonin is liberated from aggregating platelets during the clotting process; it causes vasoconstriction and plays a major role in control of bleeding. Serotonin is found in brain and lung tissues, and there is some speculation that it may be involved in the vascular spasm associated with some allergic pulmonary reactions and migraine headaches.

Bradykinin. The kinins (i.e., kallidins and bradykinin) are liberated from the globulin kininogen, which is present in body fluids. Bradykinin causes intense dilation of arterioles, increased capillary permeability, and constriction of venules. It is thought that the kinins play special roles in regulating blood flow and capillary leakage in inflamed tissues. It is also believed that bradykinin helps to regulate blood flow in the skin as well in the salivary and gastrointestinal glands.

Prostaglandins. Prostaglandins are synthesized from constituents of the cell membrane (i.e., the long-chain fatty acid *arachidonic acid*). Tissue injury incites the release of arachidonic acid from the cell membrane, which initiates prostaglandin synthesis. There are several prostaglandins (e.g., E2, F2, D2), which are subgrouped according to their solubility; some produce vasoconstriction and some produce vasodilation. As a rule of thumb, those in the E group are vasodilators and those in the F group are vasoconstrictors. The corticosteroid hormones produce an anti-inflammatory response by blocking the release of arachidonic acid, preventing prostaglandin synthesis.

Collateral Circulation

Collateral circulation is a mechanism for the long-term regulation of local blood flow. In the heart and other vital structures, anastomotic channels exist between some of the smaller arteries. These channels permit perfusion of an area by more than one artery. When one artery becomes occluded, these anastomotic channels increase in size, allowing blood from a patent artery to perfuse the area supplied by the occluded vessel. For example, persons with extensive obstruction of a coronary blood vessel may rely on collateral circulation to meet the oxygen needs of the myocardial tissue normally supplied by that vessel. As with other long-term compensatory mechanisms, the recruitment of collateral circulation is most efficient when obstruction to flow is gradual, rather than sudden.

In summary, the walls of all blood vessels, except the capillaries, are composed of three layers: the tunica externa, tunica media, and tunica intima. The layers of the vessel vary with its function. Arteries are thick-walled vessels with large amounts of elastic fibers. The walls of the arterioles, which control blood pressure, have large amounts of smooth muscle. Veins are thin-walled, distensible, and collapsible vessels. Venous flow is designed to return blood to the heart. It is a low-pressure system and relies on venous valves and the action of muscle pumps to offset the effects of gravity. Capillaries are single-cell–thick vessels designed for the exchange of gases, nutrients, and waste materials.

The mechanisms that control blood flow are designed to ensure adequate delivery of blood to the capillaries in the microcirculation, where the exchange of cellular nutrients and wastes occurs. Local control is governed largely by the needs of the tissues and is regulated by local tissue factors such as lack of oxygen and the accumulation of metabolites. Hyperemia is a local increase in blood flow that occurs after a temporary occlusion of blood flow. It is a compensatory mechanism that decreases the oxygen debt of the deprived tissues. Collateral circulation is a mechanism for long-term regulation of local blood flow that involves the development of collateral vessels.

Neural Control of Circulatory Function

The neural control centers for the integration and modulation of cardiac function and blood pressure are located bilaterally in the medulla oblongata. The medullary cardiovascular neurons are grouped into three distinct pools that lead to sympathetic innervation of the heart and blood vessels and parasympathetic innervation of the heart. The first two, which control sympathetic-mediated acceleration of heart rate and blood vessel tone, are called the *vasomotor center*. The third, which controls parasympathetic-mediated slowing of heart rate, is called the *cardioinhibitory center*. These brain stem centers receive information from many areas of the nervous system, including the hypothalamus. The arterial baroreceptors and chemoreceptors provide the medullary cardiovascular center with continuous information regarding changes in blood pressure (see Chapter 18).

Autonomic Nervous System Regulation

The neural control of the circulatory system occurs primarily through the *sympathetic* and *parasympathetic* divisions of the autonomic nervous system (ANS). The ANS contributes to the control of cardiovascular function through modulation of cardiac (i.e., heart rate and cardiac contractility) and vascular (i.e., peripheral vascular resistance) function.

Autonomic Regulation of Vascular Function

The sympathetic nervous system serves as the final common pathway for controlling the smooth muscle tone of the blood vessels. Most of the sympathetic preganglionic fibers that control vessel function originate in the vasomotor center of the brain stem, travel down the spinal cord, and exit in the thoracic and lumbar (T1 to L2) segments. The sympathetic neurons that supply the blood vessels maintain them in a state of tonic activity, so that even under resting conditions, the blood vessels are partially constricted. Vessel constriction and relaxation are accomplished by altering this basal input. Increasing sympathetic activity causes constriction of some vessels, such as those of the skin, the gastrointestinal tract, and the kidneys. Blood vessels in skeletal muscle are supplied by both vasoconstrictor and vasodilator fibers. Activation of sympathetic vasodilator fibers causes vessel relaxation and provides the muscles with increased blood flow during exercise. Although the parasympathetic nervous system contributes to the regulation of heart function, it has little or no control over blood vessels.

Autonomic Neurotransmitters

The actions of the ANS are mediated by chemical neurotransmitters. *Acetylcholine* is the postganglionic neurotransmitter for parasympathetic neurons and *norepinephrine* is the main neurotransmitter for postganglionic sympathetic neurons. Sympathetic neurons also respond to epinephrine, which is released into the bloodstream by the adrenal medulla. The neurotransmitter *dopamine* can also act as a neurotransmitter for some sympathetic neurons. The synthesis, release, and inactivation of the autonomic neurotransmitters are discussed in Chapter 34.

Central Nervous System Responses

It is not surprising that the central nervous system (CNS), which plays an essential role in regulating vasomotor tone and blood pressure, would have a mechanism for controlling the blood flow to the cardiovascular centers that control circulatory function. When the blood flow to the brain has been sufficiently interrupted to cause ischemia of the vasomotor center, these vasomotor neurons become strongly excited, causing massive vasoconstriction as a means of raising the blood pressure to levels as high as the heart can pump against. This response is called the *CNS ischemic response*, and it can raise the blood pressure to levels as high as 270 mm Hg for as long as 10 minutes. The CNS ischemic response is a last-ditch stand to preserve the blood flow to vital brain centers; it does not become activated until blood pressure has fallen to at least 60 mm Hg, and it is most effective in the range of 15 to 20 mm Hg. If the cerebral circulation is not reestablished within 3 to 10 minutes, the neurons of the vasomotor center cease to function, so that the tonic impulses to the blood vessels stop and the blood pressure falls precipitously.

The *Cushing reflex* is a special type of CNS reflex resulting from an increase in intracranial pressure. When the intracranial pressure rises to levels that equal intra-arterial pressure, blood vessels to the vasomotor center become compressed, initiating the CNS ischemic response. The purpose of this reflex is to produce a rise in arterial pressure to levels above intracranial pressure so that the blood flow to the vasomotor center can be reestablished. Should the intracranial pressure rise to the point that the blood supply to the vasomotor center becomes inadequate, vasoconstrictor tone is lost, and the blood pressure begins to fall. The elevation in blood pressure associated with the Cushing reflex is usually of short duration and should be considered a protective homeostatic mechanism. The brain and other cerebral structures are located within the rigid confines of the skull, with no room for expansion, and any increase in intracranial pressure tends to compress the blood vessels that supply the brain.

In summary, the neural control centers for the regulation of cardiac function and blood pressure are located in the reticular formation of the lower pons and medulla of the brain stem, where the integration and modulation of ANS responses occur. These brain stem centers receive information from many areas of the nervous system, including the hypothalamus. Both the parasympathetic and sympathetic nervous systems innervate the heart. The parasympathetic nervous system functions in regulating heart rate through the vagus nerve, with increased vagal activity producing a slowing of heart rate. The sympathetic nervous system has an excitatory influence on heart rate and contractility, and it serves as the final common pathway for controlling the smooth muscle tone of the blood vessels.

REVIEW EXERCISES

1. In persons with atherosclerosis of the coronary arteries, symptoms of myocardial ischemia do not usually occur until the vessel has been 75% occluded. Use Poiseuille law to explain.

2. Once an arterial aneurysm has begun to form it continues to enlarge as the result of the increased tension in its wall.

A. Explain the continued increase in size using the law of LaPlace.
B. Using information related to cross-sectional area and velocity of flow, explain why there is stasis of blood flow with the tendency to form clots in aneurysms with a large cross-sectional area.

3. Use events in the cardiac cycle depicted in Figure 17-11 to explain:

A. The effect of hypertension on the isovolumetric contraction period.
B. The effect of an increase in heart rate on the time spent in diastole.
C. The effect of an increase in the isovolumetric relaxation period on the diastolic filling of the ventricle.

4. Use the Frank-Starling ventricular function curve depicted in Figure 17-16 to explain the changes in cardiac output that occur with the following changes in respiratory effort:

A. What happens to cardiac output during increased inspiratory effort in which a marked decrease in intrathoracic pressure produces an increase in venous return to the right heart?
B. What happens to cardiac output during increased expiratory effort in which a marked increase in intrathoracic pressure produces a decrease in venous return to the right heart?
C. Given these changes in cardiac output that occur during increased respiratory effort, what would you propose as one of the functions of the Frank-Starling curve?

BIBLIOGRAPHY

Aukland K., Reed R.K. (1993). Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. *Physiological Reviews* 73(1), 1–78.

Costano L.S. (2002). *Physiology* (2nd ed., pp. 101–166). Philadelphia: Saunders.

Davis M.J., Hill M.A. (1999). Signaling mechanisms underlying the vascular myogenic response. *Physiological Reviews* 79, 387.

Ellis C.G., Jagger J., Sharpe M. (2005). The microcirculation as a functional system. *Critical Care* 9, S3–S8.

Feletou M., Vanhoutte P.M. (1999). The alternative: EDHF. *Journal of Molecular and Cellular Cardiology* 31, 15–22.

Ganong W.F. (2005). *Review of medical physiology* (22nd ed., pp. 515–630). New York: Lange Medical Books/McGraw-Hill.

Guyton A.C., Hall J.E. (2006). *Medical physiology* (11th ed., pp. 161–277). Philadelphia: Elsevier Saunders.

Klabunde R.E. (2005). *Cardiovascular physiology concepts*. Philadelphia: Lippincott Williams & Wilkins.

Levy M.N., Pappano A.J. (2007). *Cardiovascular physiology* (9th ed.). Philadelphia: Mosby Elsevier.

Mifflin S.W. (2001). What does the brain know about blood pressure? *News in Physiological Science* 16, 266.

Norton J.M. (2001). Toward consistent definitions for preload and afterload. *Advances in Physiological Education* 25(1), 53–61.

Rhoades R.S., Tanner G.A. (2003). *Medical physiology* (2nd ed. pp. 191–308). Boston: Little, Brown.

Ross M.H., Kaye G.L., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 364–429). Philadelphia: Lippincott Williams & Wilkins.

Segal S.S. (2005). Regulation of blood flow in the microcirculation. *Microcirculation* 12(1), 33–45.

Smith J.J., Kampine J.P. (1989). *Circulatory physiology* (3rd ed.). Baltimore: Williams & Wilkins.

Toda N., Okamura T. (2003). The pharmacology of nitric oxide in the peripheral nervous system of blood vessels. *Pharmacology Review* 55(2), 271–324.

Vanhoutte P.M. (1999). How to assess endothelial function in human blood vessels. *Journal of Hypertension* 17, 1047–1058.

Blood Vessel Structure and Function
Endothelial Cells
Vascular Smooth Muscle Cells
Disorders of the Arterial Circulation
Hyperlipidemia and Atherosclerosis
Hyperlipidemia
Atherosclerosis
The Vasculitides
Arterial Disease of the Extremities
Peripheral Arterial Disease
Thromboangiitis Obliterans
Raynaud Phenomenon
Aneurysms and Dissection
Aortic Aneurysms
Aortic Dissection
Disorders of Arterial Blood Pressure
Mechanisms of Blood Pressure Regulation
Short-Term Regulation
Long-Term Regulation
Measurement of Blood Pressure
Hypertension
Primary (Essential) Hypertension
Secondary Hypertension
Target-Organ Damage
Diagnosis and Treatment
Hypertensive Crisis
Hypertension in Special Populations
High Blood Pressure in Pregnancy
High Blood Pressure in Children and Adolescents
High Blood Pressure in the Elderly
Orthostatic Hypotension
Causes
Diagnosis and Treatment
Disorders of the Venous Circulation
Venous Circulation of the Lower Extremities
Varicose Veins
Chronic Venous Insufficiency
Venous Thrombosis

Chapter 18

Disorders of Blood Flow and Blood Pressure

Disorders of the blood vessels are directly or indirectly responsible for many diseases of the human body. Arterial diseases, such as stroke and coronary heart disease, are responsible for more morbidity and mortality than any other type of disease. Hypertension, or elevation of the arterial blood pressure, is probably the most common of all health problems in adults and is the leading risk factor for cardiovascular disorders. Although disorders of veins are less common, they also cause clinically significant problems. The discussion in this chapter is organized into four parts: blood vessel structure and function, disorders of the arterial circulation, disorders of the arterial blood pressure, and disorders of the venous circulation.

Blood Vessel Structure and Function

The walls of all blood vessels, arteries, and veins are composed of three layers called *tunica* (Fig. 18-1). The outermost layer of a vessel, called the *externa* or *adventitia,* is composed primarily of loosely woven collagen fibers that protect the blood vessel and anchor it to the surrounding structures. The tunica externa is infiltrated with nerve fibers and, in larger vessels, a system of tiny blood vessels called the *vasa vasorum*. The middle layer, the *tunica media,* is composed mainly of circularly arranged smooth muscle cells and sheets of elastin. Larger arteries have an external elastic lamina that separates the tunica media from the tunica externa. The innermost layer, the *tunica intima,* consists of a single layer of flattened endothelial cells with minimal underlying subendothelial connective tissue. Beneath the subendothelial tissue is an internal elastic lamina that is especially well developed in muscular arteries. As the main cellular component of the blood vessel wall, the endothelial and smooth muscle cells play an important role in the pathogenesis of many blood vessel diseases.

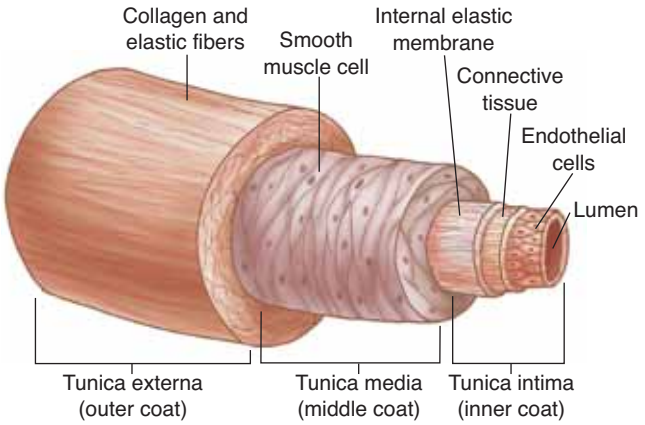


FIGURE 18-1. Diagram of a typical artery showing the tunica externa, tunica media, and tunica intima.

Endothelial Cells

Endothelial cells form a continuous lining for the entire vascular system called the *endothelium*. Once thought to be nothing more than a lining for blood vessels, it is now known that the endothelium is a versatile, multifunctional tissue that plays an active role in controlling vascular function[1–4] (Table 18-1). As a selectively permeable monolayer, the endothelium controls the transfer of molecules across the vessel wall. The endothelium also plays a role in the modulation of blood flow and vascular resistance; control of platelet adhesion and blood clotting; metabolism of hormones; regulation of immune and inflammatory reactions; and elaboration of factors that influence the growth of other cell types, especially vascular smooth muscle cells.

Structurally intact endothelial cells respond to various abnormal stimuli by adjusting their usual functions and by expressing newly acquired functions.[1] The term *endothelial dysfunction* describes several types of potentially reversible changes in endothelial function that occur in response to environmental stimuli. Endothelial cell dysfunction has been implicated in a number of pathologies including thrombosis, atherosclerosis, and hypertensive vascular lesions.[3–5] There is also evidence that the dysfunction contributes to conditions such as erectile dysfunction, disorders of the retina, chronic kidney disease, pulmonary hypertension, and septic shock. Inducers of endothelial dysfunction include cardiovascular risk factors such as smoking, hypercholesteremia, hypertension, insulin resistance and diabetes, obesity, and aging that are critical to the pathogenesis of atherosclerosis. Dysfunctional endothelial cells, in turn, produce proinflammatory cytokines, growth factors (e.g., vascular endothelial growth factor), reactive oxygen species, procoagulant or anticoagulant substances, and a variety of other disease-producing products. They also influence the reactivity of underlying smooth muscle cells through production of both relaxing factors (e.g., nitric oxide) and contracting factors (e.g., endothelins; see Chapter 17).

Vascular Smooth Muscle Cells

Vascular smooth muscle cells, which form the predominant cellular layer in the tunica media, produce vasoconstriction or dilation of blood vessels. A network of vasomotor nerves of the sympathetic component of the autonomic nervous system supplies the smooth muscle in the blood vessels. These nerves are responsible for constriction of the vessel walls. Because they do not enter the tunica media of the blood vessel, the nerves do not synapse directly on the smooth muscle cells. Instead, they release the neurotransmitter norepinephrine, which diffuses into the media and acts on the nearby smooth muscle cells. The resulting impulses are propagated along the smooth muscle cells through their gap junctions, causing contraction of the entire smooth muscle cell layer and thus reducing the radius of the vessel lumen.

TABLE 18-1 Endothelial Cell Properties and Functions

Major Properties	Associated Functions/Factors
Maintenance of a selectively permeable barrier	Controls the transfer of small and large molecules across the vessel wall
Regulation of thrombosis	Elaboration of pro- and antithrombotic molecules (von Willebrand factor, plasminogen activator) and antithrombotic molecules (prostacyclin, heparin-like molecules, plasminogen activator)
Modulation of blood flow and vascular reactivity	Elaboration of vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (endothelins, angiotensin-converting enzyme)
Regulation of cell growth, particularly smooth muscle cells	Production of growth-stimulating factors (platelet-derived growth factor, hematopoietic colony-stimulating factor) and growth-inhibiting factors (heparin, transforming growth factor-β)
Regulation of inflammatory/immune responses	Expression of adhesion molecules that regulate leukocyte migration and release of inflammatory and immune system mediators (e.g., interleukins, interferons)
Maintenance of the extracellular matrix	Synthesis of collagen, laminin, proteoglycans
Involvement in lipoprotein metabolism	Oxidation of VLDL, LDL, cholesterol

Data from Schoen F.J. (2005). Blood vessels. In Kumar V., Abbas A.K., Fausto N. (Eds.), *Robbins and Cotran pathologic basis of disease* (7th ed., p. 514). Philadelphia: Elsevier Saunders; and Ross M.H., Kaye G.L., Pawlina W. (2003). *Histology: A text and atlas* (4th ed., p. 332). Philadelphia: Lippincott Williams & Wilkins.

Vascular smooth muscle cells also synthesize collagen, elastin, and other components of the extracellular matrix; elaborate growth factors and cytokines; and after vascular injury migrate into the intima and proliferate.[1] Thus, smooth muscle cells are important in both normal vascular repair and pathologic processes such as atherosclerosis. The migratory and proliferative activities of vascular smooth muscle cells are stimulated by growth promoters and inhibitors. Promoters include platelet-derived growth factor, thrombin, fibroblast growth factor, and cytokines such as interferon-γ and interleukin-1. Growth inhibitors include nitric oxide. Other regulators include the renin-angiotensin system (angiotensin II) and the catecholamines.

In summary, the walls of blood vessels are composed of three layers: an outer layer of loosely woven collagen tissue, a middle layer of vascular smooth muscle, and an inner layer of endothelial cells. The endothelium controls the transfer of molecules across the vascular wall and plays a role in the control of platelet adhesion and blood clotting, modulation of blood flow and vascular resistance, metabolism of hormones, regulation of immune and inflammatory reactions, and elaboration of factors that influence the growth of other cell types, particularly the smooth muscle cells. The term *endothelial dysfunction* describes changes in endothelial function that occur in response to stimuli derived from cardiovascular risk factors such as smoking, hypercholesteremia, hypertension, insulin resistance and diabetes, and obesity. Vascular smooth muscle cells not only control dilation and constriction of blood vessels, but also elaborate growth factors and synthesize collagen, elastin, and other components of the extracellular matrix that are important in both normal vascular repair and pathologic processes such as atherosclerosis.

Disorders of the Arterial Circulation

- The arterial system delivers oxygen and nutrients to the tissues.
- Disorders of the arterial circulation produce ischemia owing to narrowing of blood vessels, thrombus formation associated with platelet adhesion, and weakening of the vessel wall.
- Atherosclerosis is a progressive disease characterized by the formation of fibrofatty plaques in the intima of large and medium-sized vessels, including the aorta, coronary arteries, and cerebral vessels. The major risk factors for atherosclerosis are hypercholesterolemia and inflammation.
- Vasculitis is an inflammation of the blood vessel wall resulting in vascular tissue injury and necrosis. Arteries, capillaries, and veins may be affected. The inflammatory process may be initiated by direct injury, infectious agents, or immune processes.
- Aneurysms represent an abnormal localized dilatation of an artery due to a weakness in the vessel wall. As the aneurysm increases in size, the tension in the wall of the vessel increases and it may rupture. The increased size of the vessel also may exert pressure on adjacent structures.

Disorders of the Arterial Circulation

The arterial system distributes blood to all the tissues in the body. There are three types of arteries: large elastic arteries, including the aorta and its distal branches; medium-sized arteries, such as the coronary and renal arteries; and small arteries and arterioles that pass through the tissues. Each of these different types of arteries tends to be affected by different disease processes. The discussion in this section focuses on hyperlipidemia and atherosclerosis, the vasculitides, arterial disease of the extremities, and arterial aneurysms.

Hyperlipidemia and Atherosclerosis

Hyperlipidemia with its associated risk for development of atherosclerosis is a major cause of cardiovascular disease. Atherosclerosis causes more morbidity and mortality in the Western world than any other disorder. By the year 2025, it is predicted that cardiovascular mortality will likely exceed that of every other major disease group including infections, cancer, and trauma.[6]

Hyperlipidemia

Because lipids, namely, cholesterol and triglycerides, are insoluble in plasma, they are encapsulated by special fat-carrying proteins called *lipoproteins* for transport in the blood.[7] There are five main types of lipoproteins, classified by their densities, which reflect their protein content: chylomicrons, very–low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). VLDL carries large amounts of triglycerides that have a lower density than cholesterol. LDL is the main carrier of cholesterol, whereas HDL is about 50% protein and carries less cholesterol (Fig. 18-2).

Each type of lipoprotein consists of a large molecular complex of lipids combined with proteins called *apoproteins*.[7] The lipoprotein macromolecule is made up of a hydrophobic core of insoluble cholesterol esters and

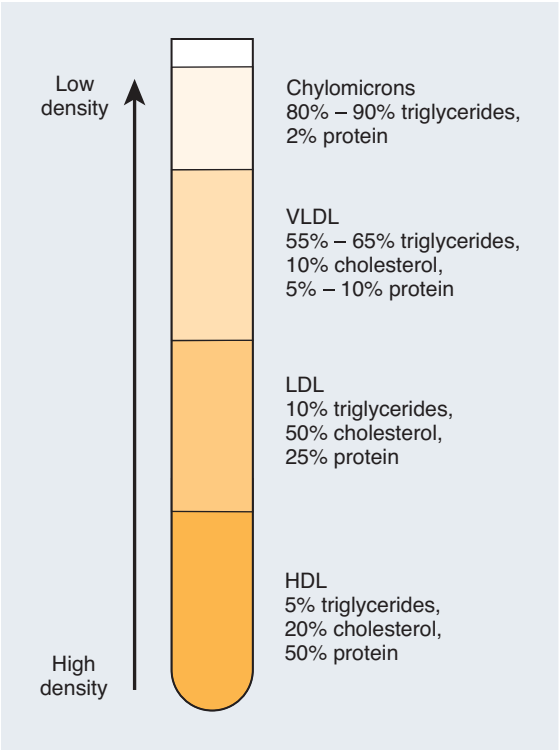


FIGURE 18-2. Lipoproteins are named based on their protein content, which is measured in density. Because fats are less dense than proteins, as the proportion of triglycerides decreases, the density increases. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very–low-density lipoprotein.

triglycerides, surrounded by a hydrophilic outer shell of soluble phospholipids, and nonesterified cholesterol (Fig. 18-3). In addition, the shell contains a variety of apoproteins that increase the stability and water solubility of the lipoprotein. The apoproteins not only add to the stability of lipoproteins, but have other functions as well: they activate certain enzymes required for normal lipoprotein metabolism, and they serve as reactive sites that specific receptors on peripheral tissues can recognize and use in the endocytosis and metabolism of the lipoproteins. Research findings suggest that genetic defects in the apoproteins may be involved in hyperlipidemia and accelerated atherosclerosis.[2,7]

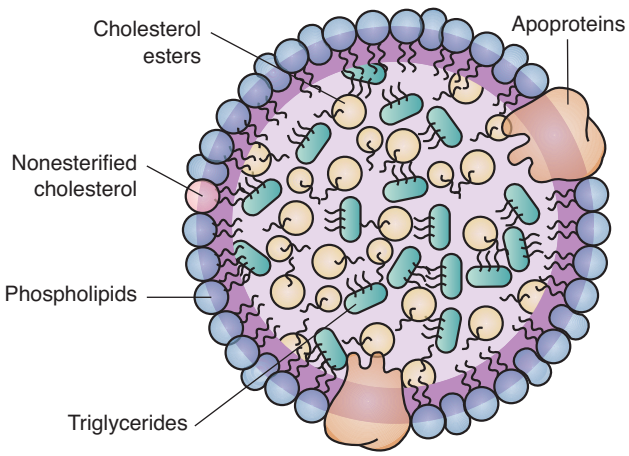


FIGURE 18-3. General structure of a lipoprotein. The cholesterol esters and triglycerides are located in the hydrophobic core of the macromolecule, surrounded by an outer hydrophilic shell of phospholipids, nonesterified lipoproteins, and apoproteins.

There are two sites of lipoprotein synthesis: the small intestine and the liver (Fig. 18-4). The chylomicrons, which are the largest of the lipoprotein molecules, are synthesized in the wall of the small intestine.[1,7] They are involved, through the exogenous pathway, in the transport of dietary triglycerides and cholesterol that have been absorbed from the gastrointestinal tract. Chylomicrons transfer their triglycerides to the cells of adipose and skeletal muscle tissue. The remnant chylomicron particles, which contain cholesterol, are then taken up by the liver and the cholesterol is used in the synthesis of VLDL or excreted in the bile.

The liver synthesizes and releases VLDL and HDL. The VLDLs contain large amounts of triglycerides and lesser amounts of cholesterol esters. They provide the primary pathway for the transport of endogenous triglycerides produced in the liver, as opposed to those obtained from the diet. Like chylomicrons, VLDLs carry their triglycerides to fat and muscle cells, where the triglycerides are removed. The resulting IDL particles, which are the main source of LDL, are reduced in triglyceride content and enriched in cholesterol. They are either taken to the liver and recycled to form VLDL or converted to LDL in the vascular compartment.

LDL, sometimes called the *bad cholesterol,* is the main carrier of cholesterol. LDL particles are rich in cholesterol and cholesterol esters. Approximately 60% of the LDL is transported back to the liver, where its apoprotein (apo)B-100 binds to specific apoB-100 receptors on liver cells, allowing the particles to be enodocytosed.[7] The remaining 40% of LDL particles are carried to extrahepatic tissues, such as those of the adrenal cortex and gonads that also have apoB-100 receptors that allow them to internalize the LDL particles and use their cholesterol in the synthesis of their cell membranes and steroid hormones.

Some cells, particularly the phagocytic macrophages, have nonspecific receptors known as *scavenger receptors* that bind various types of molecules, including oxidatively modified LDL. If excess LDL is present in the blood, as in hypercholesteremia, the receptor-mediated uptake of LDL by hepatic and extrahepatic tissues becomes saturated. The "excess" LDL is then available for uptake by scavenger cells present near the endothelial cells of arteries.[7,8] The uptake of LDL by macrophages in the arterial wall is believed to be involved in the development of atherosclerosis.

HDL, which is often referred to as the *good cholesterol,* is synthesized in the liver. It participates in the reverse transport of cholesterol—that is, carrying cholesterol from the peripheral tissues back to the liver. Epidemiologic studies show an inverse relation between HDL levels and the development of atherosclerosis.[6] It is thought that HDL, which is low in cholesterol and rich

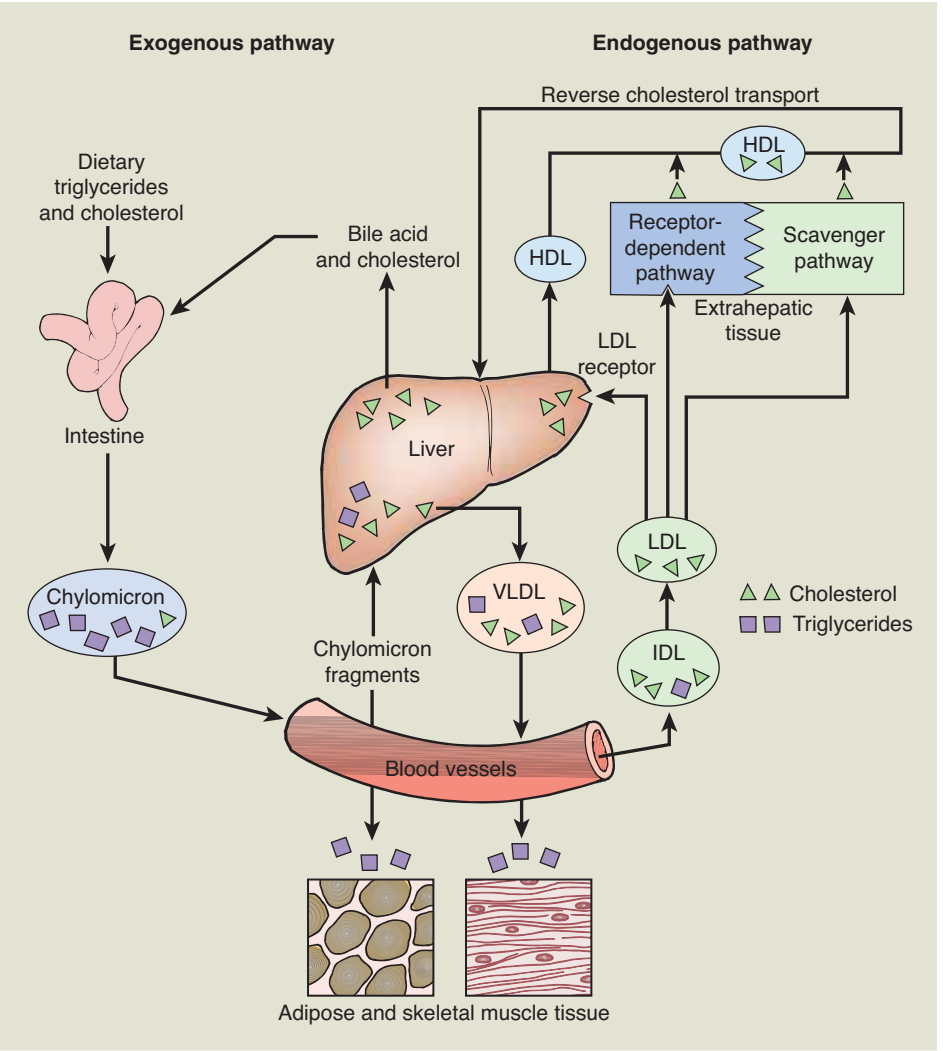


FIGURE 18-4. Schematic representation of the exogenous and endogenous pathways for triglyceride and cholesterol transport. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very–low-density lipoprotein.

in surface phospholipids, facilitates the clearance of cholesterol from atheromatous plaques and transports it to the liver, where it may be excreted rather than reused in the formation of VLDL. The mechanism whereby HDL takes up cholesterol from peripheral cells has recently been elucidated. A lipid transporter (adenosine triphosphate [ATP]–binding cassette transporter A class 1, or ABCA1) promotes the movement of cholesterol from peripheral cells to the lipid-poor HDL cholesterol.[7,9] Defects in this system (resulting from mutations in the ABCA1 transporter gene) are responsible for a condition called *Tangier disease*, which is characterized by accelerated atherosclerosis and little or no HDL cholesterol.[9]

Hypercholesteremia. Hypercholesteremia refers to increased levels of cholesterol in the blood. Blood cholesterol in adults can be described according to the classification system of the Third Report of the National Cholesterol Educational Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults that describes optimal to very high levels of LDL cholesterol, triglycerides, and low and high levels of HDL cholesterol[10] (Table 18-2).

TABLE 18-2 NCEP Adult Treatment Panel III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100–129	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200–239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

National Institutes of Health Expert Panel [2001]. *Third report of the National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III].* NIH Publication No. 01-3670. Bethesda, MD: National Institutes of Health.

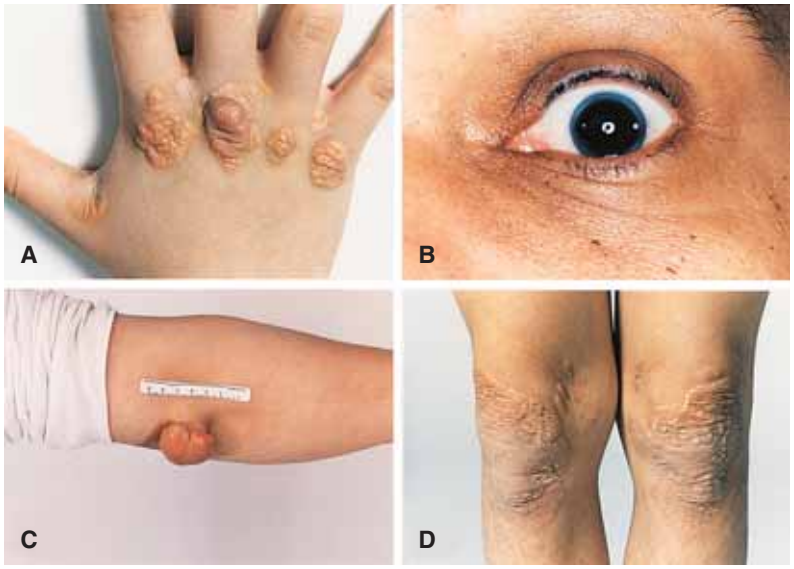


FIGURE 18-5. Xanthomas in the skin and tendons **(A, C, D)**. Arcus lipoides represents the deposition of lipids in the peripheral cornea **(B)**. (From Gotlieb A.I. [2005]. Blood vessels. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Pathology: Clinicopathologic foundations of medicine* [4th ed., p. 499]. Philadelphia: Lippincott Williams & Wilkins.)

Diagnosis of hyperlipidemia depends on blood lipid studies. A fasting serum lipoprotein profile includes a person's total serum cholesterol, LDL, HDL, and triglycerides.[10,11] The relationship between the different lipid fractions can then be used as a means for determining an individual's risk for coronary heart disease and other atherosclerosis-related diseases. Cholesterol is carried in the blood as VLDL, LDL, and HDL, with the total cholesterol being equal to the sum of these three components. Most clinical laboratories measure the total serum cholesterol, total triglycerides, and the amount of cholesterol carried in the HDL fraction. The LDL is then estimated by subtracting the HDL from the total serum cholesterol and the triglycerides divided by 5* (i.e., LDL [mg/dL] = total cholesterol [mg/dL] − HDL [mg/dL] − triglycerides [mg/dL]/5).[11,12] Thus, serum cholesterol levels may be elevated as a result of an increase in any of the lipoproteins. For example, two persons with the same total cholesterol of 275 mg/dL may have very different lipid profiles.[11] One person may have a favorable lipid profile with an HDL of 110 mg/dL, a triglyceride level of 175 mg/dL, and an LDL of 130 mg/dL, whereas another person with an HDL of 40 mg/dL, a triglyceride level of 150 mg/dL, and an LDL cholesterol of 205 mg/dL would be at much greater risk for cardiovascular disease.

Several factors, including nutrition, genetics, comorbid conditions, medications, and metabolic diseases, can raise blood lipid levels. Most cases of elevated levels of cholesterol are probably multifactorial. Some persons may have increased sensitivity to dietary cholesterol, others a lack of LDL receptors, and still others altered apoprotein synthesis. Hypercholesterolemia can be divided into two types: primary or secondary. Primary hypercholesterolemia describes elevated cholesterol levels that develop independent of other causes, whereas secondary hypercholesterolemia is associated with other health problems and behaviors.

Many types of primary hypercholesterolemia have a genetic basis. There may be a defective synthesis of the apoproteins, a lack of receptors, defective receptors, or defects in the handling of cholesterol in the cell that are genetically determined.[1,2] For example, the LDL receptor is deficient or defective in the genetic disorder known as *familial hypercholesterolemia (type 2A)*. This autosomal dominant type of hyperlipoproteinemia results from a mutation in the gene specifying the receptor for LDL. The disorder is probably one of the most common of all mendelian disorders; the frequency of heterozygotes is 1 in 500 persons in the general population.[2] Because most of the circulating cholesterol is removed by receptor-dependent mechanisms, blood cholesterol levels are markedly elevated in persons with this disorder. Plasma LDL levels in heterozygotes range between 250 and 500 mg/dL, whereas in homozygotes LDL cholesterol levels may rise to 1000 mg/dL.[2] Although heterozygotes commonly have an elevated cholesterol level from birth, they do not develop symptoms until adult life, when they often develop *xanthomas* (i.e., cholesterol deposits) along the tendons and atherosclerosis appears (Fig. 18-5). Myocardial infarction before 40 years of age is common. Homozygotes are much more severely affected; they have cutaneous xanthomas in childhood and may experience myocardial infarction by as early as 1 to 2 years of age.

Secondary causes of hyperlipoproteinemia include obesity with high-calorie intake, sedentary lifestyle, and diabetes mellitus.[11] High-calorie diets increase the production of VLDL, with triglyceride elevation and high conversion of VLDL to LDL. Excess ingestion of cholesterol may reduce the formation of LDL receptors and thereby decrease LDL removal from the blood. Diets that are high in triglycerides and saturated fats increase cholesterol synthesis and suppress LDL receptor activity. A sedentary lifestyle influences interactions among lipids and lipoproteins. Diabetes mellitus and the metabolic

*When using SI units (expressed in mmol/L), the triglycerides are divided by 2.2.

syndrome predispose to dyslipidemia with elevation of triglycerides, low HDL, and minimal or modest elevation of LDL. Other systemic disorders that can elevate lipids include hypothyroidism, the nephrotic syndrome, and obstructive liver disease. Medications such as beta blockers, estrogens, and protease inhibitors (used in the treatment of human immunodeficiency virus [HIV] infection) can also increase lipid levels.

Management of Hyperlipidemia. A reduction in LDL cholesterol continues to be the primary target for cholesterol-lowering therapy, particularly in people at risk for coronary artery disease (CAD).[13] The major risk factors for CAD, exclusive of LDL cholesterol levels, that modify LDL cholesterol goals include cigarette smoking, hypertension, family history of premature CAD in a first-degree relative, age (men ≥45 years; women ≥55 years), an HDL cholesterol level less than 40 mg/dL, and diabetes mellitus. Guidelines recommend that persons with zero or no major risk factors should have an LDL cholesterol goal of 160 mg/dL or less; those with two or more of the major risk factors should have an LDL cholesterol goal of less than 130 mg/dL; persons with *high-risk* factors (i.e., those with CAD, other forms of atherosclerotic disease, or diabetes) should have an LDL cholesterol goal of less than 100 mg/dL; and persons with *very–high-risk* factors (i.e., acute coronary syndromes or CAD with other risk factors) should have an LDL cholesterol goal of less than 70 mg/dL.[14] It is also recommended that persons with a greater than 20% 10-year risk of experiencing myocardial infarction or coronary death, as determined by the risk assessment tool developed from Framingham Heart Study data, should have an LDL cholesterol goal of less than 100 mg/dL (to calculate a risk score go to http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof , or http://bodyandhealth.canada.com/health_tools.asp?t=12&text_id=2751&channel_id=131&relation_id=10842).

The management of hypercholesterolemia focuses on dietary and therapeutic lifestyle changes; when these are unsuccessful, pharmacologic treatment may be necessary. Therapeutic lifestyle changes include an increased emphasis on physical activity, dietary measures to reduce LDL levels, smoking cessation, and weight reduction for people who are overweight.

Several dietary elements affect cholesterol and its lipoprotein fractions: (1) excess calorie intake, (2) saturated and trans fats, and (3) cholesterol.[13] Excess calories consistently lower HDL and less consistently elevate LDL. Saturated fats in the diet can strongly influence cholesterol levels. Depending on individual differences, they raise VLDL and LDL levels. Trans fats, which are manufactured from vegetable oils and are used to enhance the taste and extend the shelf life of fast foods, are more atherogenic than saturated fats. Dietary cholesterol tends to increase LDL cholesterol. A diet that is low in saturated fats and cholesterol can lower LDL by 11% to 15% and possibly by as much as 20%.[13]

Lipid-lowering drugs work in several ways, including decreasing cholesterol production, decreasing cholesterol absorption from the intestine, and removing cholesterol from the bloodstream. Drugs that act directly to decrease cholesterol levels also have the beneficial effect of further lowering cholesterol levels by stimulating the production of additional LDL receptors. There currently are five major types of medications available for treating hypercholesterolemia: 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), bile acid–binding resins, cholesterol absorption inhibitor agents, niacin and its congeners, and the fibrates.[13] Inhibitors of HMG-CoA reductase, a key enzyme in the cholesterol biosynthetic pathway, can reduce or block the hepatic synthesis of cholesterol and are the cornerstone of LDL-reducing therapy. Statins also reduce triglyceride levels. The bile acid–binding resins bind and sequester cholesterol-containing bile acids in the intestine. This leads to increased production of LDL receptors by the liver, with resulting increased removal of cholesterol from the blood for synthesis of new bile acids. The cholesterol absorption inhibitor (ezetimibe) interferes with the absorption of cholesterol. Nicotinic acid, a niacin congener, blocks the synthesis and release of VLDL by the liver, thereby lowering not only VLDL levels but also IDL and LDL levels. Nicotinic acid also increases HDL concentrations up to 30%. The fibrates decrease the synthesis of VLDL by the liver and also enhance the clearance of triglycerides from the circulation.

Atherosclerosis

Atherosclerosis is a type of arteriosclerosis or hardening of the arteries. The term *atherosclerosis*, which comes from the Greek words *atheros* ("gruel" or "paste") and *sclerosis* ("hardness"), denotes the formation of fibrofatty lesions in the intimal lining of the large and medium-sized arteries such as the aorta and its branches, the coronary arteries, and the cerebral arteries that supply the brain (Fig. 18-6). The disorder remains a leading cause of coronary artery disease, stroke, and peripheral artery disease.

Epidemiology and Risk Factors. Although the cause or causes of atherosclerosis have not been determined with certainty, epidemiologic studies have identified predisposing risk factors (Chart 18-1).[1,2,6,11,14] Some of these are constitutional and cannot be changed and others are affected by lifestyle and can be modified. The major risk factor, hypercholesteremia, has both constitutional and lifestyle components.

Constitutional risk factors such as increasing age, male gender, and family history of premature coronary artery disease cannot be changed. The tendency toward the development of atherosclerosis appears to run in families. Persons who come from families with a strong history of heart disease or stroke due to atherosclerosis are at greater risk for developing atherosclerosis than those with a negative family history. Several genetically determined alterations in lipoprotein and cholesterol metabolism have been identified, and it seems likely that others will be identified in the future.[2] The incidence of atherosclerosis increases with age. Other factors being equal, men are at greater risk for the development of

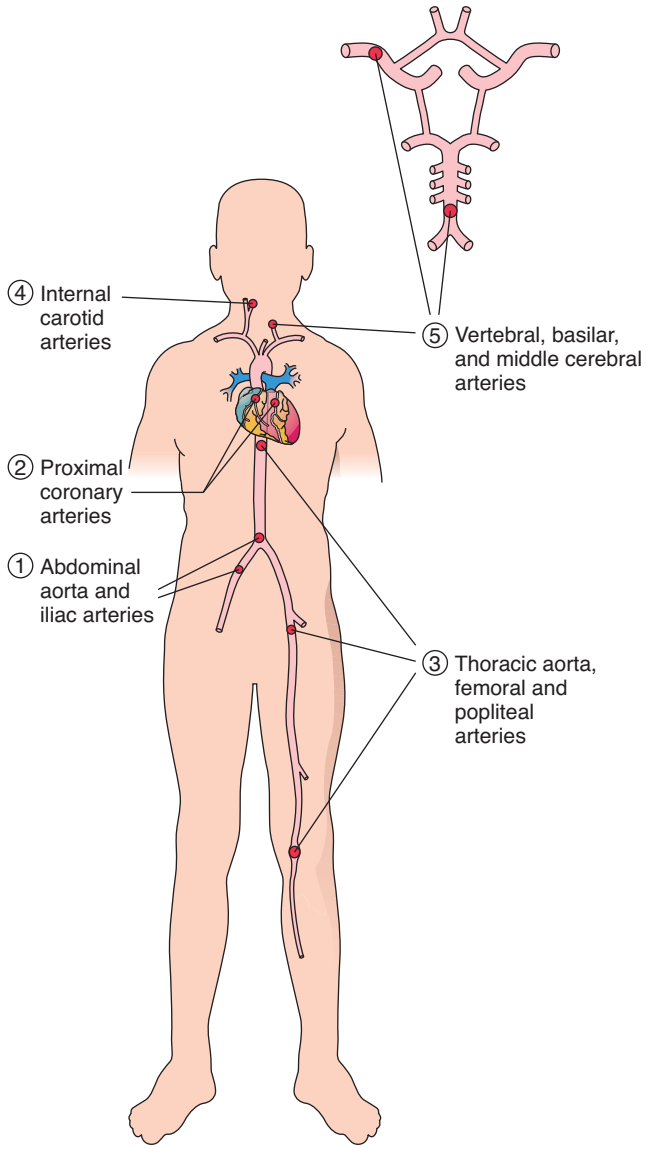


FIGURE 18-6. Sites of severe atherosclerosis in order of frequency. (From Gotlieb A.I. [2008]. Blood vessels. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 403]. Philadelphia: Lippincott Williams & Wilkins.)

CAD than are premenopausal women, probably because of the protective effects of natural estrogens. After menopause, the incidence of atherosclerosis-related diseases in women increases, and by the seventh to eighth decade of life, the frequency of myocardial infarction in the two genders tends to equalize.[1]

The major risk factors that can be modified by a change in health care behaviors include cigarette smoking, obesity, hypertension, hyperlipidemia and elevated LDL cholesterol, and diabetes mellitus (traditional cardiovascular risk factors). Smoking affects atherosclerosis by several mechanisms other than its unfavorable effects on blood pressure, sympathetic vascular tone, and reduction in myocardial oxygen supply.[6] It has adverse hemostatic and inflammatory effects and it may enhance the oxidation of LDL cholesterol, causing damage to the endothelial lining of blood vessels. Obesity, type 2 diabetes, high blood pressure, and high blood cholesterol levels (all components of the metabolic syndrome; see Chapter 33) often can be controlled with a change in health care behaviors and medications.

However, not all atherothrombotic vascular disease can be explained by the established genetic and environmental risk factors. Other so-called nontraditional risk factors have been associated with increased risk for development of atherosclerosis, including C-reactive protein (CRP), serum homocysteine, and lipoprotein (a).[6,15] There also has been increased interest in the possible connection between infectious agents (e.g., *Chlamydia pneumoniae,* herpesvirus, cytomegalovirus) and the development of vascular disease.[2] Genomic evidence of these organisms has been found in atherosclerotic lesions, but whether they are causally associated with lesions or simply enter the disease vessel is unknown.[2]

Considerable interest in the role of inflammation in the etiology of atherosclerosis has emerged over the past two decades. CRP is an acute-phase reactant synthesized in the liver that is a marker for systemic inflammation (see Chapter 3). A number of population-based studies have demonstrated that baseline CRP levels can predict future cardiovascular events among apparently healthy individuals.[1,16] High-sensitivity CRP (hs-CRP) may be a better predictor of cardiovascular risk than lipid measurement alone.[6] Because CRP is an acute inflammatory phase reactant, major infections, trauma, or acute hospitalization can elevate CRP levels (usually 100-fold or more). Thus, CRP levels to determine cardiovascular risk should be performed when the person is clinically stable.

Homocysteine is derived from the metabolism of dietary methionine, an amino acid that is abundant in animal protein. Homocysteine inhibits elements of the anticoagulant cascade and is associated with endothelial

CHART 18-1 Risk Factors for Atherosclerosis

Nonmodifiable
- Increasing age
- Male gender
- Genetic disorders of lipid metabolism
- Family history of premature coronary artery disease

Potentially Modifiable
- Cigarette smoking
- Obesity
- Hypertension
- Hyperlipidemia with elevated low-density lipoprotein and low high-density lipoprotein cholesterol
- Diabetes mellitus

Additional Nontraditional
- Inflammation marked by elevated C-reactive protein levels
- Hyperhomocystinemia
- Increased lipoprotein (a) levels

damage, which is thought to be an important first step in the development of atherosclerosis.[6,16] The normal metabolism of homocysteine requires adequate folate and vitamin B_6 intake, although the jury is still out on whether supplemental folate and vitamin B_6 can reduce the incidence of cardiovascular disease.[1] Homocysti nuria, due to rare hereditary errors of metabolism, results in elevated homocysteine levels and premature cardiovascular disease.[1]

Lipoprotein(a) (Lp[a]), which is an altered form of LDL that contains apoB-100 linked to apoA, is considered to be an independent risk factor for the development of atherosclerosis.[1,2] Lp(a) enhances cholesterol delivery to injured blood vessels, suppresses the generation of plasmin, and promotes smooth muscle proliferation. LP(a) levels are heritable and are not altered by most cholesterol-lowering drugs.[2]

Mechanisms of Development. The lesions associated with atherosclerosis are of three types: the fatty streak, the fibrous atheromatous plaque, and the complicated lesion. The latter two are responsible for the clinically significant manifestations of the disease. *Fatty streaks* are thin, flat, yellow intimal discolorations that progressively enlarge by becoming thicker and slightly elevated as they grow in length. Histologically, they consist of macrophages and smooth muscle cells that have become distended with lipid to form foam cells. Fatty streaks are present in children, often in the first year of life.[1,2] This occurs regardless of geographic setting, gender, or race. They increase in number until about 20 years of age, and then remain static or regress. There is controversy about whether fatty streaks, in and of themselves, are precursors of atherosclerotic lesions.

The *fibrous atheromatous plaque* is the basic lesion of clinical atherosclerosis. It is characterized by the accumulation of intracellular and extracellular lipids, proliferation of vascular smooth muscle cells, formation of scar tissue, and calcification. The lesions begin as a gray to pearly white, elevated thickening of the vessel intima with a core of extracellular lipid covered by a fibrous cap of connective tissue and smooth muscle (Fig. 18-7). As the lesions increase in size, they encroach on the lumen of the artery and eventually may occlude the vessel or predispose to thrombus formation, causing a reduction of blood flow. Because blood flow is related to the fourth power of the vessel radius (see Chapter 17), the reduction in blood flow becomes increasingly greater as the disease progresses. The more advanced atherosclerotic lesions contain hemorrhage, ulceration, and scar tissue deposits. Thrombosis is the most important complication of atherosclerosis. It is caused by slowing and turbulence of blood flow in the region of the plaque and ulceration of the plaque.

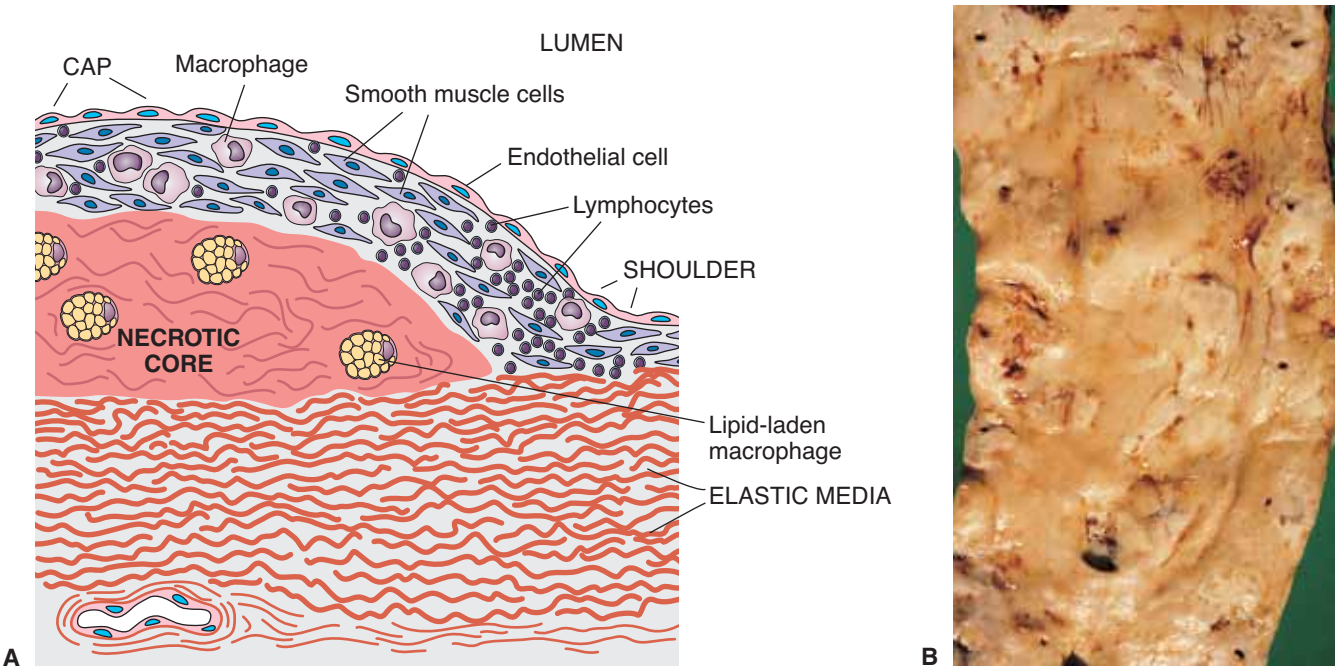


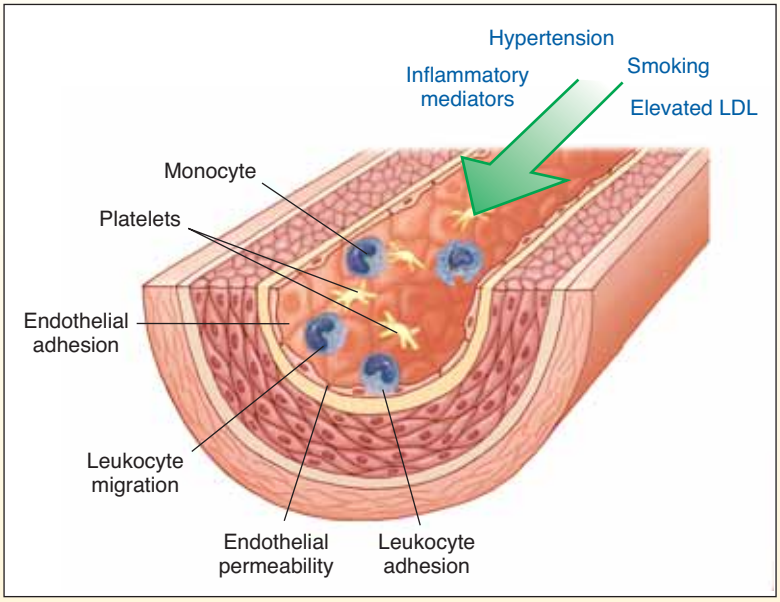
FIGURE 18-7. Fibrofatty plaque of atherosclerosis. **(A)** In this fully developed fibrous plaque, the core contains lipid-filled macrophages and necrotic smooth muscle cell debris. The "fibrous" cap is composed largely of smooth muscle cells, which produce collagen, small amounts of elastin, and glycosaminoglycans. Also shown are infiltrating macrophages and lymphocytes. Note that the endothelium over the surface of the fibrous cap frequently appears intact. **(B)** The aorta shows discrete raised, tan plaques. Focal plaque ulcerations are also evident. (From Gotlieb A.I. [2008]. Blood vessels. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 401]. Philadelphia: Lippincott Williams & Wilkins.)

UNDERSTANDING → Development of Atherosclerosis

Atherosclerosis is characterized by the development of atheromatous lesions within the intimal lining of the large and medium-sized arteries that protrude into and can eventually obstruct blood flow. The development of atherosclerotic lesions is a progressive process involving (1) endothelial cell injury, (2) migration of inflammatory cells, (3) smooth muscle cell proliferation and lipid deposition, and (4) gradual development of the atheromatous plaque with a lipid core.

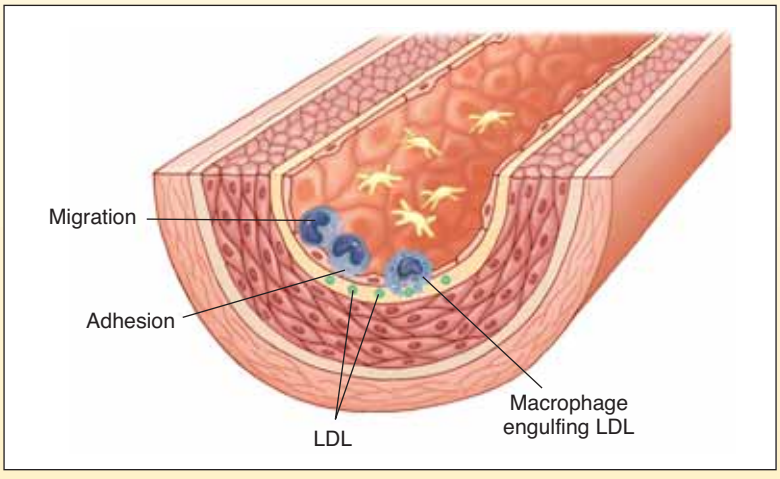
1

Endothelial Cell Injury. The vascular endothelium consists of a single layer of cells with cell-to-cell attachments, which normally protects the subendothelial layers from interacting with blood cells and other blood components. Agents such as smoking, elevated low-density lipoprotein (LDL) levels, immune mechanisms, and mechanical stress associated with hypertension share the potential for causing endothelial injury with adhesion of monocytes and platelets.



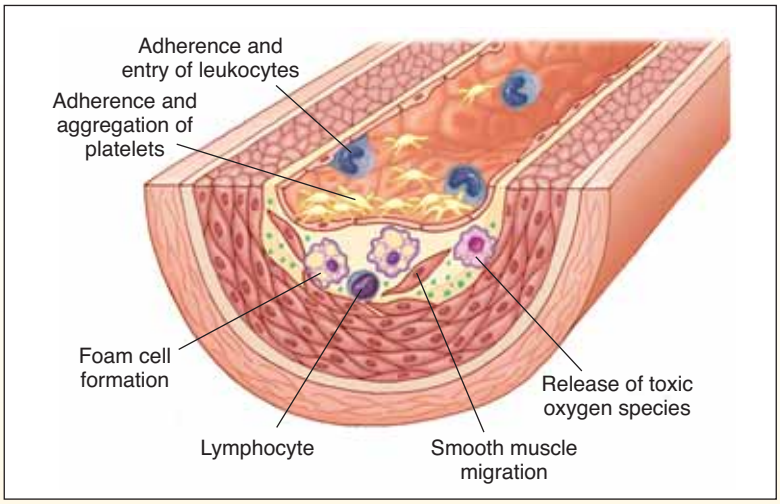
2

Migration of Inflammatory Cells. Early in the development of atherosclerotic lesions, endothelial cells begin to express selective adhesion molecules that bind monocytes and other inflammatory cells that initiate the atherosclerotic lesions. After monocytes adhere to the endothelium, they migrate between the endothelial cells to localize in the intima, transform into macrophages, and engulf lipoproteins, largely LDL.



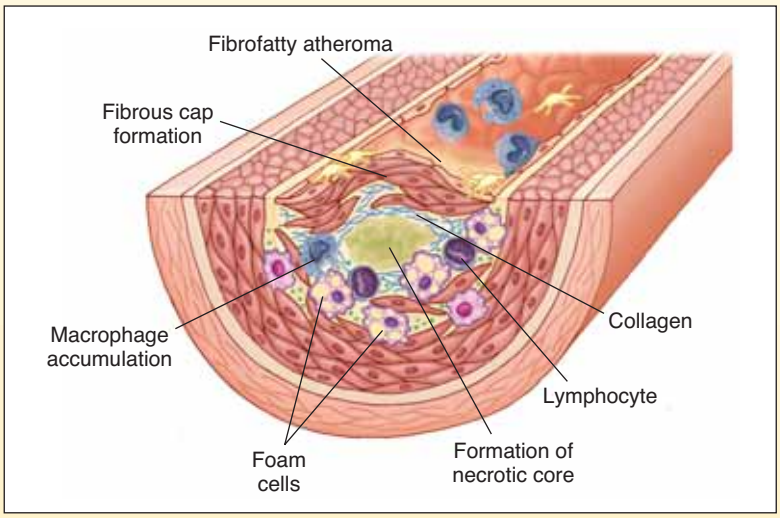
3

Lipid Accumulation and Smooth Muscle Cell Proliferation. Although the recruitment of monocytes to the arterial wall and their subsequent differentiation into activated macrophages that remove LDL from the circulation is protective, it also contributes to the development of atherosclerosis. Activated macrophages release toxic oxygen species that oxidize LDL. The oxidized LDL is then ingested by the macrophages through a scavenger receptor, which is distinct from the LDL receptor, resulting in the formation of foam cells, which are the primary component of atherosclerotic lesions. Activated macrophages also produce growth factors that contribute to the migration and proliferation of smooth muscle cells (SMCs) and the elaboration of extracellular matrix (ECM).



4

Plaque Structure. Atherosclerotic plaques consist of an aggregation of SMCs, macrophages, and other leukocytes; ECM, including collagen and elastic fibers; and intracellular and extracellular lipids. Typically, the superficial fibrous cap is composed of SMCs and dense ECM. Immediately beneath and to the side of the fibrous cap is a cellular area (the shoulder) consisting of macrophages, SMCs, and lymphocytes. Below the fibrous cap is a central core of lipid-laden foam cells and fatty debris. Rupture, ulceration, or erosion of an unstable or vulnerable fibrous cap may lead to hemorrhage into the plaque or thrombotic occlusion of the vessel lumen.



Although the risk factors associated with atherosclerosis have been identified through epidemiologic studies, many unanswered questions remain regarding the mechanisms that contribute to the development of atherosclerotic lesions. The vascular endothelial layer, which consists of a single layer of cells with cell-to-cell attachments, normally serves as a selective barrier that protects the subendothelial layers by interacting with blood cells and other blood components. One hypothesis of plaque formation suggests that injury to the endothelial vessel layer is the initiating factor in the development of atherosclerosis.[1,2] A number of factors are regarded as possible injurious agents, including products associated with smoking, immune mechanisms, and mechanical stress such as that associated with hypertension. The fact that atherosclerotic lesions tend to form where vessels branch or where there is turbulent flow suggests that hemodynamic factors may also play a role.

Hyperlipidemia, particularly LDL with its high cholesterol content, is also believed to play an active role in the pathogenesis of the atherosclerotic lesion. Interactions between the endothelial layer of the vessel wall and white blood cells, particularly the monocytes (blood macrophages), normally occur throughout life; these interactions increase when blood cholesterol levels are elevated. One of the earliest responses to elevated cholesterol levels is the attachment of monocytes to the endothelium. The monocytes have been observed to move through the cell-to-cell attachments of the endothelial layer into the subendothelial spaces, where they are transformed into macrophages.

Activated macrophages release free radicals that oxidize LDL, which, in turn, is toxic to the endothelium, causing endothelial cell loss and exposure of the subendothelial tissue to blood components. This leads to platelet adhesion and aggregation and fibrin deposition. Platelets and activated macrophages release various factors that are thought to promote growth factors that modulate the proliferation of smooth muscle cells and the deposition of extracellular matrix in the lesions.[1,2,17,18] Activated macrophages also ingest the oxidized LDL (by uptake through the scavenger receptor) to become foam cells, which are present in all stages of atherosclerotic plaque formation. Lipids released from necrotic foam cells accumulate to form the lipid core of unstable plaques. Unstable plaques typically are characterized histologically by a large central lipid core, an inflammatory infiltrate, and a thin fibrous cap. These "vulnerable plaques" are at risk of rupture, often at the shoulder of the plaque (see Fig. 18-7A) where the fibrous cap is thinnest and the mechanical stresses highest.[2,17]

Clinical Manifestations. The clinical manifestations of atherosclerosis depend on the vessels involved and the extent of vessel obstruction. Atherosclerotic lesions produce their effects through narrowing of the vessel and production of ischemia; sudden vessel obstruction due to plaque hemorrhage or rupture; thrombosis and formation of emboli resulting from damage to the vessel endothelium; and aneurysm formation due to weakening of the vessel wall.[1,2] In larger vessels, such as the aorta, the important complications are those of thrombus formation and weakening of the vessel wall. In medium-sized arteries, such as the coronary and cerebral arteries, ischemia and infarction due to vessel occlusion are more common. Although atherosclerosis can affect any organ or tissue, the arteries supplying the heart, brain, kidneys, lower extremities, and small intestine are most frequently involved (see Fig. 18-6).

The Vasculitides

The vasculitides are a group of vascular disorders that cause inflammatory injury and necrosis of the blood vessel wall (i.e., vasculitis). Vasculitis, which is a common pathway for tissue and organ involvement in many different disease conditions, involves the endothelial cells and smooth muscle cells of the vessel wall.[1,2,19,20] Vessels of any type (arteries, veins, and capillaries) in virtually any organ can be affected. Because they may affect veins and capillaries, the terms *vasculitis, angiitis,* and *arteritis* often are used interchangeably. Clinical manifestations often include fever, myalgia, arthralgia, and malaise. Vasculitis may result from direct injury to the vessel, infectious agents, or immune processes, or they may develop secondary to other disease states such as systemic lupus erythematosus. Physical agents such as cold (i.e., frostbite), irradiation (i.e., sunburn), mechanical injury, and toxins may secondarily cause vessel damage, often leading to necrosis of the vessels. A number of persons with vasculitis have circulating antibodies called *antineutrophil cytoplasmic antibodies* (ANCAs) that react with antigens in the cytoplasm of neutrophils.[1] Although the precise pathologic mechanism is unknown, these antibodies may serve to initiate an inflammatory state that continually recruits and stimulates neutrophils to release reactive oxygen species and proteolytic enzymes.[1] Serum ANCA titers, which can correlate with disease activity, may serve as a useful quantitative diagnostic marker for ANCA-associated vasculitides.

The vasculitides are commonly classified based on etiology, pathologic findings, and prognosis. One classification system divides the conditions into three groups: (1) small vessel, (2) medium-sized vessel, and (3) large vessel vasculitides[1,2] (Table 18-3). Small vessel refers to small arteries (ANCA-associated disease only), arterioles, venules, and capillaries; medium vessels refer to medium- and small-sized arteries and arterioles; and large vessel refers to the aorta and its major tributaries. The small vessel vasculitides are involved in a number of different diseases, most of which are mediated by the type III immune complex hypersensitivity reaction (see Chapter 16). They commonly involve the skin and are often a complication of an underlying disease (i.e., vasculitis associated with neoplasms or connective tissue disease) and exposure to environmental agents (i.e., serum sickness and urticarial vasculitis).

Medium-sized vessel vasculitides produce necrotizing damage to medium-sized muscular arteries of major organ systems. This group includes polyarteritis nodosa, Kawasaki disease (discussed in Chapter 19), and thromboangiitis obliterans (discussed in the section on arterial disease of the extremities). Polyarteritis nodosa is an

TABLE 18-3 Classification of the Vasculitides

Group	Examples	Characteristics
Small vessel vasculitis	Microscopic polyangiitis	Necrotizing vasculitis with few or no immune deposits affecting medium and small blood vessels, including capillaries, venules, and arterioles; necrotizing glomerulonephritis and involvement of the pulmonary capillaries is common
	Wegener granulomatosis	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting capillaries, venules, arterioles, and arteries; necrotizing glomerulonephritis is common
Medium-sized vessel vasculitis	Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without vasculitis in arteries, capillaries, or venules; usually associated with underlying disease or environmental agents
	Kawasaki disease	Involves large, medium-sized, and small arteries (frequently the coronaries) and is associated with mucocutaneous lymph node syndrome; usually occurs in small children
	Thromboangiitis obliterans	Segmental, thrombosing, acute and chronic inflammation of the medium-sized and small arteries, principally the tibial and radial arteries but sometimes extending to the veins and nerves of the extremities; occurs almost exclusively in men who are heavy smokers
Large vessel vasculitis	Giant cell (temporal) arteritis	Granulomatous inflammation of the aorta and its major branches with predilection for extracranial vessels of the carotid artery; infiltration of vessel wall with giant cells and mononuclear cells; usually occurs in people older than 50 years of age and is often associated with polymyalgia rheumatica
	Takayasu arteritis	Granulomatous inflammation of the aorta and its branches; usually occurs in people younger than 50 years of age

uncommon, acute multisystem inflammatory disease of small and medium-sized blood vessels of the kidney, liver, intestine, peripheral nerves, skin, and muscle. The usual course of the disease is progressive with various signs and symptoms according to the pattern of organ involvement. Most cases were fatal before corticosteroid and immunosuppressant agents became available for use in treatment of the disorder.[1]

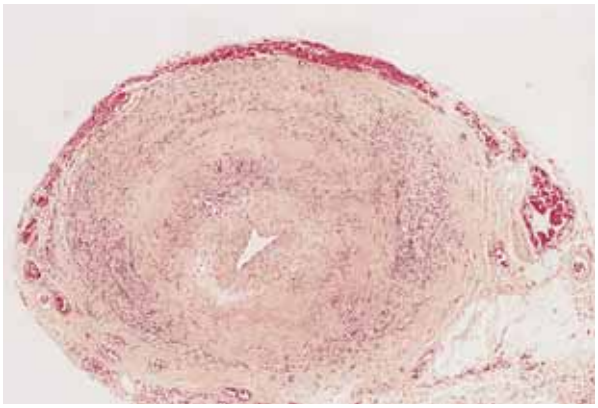


FIGURE 18-8. Temporal arteritis. A photomicrograph of a temporal artery showing chronic inflammation throughout the wall, giant cells, and a lumen severely narrowed by intimal thickening. (From Gotlieb A.I. [2008]. Blood vessels. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 401]. Philadelphia: Lippincott Williams & Wilkins.)

Large vessel vasculitides involve large elastic arteries; they commonly are called *giant cell arterides* because they involve infiltration of the vessel wall with giant cells and mononuclear cells. Giant cell (temporal) arteritis, the most common of the large vessel vasculitides, is an acute and chronic inflammation of large to small arteries. It mainly affects arteries of the head—especially the temporal arteries—but may include the vertebral and ophthalmic arteries. About half of persons with the disease have accompanying pain and stiffness of the shoulder and hip (polymyalgia rheumatica; see Chapter 44). The most common clinical presentation is headache and tenderness over the superficial temporal artery. Diagnosis is by biopsy of the artery (Fig. 18-8). Diagnosis followed by treatment with corticosteroid drugs is important because involvement of the ophthalmic artery can cause blindness.[1,2]

Arterial Disease of the Extremities

Disorders of the circulation in the extremities often are referred to as *peripheral vascular disorders*. In many respects, the disorders that affect arteries in the extremities are the same as those affecting the coronary and cerebral arteries in that they produce ischemia, pain, impaired function, and in some cases infarction and tissue necrosis. Not only are the effects similar, but also the pathologic conditions that impair circulation in the extremities are identical. This section focuses on peripheral arterial disease, thromboangiitis obliterans, and Raynaud phenomenon.

Peripheral Arterial Disease

Peripheral arterial disease (PAD) is the presence of systemic atherosclerosis distal to the arch of the aorta.[21] The disease is seen most commonly in men in their 60s and 70s. The risk factors for this disorder are similar to those for atherosclerosis. Cigarette smoking and diabetes mellitus are the strongest risk factors, with more than 80% of persons with the disorder being current or former smokers.[22]

As with atherosclerosis in other locations, the signs and symptoms of vessel occlusion are gradual. The primary symptom of chronic obstructive arterial disease is *intermittent claudication* or pain with walking.[21,22] Typically, persons with the disorder complain of calf pain because the gastrocnemius muscle has the highest oxygen consumption of any muscle group in the leg during walking. Some persons may complain of a vague aching feeling or numbness, rather than pain. Other activities such as swimming, bicycling, and climbing stairs use other muscle groups and may not incite the same degree of discomfort as walking. Other signs of ischemia include atrophic changes and thinning of the skin and subcutaneous tissues of the lower leg and diminution in the size of the leg muscles. The foot often is cool, and the popliteal and pedal pulses are weak or absent. Limb color blanches with elevation of the leg because of the effects of gravity on perfusion pressure and becomes deep red when the leg is in the dependent position because of an autoregulatory increase in blood flow and a gravitational increase in perfusion pressure.

When blood flow is reduced to the extent that it no longer meets the minimal needs of resting muscle and nerves, ischemic pain at rest, ulceration, and gangrene develop. As tissue necrosis develops there typically is severe pain in the region of skin breakdown, which is worse at night with limb elevation and is improved with standing.

Diagnostic methods include inspection of the limbs for signs of chronic low-grade ischemia such as subcutaneous atrophy, brittle toenails, hair loss, pallor, coolness, or dependent rubor. Palpation of the femoral, popliteal, posterior tibial, and dorsalis pedis pulses allows for an estimation of the level and degree of obstruction. The ratio of ankle to arm (i.e., tibial and brachial arteries) systolic blood pressure is used to detect significant obstruction, with a ratio of less than 0.9 indicating occlusion. Blood pressures may be taken at various levels on the leg to determine the level of obstruction. A Doppler ultrasound stethoscope may be used for detecting pulses and measuring blood pressure. Ultrasound imaging, magnetic resonance imaging (MRI) arteriography, spiral computed tomographic (CT) arteriography, and invasive contrast angiography also may be used as diagnostic methods.[21,22]

Treatment includes measures directed at protection of the affected tissues and preservation of functional capacity. Walking (slowly) to the point of claudication usually is encouraged because it increases collateral circulation. Avoidance of injury is important because tissues of extremities affected by atherosclerosis are easily injured and slow to heal. It is important to address other cardiovascular risk factors such as smoking, hypertension, hyperlipidemia, and diabetes. Drug therapy includes antiplatelet therapy (e.g., aspirin or clopidogrel). Other medications that are useful include statins, cilostazol (a vasodilator with antiplatelet properties), and pentoxifylline (an antiplatelet agent that decreases blood viscosity and improves erythrocyte flexibility). Percutaneous or surgical intervention is typically reserved for the patient with disabling claudication or limb-threatening ischemia. Surgery (i.e., femoropopliteal bypass grafting using a section of saphenous vein) may be indicated in severe cases. Percutaneous transluminal angioplasty and stent placement, in which a balloon catheter is inserted into the area of stenosis and the balloon inflated to increase vessel diameter, is another form of treatment.[21,22]

Thromboangiitis Obliterans

Thromboangiitis obliterans (Buerger disease) is a vasculitis affecting the medium-sized arteries, usually the plantar and digital vessels in the foot and lower leg.[1,2,23] Arteries in the arm and hand also may be affected. Although primarily an arterial disorder, the inflammatory process often extends to involve adjacent veins and nerves. Usually it is a disease of men between the ages of 25 and 40 years who are heavy cigarette smokers, but it is now also being reported with increasing frequency in young female smokers. The pathogenesis of Buerger disease remains elusive, although cigarette smoking and in some instances tobacco chewing seem to be involved. It has been suggested that the tobacco may trigger an immune response in susceptible persons or it may unmask a clotting defect, either of which could incite an inflammatory reaction of the vessel wall.[23]

Pain is the predominant symptom of the disorder. It usually is related to distal arterial ischemia. During the early stages of the disease, there is intermittent claudication in the arch of the foot and the digits. In severe cases, pain is present even when the person is at rest. The impaired circulation increases sensitivity to cold. The peripheral pulses are diminished or absent, and there are changes in the color of the extremity. In moderately advanced cases, the extremity becomes cyanotic when the person assumes a dependent position, and the digits may turn reddish blue even when in a nondependent position. With lack of blood flow, the skin assumes a thin, shiny look and hair growth and skin nutrition suffer. Chronic ischemia causes thick, malformed nails. If the disease continues to progress, tissues eventually ulcerate and gangrenous changes arise that may necessitate amputation.

Diagnostic methods are similar to those for atherosclerotic disease of the lower extremities. It is essential that the person stop smoking cigarettes or using tobacco. Even passive smoking and nicotine replacement therapy should be eliminated. Other treatment measures are of secondary importance and focus on methods for producing vasodilation and preventing tissue injury. Sympathectomy may be done to alleviate the vasospastic manifestations of the disease.

Raynaud Phenomenon

Raynaud phenomenon is a functional disorder caused by intense vasospasm of the arteries and arterioles in the fingers and, less often, the toes.[1,2,24,25] The disorder is divided into two types: the primary type, which occurs without demonstrable cause, and the secondary type, which is associated with other disease states or known causes of vasospasm.

Primary Raynaud phenomenon is seen in otherwise healthy young women, and it often is precipitated by exposure to cold or by strong emotions and usually is limited to the fingers. The cause of vasospasm in primary Raynaud phenomenon is unknown. Hyperreactivity of the sympathetic nervous system has been suggested as a contributing cause. Secondary Raynaud phenomenon is associated with previous vessel injury, such as frostbite, occupational trauma associated with the use of heavy vibrating tools, collagen diseases, neurologic disorders, and chronic arterial occlusive disorders. Another occupation-related cause is the exposure to alternating hot and cold temperatures such as that experienced by butchers and food preparers. Raynaud phenomenon often is the first symptom of collagen diseases. It occurs in almost all persons with scleroderma and can precede the diagnosis of scleroderma by many years.[25]

The ischemic phase of Raynaud phenomenon is manifested by changes in skin color that progress from pallor to cyanosis, a sensation of cold, and changes in sensory perception, such as numbness and tingling. The color changes usually are first noticed in the tips of the fingers, later moving into one or more of the distal phalanges (Fig. 18-9). After the ischemic episode, there is a period of hyperemia with intense redness, throbbing, and paresthesias. The period of hyperemia is followed by a return to normal color. Primary Raynaud phenomenon attacks typically involve all fingers in a symmetric fashion and are associated with minimal pain, whereas asymmetric finger involvement and intense pain suggest secondary Raynaud phenomenon.[24] In severe progressive cases, trophic skin changes may develop. The nails may become brittle, and the skin over the tips of the affected fingers may thicken. Ulceration and superficial gangrene of the fingers, although infrequent, may occur.

FIGURE 18-9. Raynaud phenomenon. The tips of the fingers show marked pallor. (From Gotlieb A.I. [2008]. Blood vessels. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 413]. Philadelphia: Lippincott Williams & Wilkins.)

The initial diagnosis is based on a history of vasospastic attacks supported by other evidence of the disorder. Immersion of the hand in cold water may be used to initiate an attack as an aid to diagnosis. Laser Doppler flow velocimetry may be used to quantify digital blood flow during changes in temperature. Primary Raynaud phenomenon is differentiated from secondary Raynaud phenomenon by excluding other disorders known to cause vasospasm.

Treatment measures are directed toward eliminating factors that cause vasospasm and protecting the digits from trauma during an ischemic episode. Abstinence from smoking and protection from cold are priorities. The entire body must be protected from cold, not just the extremities. Avoidance of emotional stress is another important factor in controlling the disorder because anxiety and stress may precipitate a vascular spasm in predisposed persons. Vasoconstrictor medications, such as the decongestants contained in allergy and cold preparations, should be avoided. Treatment with vasodilator drugs may be indicated, particularly if episodes are frequent, because frequency encourages the potential for development of thrombosis and gangrene. Surgical interruption of sympathetic nerve pathways (sympathectomy) may be used for persons with severe symptoms.[25]

Aneurysms and Dissection

An *aneurysm* is an abnormal localized dilation of a blood vessel. Aneurysms can occur in arteries and veins, but they are most common in the aorta. There are two types of aneurysms: true aneurysms and false aneurysms.[1,26] A *true aneurysm* is one in which the aneurysm is bounded by a complete vessel wall. The blood in a true aneurysm remains within the vascular compartment. A *false aneurysm* or *pseudoaneurysm* represents a localized dissection or tear in the inner wall of the artery with formation of an extravascular hematoma that causes vessel enlargement. Unlike true aneurysms, false aneurysms are bounded only by the outer layers of the vessel wall or supporting tissues.

Aneurysms can assume several forms and may be classified according to their cause, location, and anatomic features (Fig. 18-10). A *berry aneurysm* consists of a small, spherical dilation of the vessel at a bifurcation.[1,2] This type of aneurysm usually is found in the circle of Willis in the cerebral circulation. A *fusiform aneurysm* involves the entire circumference of the vessel and is characterized by a gradual and progressive dilation of the vessel. These aneurysms, which vary in diameter (up to 20 cm) and length, may involve the entire ascending and transverse portions of the thoracic aorta or may extend over large segments of the abdominal aorta. A *saccular aneurysm* extends over part of the circumference of the vessel and appears saclike. A *dissecting aneurysm* is a

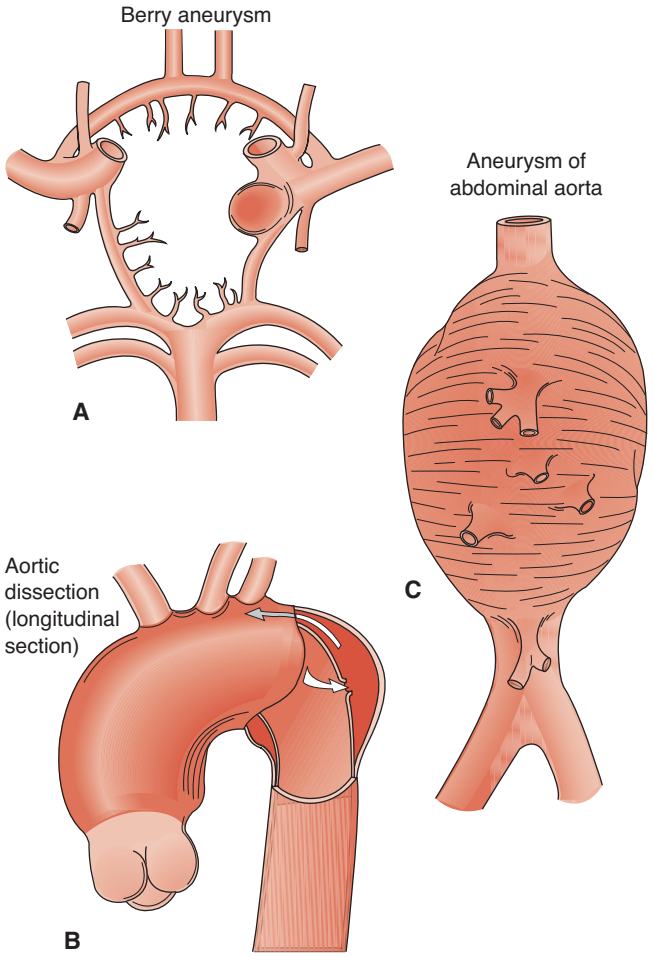


FIGURE 18-10. Three forms of aneurysms: **(A)** berry aneurysm in the circle of Willis, **(B)** aortic dissection, and **(C)** fusiform-type aneurysm of the abdominal aorta.

false aneurysm resulting from a tear in the intimal layer of the vessel that allows blood to enter the vessel wall, dissecting its layers to create a blood-filled cavity.

The weakness that leads to aneurysm formation may be caused by a number of factors, including congenital defects, trauma, infections, and atherosclerosis. Once initiated, the aneurysm grows larger as the tension in the vessel increases. This is because the tension in the wall of a vessel is equal to the pressure multiplied by the radius (i.e., tension = pressure × radius; see Chapter 17). In this case, the pressure in the segment of the vessel affected by the aneurysm does not change but remains the same as that of adjacent portions of the vessel. As an aneurysm increases in diameter, the tension in the wall of the vessel increases in direct proportion to its increased size. If untreated, the aneurysm may rupture because of the increased tension. Even an unruptured aneurysm can cause damage by exerting pressure on adjacent structures and interrupting blood flow.

Aortic Aneurysms

Aortic aneurysms may involve any part of the aorta: the ascending aorta, aortic arch, descending aorta, thoracoabdominal aorta, or abdominal aorta. Multiple aneurysms may be present. The signs and symptoms of aortic aneurysms depend on the size and location. With both thoracic and abdominal aneurysms, the most dreaded complication is rupture. The likelihood of rupture correlates with increasing aneurysm size. The risk of rupture rises from less than 2% for small abdominal aneurysms (<4 cm in diameter) to 11% per year for aneurysms larger than 5 cm in diameter.[1]

Thoracic aneurysms, which are less common than abdominal aortic aneurysms, may involve one or more aortic segments. Most thoracic aneurysms are due to atherosclerosis. Disorders of connective tissue, such as Marfan syndrome (Chapter 6), are rare causes but of important clinical significance. The majority of thoracic aneurysms are asymptomatic. When symptoms occur, they depend largely on the size and position of the aneurysm. Substernal, back, or neck pain may occur. There may be dyspnea, stridor, or a brassy cough caused by pressure on the trachea. Hoarseness may result from pressure on the recurrent laryngeal nerve, and there may be difficulty swallowing because of pressure on the esophagus.[27] The aneurysm also may compress the superior vena cava, causing distention of neck veins and edema of the face and neck.

Abdominal aortic aneurysms, which are the most frequent form of aneurysm, usually develop after age 50 and are associated with severe atherosclerosis. They occur more frequently in men than women, and over half of affected persons are hypertensive. Although abdominal aortic aneurysms usually occur in the context of atherosclerosis, it is thought that other factors such as smoking and a genetic predisposition may play a role.[2,28]

Abdominal aortic aneurysms are located most commonly below the level of the renal artery (>90%) and involve the bifurcation of the aorta and proximal end of the common iliac arteries.[1,2] They can involve any part of the vessel circumference (saccular) or extend to involve the entire circumference (fusiform). Most abdominal aneurysms are asymptomatic. Because an aneurysm is of arterial origin, a pulsating mass may provide the first evidence of the disorder. Typically, aneurysms larger than 4 cm are palpable. The mass may be discovered during a routine physical examination or the affected person may complain of its presence. Calcification, which frequently exists on the wall of the aneurysm, may be detected during abdominal radiologic examination. Pain may be present and varies from mild midabdominal or lumbar discomfort to severe abdominal and back pain. As the aneurysm expands, it may compress the lumbar nerve roots, causing lower back pain that radiates to the posterior aspects of the legs. The aneurysm may extend to and impinge on the renal, iliac, or mesenteric arteries, or to the vertebral arteries that supply the spinal cord. An abdominal aneurysm also may cause erosion of vertebrae. Stasis of blood favors thrombus formation along the wall of the vessel (Fig. 18-11), and peripheral emboli may develop, causing symptomatic arterial insufficiency.

Diagnostic methods include use of ultrasonography, echocardiography, CT scans, and MRI. Unruptured aneurysms are generally asymptomatic and are often

FIGURE 18-11. Atherosclerotic aneurysm of the abdominal aorta. The aneurysm has been opened longitudinally to reveal a large thrombus in the lumen. The aorta and common iliac arteries display complicated lesions of atherosclerosis. (From Gotlieb A.I. [2008]. Blood vessels. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 420]. Philadelphia: Lippincott Williams & Wilkins.)

diagnosed incidentally during clinical examination. Measures to slow aneurysm growth and risk of rupture include risk factor modification. Hypercholesterolemia and high blood pressure should be controlled and smoking discontinued. Surgical repair, in which the involved section of the aorta is replaced with a synthetic graft of woven Dacron, frequently is the treatment of choice.[26,27]

Aortic Dissection

Aortic dissection (dissecting aneurysm) is an acute, life-threatening condition.[1,2,28] It involves hemorrhage into the vessel wall with longitudinal tearing of the vessel wall to form a blood-filled channel (see Fig. 18-10B). Unlike atherosclerotic aneurysms, aortic dissection often occurs without evidence of previous vessel dilation. The dissection can originate anywhere along the length of the aorta but most often involves the ascending aorta.

Aortic dissection is caused by conditions that weaken or cause degenerative changes in the elastic and smooth muscle of the layers of the aorta. There are two risk factors that predispose to dissection: hypertension and degeneration of the medial layer of the vessel wall. It is most common in 40- to 60-year-old men with an antecedent history of hypertension.[1] Aortic dissection also is associated with connective tissue diseases, such as Marfan syndrome. It also may occur during pregnancy because of changes in the aorta that occur during this time. Other factors that predispose to dissection are congenital defects of the aortic valve (i.e., bicuspid or unicuspid valve structures) and aortic coarctation.

Aortic aneurysms are commonly classified into two types, type A and type B, as determined by the level of dissection.[1,28] Type A aneurysms, which involve the proximal aorta (ascending aorta only or both the ascending and the descending aorta), are the most common and potentially serious in terms of complications. Type B aneurysms usually begin distal to the subclavian artery and do not involve the ascending aorta. Dissections usually extend distally from the intimal tear. When the ascending aorta is involved, expansion of the wall of the aorta may impair closure of the aortic valve. There also is the risk of aortic rupture with blood moving into the pericardium and compressing the heart. Although the length of dissection varies, it is possible for the abdominal aorta to be involved with progression into the renal, iliac, or femoral arteries. Partial or complete occlusion of the arteries that arise from the aortic arch or the intercostal or lumbar arteries may lead to stroke, ischemic peripheral neuropathy, or impaired blood flow to the spinal cord.

A major symptom of a dissecting aneurysm is the abrupt presence of excruciating pain, described as tearing or ripping.[1,2,28] Pain associated with dissection of the ascending aorta frequently is located in the anterior chest, and pain associated with dissection of the descending aorta often is located in the back. In the early stages, blood pressure typically is moderately or markedly elevated. Later, the blood pressure and the pulse rate become unobtainable in one or both arms as the dissection disrupts arterial flow to the arms. Syncope, hemiplegia, or paralysis of the lower extremities may occur because of occlusion of blood vessels that supply the brain or spinal cord. Heart failure may develop when the aortic valve is involved.

Diagnosis of aortic dissection is based on history and physical examination. Aortic angiography, transesophageal echocardiography, CT scans, and MRI studies aid in the diagnosis. The treatment of dissecting aortic aneurysm may be medical or surgical. Aortic dissection is a life-threatening emergency; persons with a probable diagnosis are stabilized medically even before the diagnosis is confirmed. Two important factors that participate in propagating the dissection are high blood pressure and the steepness of the pulse wave. Without intervention, these forces produce continued extension of the dissection. Medical treatment therefore focuses on control of hypertension and the use of drugs that lessen the force of systolic blood ejection from the heart.[28] Two commonly used drugs, often given in combination, are an intravenous β-adrenergic blocking drug and sodium nitroprusside (a vasodilator). Adequate pain control is necessary to alleviate anxiety and relieve sympathetic stimulation, which will raise blood pressure. Surgical treatment consists of resection of the involved segment of the aorta and replacement with a prosthetic graft. Despite recent advances in diagnosis and treatment, the mortality rate in acute aortic dissection remains high.

In summary, the arterial system distributes blood to all the tissues of the body, and lesions of the arterial system exert their effects through ischemia or impaired blood flow. There are two types of arterial disorders: diseases such as atherosclerosis, the vasculitides, and peripheral arterial diseases that obstruct blood flow, and disorders such as aneurysms that weaken the vessel wall.

Cholesterol relies on lipoproteins, mainly LDLs and HDLs, for transport in the blood. Lipoproteins are macromolecules made up of a hydrophobic core of triglycerides and insoluble cholesterol esters surrounded by an apoprotein-containing outer shell. The apoproteins not only add solubility and stability to the molecule but also act as a recognition site that cells use in removing the particles from the blood. The HDLs, which are protective, remove cholesterol from the tissues and carry it back to the liver for disposal. The LDLs carry cholesterol to the liver and extrahepatic tissues where an apoprotein (apoB-100) in its outer shell binds to specific cell receptors, allowing the particles to be removed from the blood. LDL that is not removed from the blood by receptor-mediated mechanisms is available for uptake by phagocytic scavenger cells in the arterial wall, leading to an accumulation of cholesterol-laden macrophages and development of atherosclerosis.

Atherosclerosis, a leading cause of death in developed countries of the world, affects large and medium-sized arteries, such as the coronary and cerebral arteries. It has an insidious onset, and its lesions usually are far advanced before symptoms appear. Although the mechanisms of atherosclerosis are uncertain, risk factors associated with its development have been identified. These include factors such as heredity, gender, and age, which cannot be modified; and factors such as smoking, high blood pressure, high serum cholesterol levels, diabetes, and obesity, which can be controlled or modified.

The vasculitides are a group of vascular disorders characterized by vasculitis or inflammation and necrosis of the blood vessels in various tissues and organs of the body. They can be caused by injury to the vessel, infectious agents, or immune processes, or can occur secondary to other disease states such as systemic lupus erythematosus.

Occlusive disorders interrupt arterial flow of blood and interfere with the delivery of oxygen and nutrients to the tissues. Occlusion of flow can result from a thrombus, emboli, vessel compression, vasospasm, or structural changes in the vessel. They include peripheral arterial disease, which is characterized by severe atherosclerosis of the vessels that supply the lower extremities; thromboangiitis obliterans (Buerger disease), characterized by an inflammatory process that involves medium-sized arteries; and Raynaud phenomenon, caused by vessel spasm.

Aneurysms are localized areas of vessel dilation caused by weakness of the arterial wall. A berry aneurysm is a small spherical dilation of a cerebral artery, most often found in the circle of Willis in the brain circulation. Fusiform and saccular aneurysms, most often found in the thoracic and abdominal aorta, are characterized by gradual and progressive enlargement of the aorta. They can involve part of the vessel circumference (saccular) or extend to involve the entire circumference of the vessel (fusiform). The most serious consequence of thoracic and abdominal aortic aneurysms is rupture. A dissecting aneurysm is an acute, life-threatening condition. It involves hemorrhage into the vessel wall with longitudinal tearing (dissection) of the vessel wall to form a blood-filled channel.

Disorders of Arterial Blood Pressure

The arterial blood pressure reflects the rhythmic ejection of blood from the left ventricle into the aorta.[29] It rises as the left ventricle contracts and falls as it relaxes. In healthy adults, the highest pressure, called the *systolic pressure*, is ideally less than 120 mm Hg and the lowest pressure, called the *diastolic pressure*, is less than 80 mm Hg (Fig. 18-12). The difference between the systolic and diastolic pressure (approximately 40 mm Hg) is the *pulse pressure*. The pulse pressure reflects the pulsatile nature of arterial blood flow. It rises when the stroke volume is increased and falls when the resistance to outflow is decreased. The *mean arterial pressure* (approximately 90 to 100 mm Hg) represents the average pressure in the arterial system during ventricular contraction and relaxation and is a good indicator of tissue perfusion.

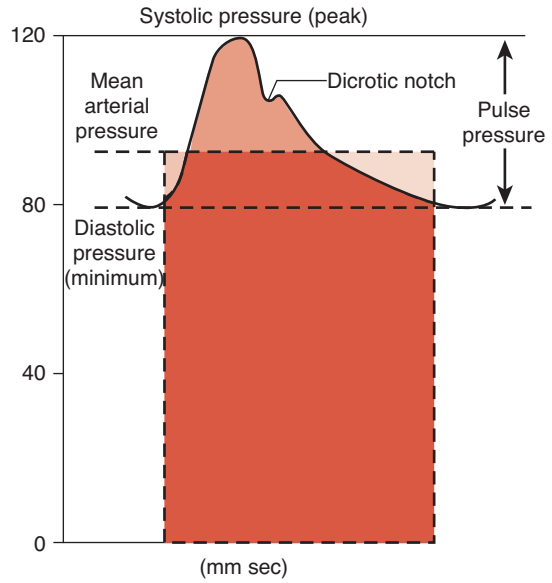


FIGURE 18-12. Intra-arterial pressure tracing made from the brachial artery. Pulse pressure is the difference between systolic and diastolic pressures. The darker area represents the mean arterial pressure, which can be calculated by using the formula of mean arterial pressure = diastolic pressure + pulse pressure/3.

The systolic and diastolic components of blood pressure are determined by the cardiac output and the peripheral vascular resistance and can be expressed as the product of the two (blood pressure = cardiac output × peripheral vascular resistance). The cardiac output is the product of the stroke volume (amount of blood ejected from the heart with each beat) and the heart rate. The peripheral vascular resistance reflects changes in the radius of the arterioles as well as the viscosity or thickness of the blood. The arterioles often are referred to as the *resistance vessels* because they can selectively constrict or relax to control the resistance to outflow of blood into the capillaries. The body maintains its blood pressure by adjusting the cardiac output to compensate for changes in peripheral vascular resistance, and it changes the peripheral vascular resistance to compensate for changes in cardiac output.

In hypertension and disease conditions that affect blood pressure, changes in blood pressure usually are described in terms of the systolic and diastolic pressures, pulse pressure, and mean arterial pressure. These pressures are influenced by the stroke volume, the rapidity with which blood is ejected from the heart, the elastic properties of the aorta and large arteries and their ability to accept various amounts of blood as it is ejected from the heart, and the properties of the resistance blood vessels that control the runoff of blood into the smaller vessels and capillaries that connect the arterial and venous circulations.

Mechanisms of Blood Pressure Regulation

Although different tissues in the body are able to regulate their own blood flow, it is necessary for the arterial pressure to remain relatively constant as blood shifts from one area of the body to another. The mechanisms used to regulate the arterial pressure depend on whether short-term or long-term adaptation is needed[29] (Fig. 18-13).

Short-Term Regulation

The mechanisms for short-term regulation of blood pressure, those acting over minutes or hours, are intended to correct temporary imbalances in blood pressure, such as occur during physical exercise and changes in body position. These mechanisms also are responsible for maintenance of blood pressure at survival levels during life-threatening situations such as during an acute hemorrhagic incident. The short-term regulation of blood pressure relies mainly on neural and humoral mechanisms, the most rapid of which are the neural mechanisms.

Neural Mechanisms. The *neural control* of blood pressure is vested in centers that are located in the reticular formation of the medulla and lower third of the pons, where integration and modulation of autonomic nervous system (ANS) responses occur.[29] This area of the

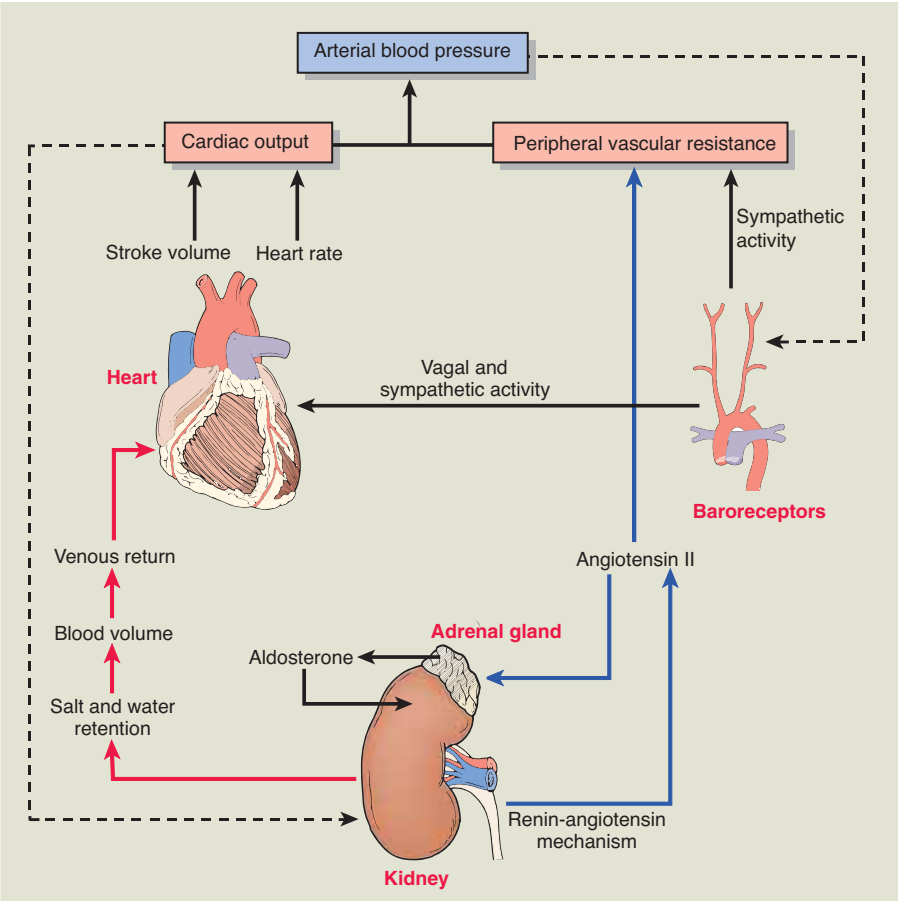
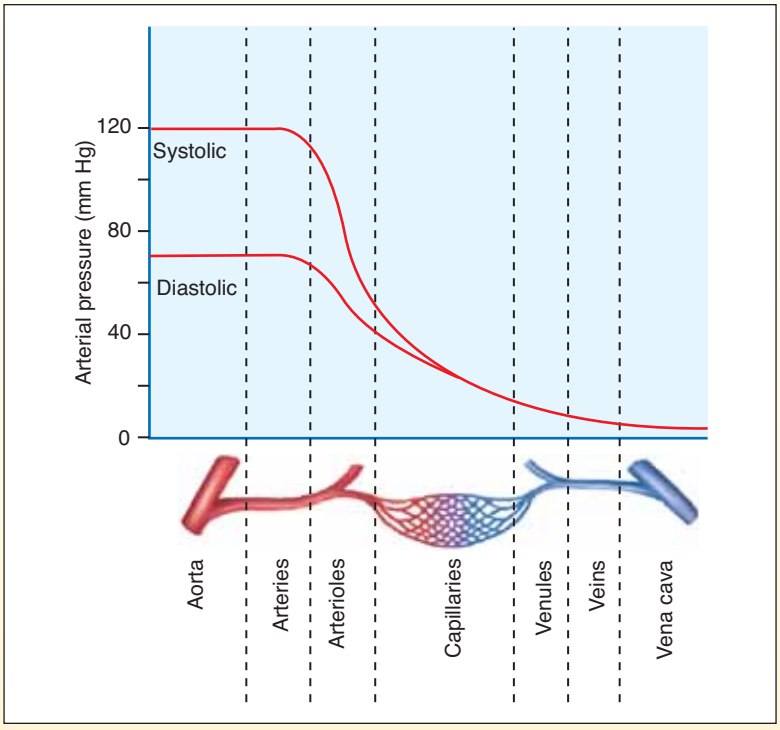


FIGURE 18-13. Mechanisms of blood pressure regulation. The *solid lines* represent the mechanisms for renal and baroreceptor control of blood pressure through changes in cardiac output and peripheral vascular resistance. The *dashed lines* represent the stimulus for regulation of blood pressure by the baroreceptors and the kidneys.

UNDERSTANDING → Determinants of Blood Pressure

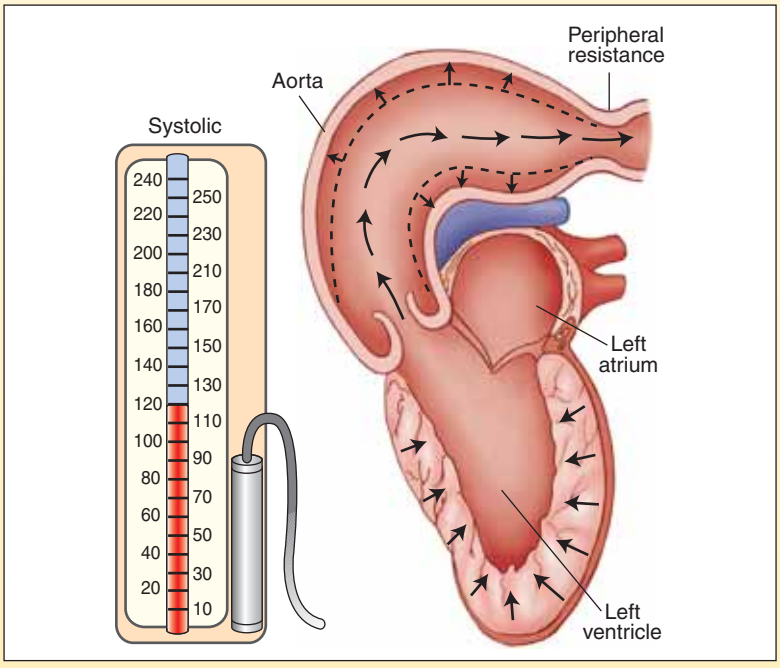
The arterial blood pressure, which is the force that moves blood through the arterial system, reflects the intermittent contraction and relaxation of the left ventricle. It is determined by (1) the properties of the arterial system and the factors that maintain (2) the systolic and (3) the diastolic components of the blood pressure. These factors include the blood volume, elastic properties of the blood vessels, cardiac output, and peripheral vascular resistance.

Arterial Pressure Regulation. The arterial blood pressure represents the force that distributes blood throughout the capillaries of the body. The aorta and large arteries have large amounts of elastin in their walls that allows them to stretch and store energy during ventricular systole and recoil during diastole. The arterioles, which are the terminal components of the arterial system, serve as resistance vessels that regulate blood pressure by controlling the distribution of blood to the capillary beds. The elastic properties of the aorta and large arteries coupled with the high resistance properties of the arterioles, allow the arterial system to act as a filter that converts the intermittent flow generated by the heart to virtually steady flow in the capillaries. The low-pressure venous system collects blood from the capillaries and returns it to the heart as a means of maintaining the cardiac output needed to sustain the arterial pressure.



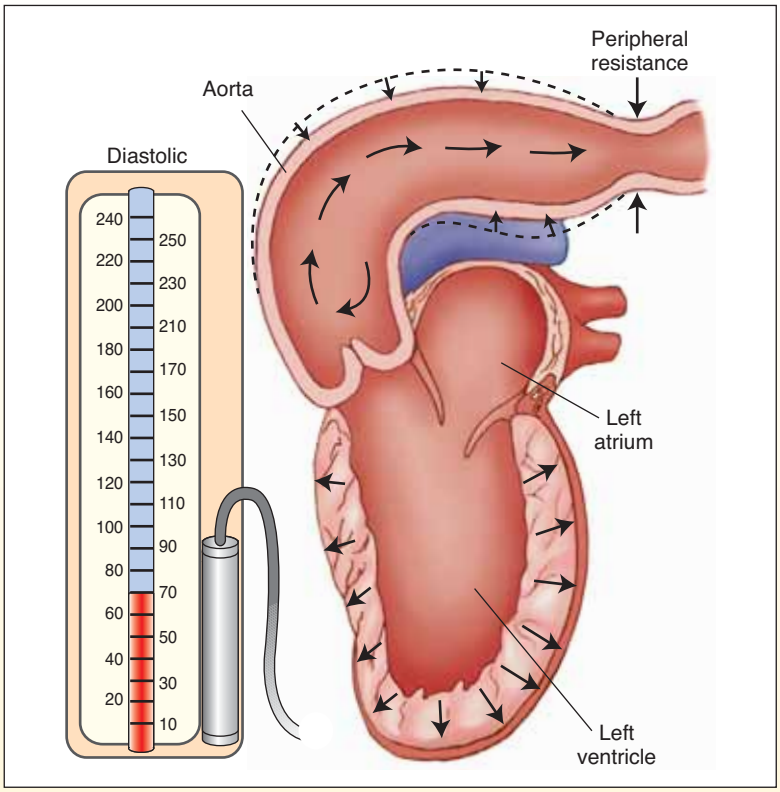
2

Systolic Pressure. The systolic blood pressure reflects the amount of blood (stroke volume) that is ejected from the heart with each beat, the rate and force with which it is ejected, and the elasticity or compliance of the aorta and large arteries. The blood that is ejected from the heart during systole does not move directly through the circulation. Instead, a substantial fraction of the stroke volume is stored in large arteries. Because the walls of these vessels are elastic, they can be stretched to accommodate a large volume of blood without an appreciable change in pressure. The systolic pressure often increases with aging as the aorta and large arteries lose their elasticity and become more rigid.



3

Diastolic Pressure. The diastolic blood pressure reflects the closure of the aortic valve, the energy that has been stored in the elastic fibers of the large arteries during systole, and the resistance to flow through arterioles into the capillaries. Closure of the aortic valve at the onset of diastole and recoil of the elastic fibers in the aorta and large arteries continue to drive the blood forward, even though the heart is not pumping. These effects, largely restricted to the elastic vessels, convert the discontinuous systolic flow in the ascending aorta into a continuous flow in the peripheral arteries.



brain contains the vasomotor and cardiac control centers and is often collectively referred to as the *cardiovascular center.* The cardiovascular center transmits parasympathetic impulses to the heart through the vagus nerve and sympathetic impulses to the heart and blood vessels through the spinal cord and peripheral sympathetic nerves. Vagal stimulation of the heart produces a slowing of heart rate, whereas sympathetic stimulation produces an increase in heart rate and cardiac contractility. Blood vessels are mainly innervated by the sympathetic nervous system, which produces constriction of the small arteries and arterioles with a resultant increase in peripheral vascular resistance.

The ANS control of blood pressure is mediated through intrinsic circulatory reflexes, extrinsic reflexes, and higher neural control centers. The *intrinsic reflexes,* including the *baroreceptor* and *chemoreceptor reflexes,* are located in the circulatory system and are essential for rapid and short-term regulation of blood pressure. The sensors for *extrinsic reflexes* are found outside the circulation. They mediate blood pressure responses associated with factors such as pain and cold. The neural pathways for these reactions are more diffuse, and their responses are less consistent than those of the intrinsic reflexes. Many of these responses are channeled through the hypothalamus, which plays an essential role in the control of sympathetic nervous system responses.

The *baroreceptors* are pressure-sensitive receptors located in the walls of blood vessels and the heart. The carotid and aortic baroreceptors are located in strategic positions between the heart and the brain (Fig. 18-14). They respond to changes in the stretch of the vessel wall by sending impulses to cardiovascular centers in the brain stem to effect appropriate changes in heart rate and vascular smooth muscle tone. For example, the fall in blood pressure that occurs on moving from the lying to the standing position produces a decrease in the stretch of the baroreceptors with a resultant increase in heart rate and sympathetically induced vasoconstriction that produces an increase in peripheral vascular resistance.

The *arterial chemoreceptors* are cells that monitor the oxygen, carbon dioxide, and hydrogen ion content of the blood. They are located in the carotid bodies, which lie in the bifurcation of the two common carotids, and in the aortic bodies of the aorta (see Fig. 18-14). Because of their location, these chemoreceptors are always in close contact with the arterial blood. Although the main function of the chemoreceptors is to regulate ventilation, they also communicate with cardiovascular centers in the brain stem and can induce widespread vasoconstriction. Whenever the arterial pressure drops below a critical level, the chemoreceptors are stimulated because of diminished oxygen supply and a buildup of carbon dioxide and hydrogen ions. In persons with chronic

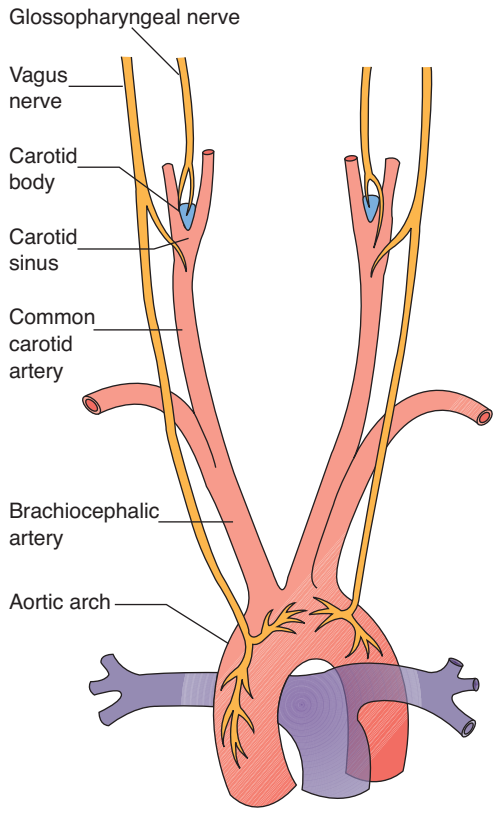


FIGURE 18-14. Location and innerv
ation of the aortic arch and carotid sinus baroreceptors and carotid body chemoreceptors.

lung disease, systemic and pulmonary hypertension may develop because of hypoxemia (see Chapter 23). Persons with sleep apnea also may experience an increase in blood pressure because of the hypoxemia that occurs during the apneic periods.

Humoral Mechanisms. The *humoral control* of blood pressure relies on a number of mechanisms, including the *renin-angiotensin-aldosterone* system and *vasopressin*. Other humoral substances, such as epinephrine, a sympathetic neurotransmitter released from the adrenal gland, have the effect of directly producing an increase in heart rate, cardiac contractility, and vascular tone.

The *renin-angiotensin-aldosterone system* plays a central role in blood pressure regulation. Renin is an enzyme that is synthesized, stored, and released by the juxtaglomerular cells of the kidneys in response to an increase in sympathetic nervous system activity or a decrease in blood pressure, extracellular fluid volume, or extracellular sodium concentration. Most of the renin that is released leaves the kidney and enters the bloodstream, where it acts enzymatically to convert an inactive circulating plasma protein called *angiotensinogen* to angiotensin I (Fig. 18-15). Angiotensin I is then converted to angiotensin II. This conversion occurs almost entirely in the small vessels of the lung, catalyzed by an enzyme called the *angiotensin-converting enzyme* that is present in the endothelium of the lung vessels. Although angiotensin II has a half-life of only several minutes, renin persists in the circulation for 30 minutes to 1 hour and continues to cause production of angiotensin II during this time.

Angiotensin II functions in both the short- and long-term regulation of blood pressure. It is a strong vasoconstrictor, particularly of arterioles and, to a lesser extent, of veins. Constriction of the arterioles increases the peripheral vascular resistance, thereby contributing to the short-term regulation of blood pressure. Angiotensin

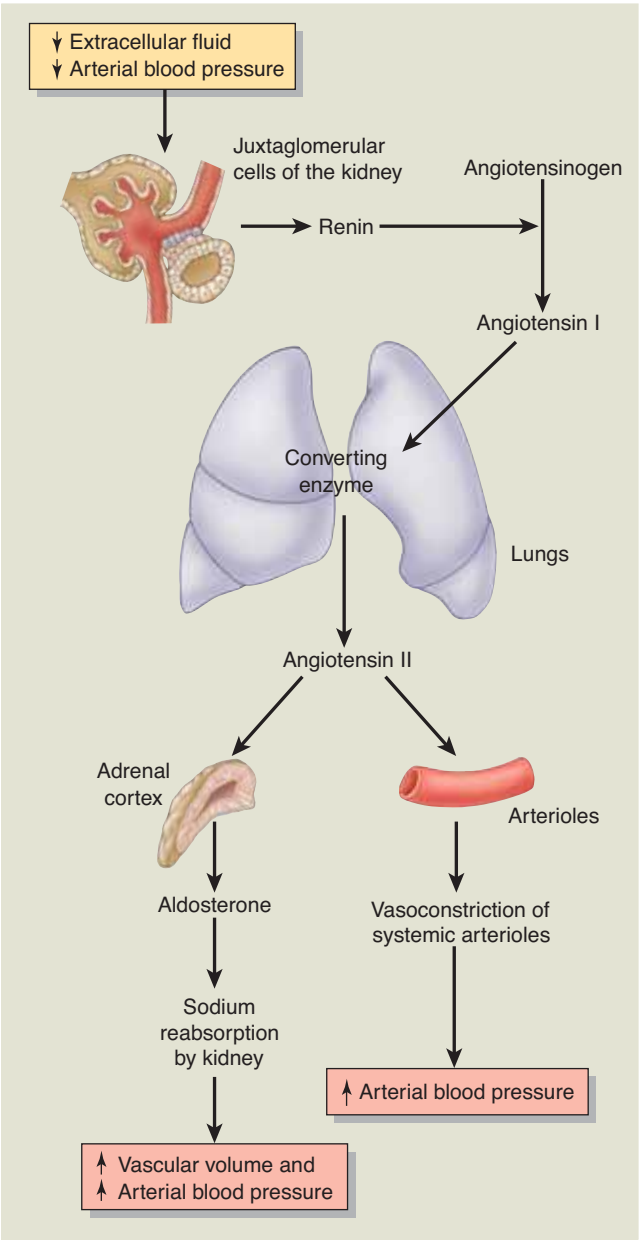


FIGURE 18-15. Control of blood pressure by the renin-angiotensin-aldosterone system. Renin enzymatically converts the plasma protein angiotensinogen to angiotensin I; angiotensin-converting enzyme in the lung converts angiotensin I to angiotensin II; and angiotensin II produces vasoconstriction and increases salt and water retention through direct action on the kidney and through increased aldosterone secretion by the adrenal cortex.

II also reduces sodium excretion by increasing sodium reabsorption by the proximal tubules of the kidney. A second major function of angiotensin II, stimulation of aldosterone secretion from the adrenal gland, contributes to the long-term regulation of blood pressure by increasing salt and water retention by the kidney.

Vasopressin, also known as antidiuretic hormone (ADH), is released from the posterior pituitary gland in response to decreases in blood volume and blood pressure, an increase in the osmolality of body fluids, and other stimuli. The antidiuretic actions of vasopressin are discussed in Chapter 8. Vasopressin has a direct vasoconstrictor effect, particularly on the vessels of the splanchnic circulation that supplies the abdominal viscera. However, long-term increases in vasopressin cannot maintain an increase in blood pressure, and vasopressin does not enhance hypertension produced by sodium-retaining hormones or other vasoconstricting substances. It has been suggested that vasopressin plays a permissive role in hypertension through its water-retaining properties or as a neurotransmitter that serves to modify ANS function.

Long-Term Regulation

Long-term mechanisms, which are responsible for the daily, weekly, and monthly regulation of blood pressure, are largely vested in the kidneys and their role in regulation of extracellular fluid volume. These mechanisms function largely by regulating the blood pressure around an equilibrium point, which represents the normal pressure for a given individual. Accordingly, when the body contains too much extracellular fluid, the arterial pressure rises and the rate at which water (i.e., *pressure diuresis*) and sodium (i.e., *pressure natriuresis*) are excreted by the kidney is increased.[29] When blood pressure returns to its equilibrium point, water and sodium excretion return to normal. A fall in blood pressure due to a decrease in extracellular fluid volume has the opposite effect. In persons with hypertension, renal control mechanisms are often altered such that the equilibrium point for blood pressure regulation is maintained at a higher level of sodium and water elimination.

There are two general mechanisms by which an increase in fluid volume can elevate blood pressure. One is through a direct effect on cardiac output and the other is indirect, resulting from the autoregulation of blood flow and its effect on peripheral vascular resistance. Autoregulatory mechanisms function in distributing blood flow to the various tissues of the body according to their metabolic needs (see Chapter 17). When the blood flow to a specific tissue bed is excessive, local blood vessels constrict, and when the flow is deficient, the local vessels dilate. In situations of increased extracellular fluid volume and a resultant increase in cardiac output, all of the tissues of the body are exposed to the same increase in flow. This results in a generalized constriction of arterioles and an increase in the peripheral vascular resistance (and blood pressure).

The role that the kidneys play in long-term regulation of blood pressure is emphasized by the fact that many antihypertensive medications produce their blood pressure–lowering effects by increasing sodium and water elimination.

Measurement of Blood Pressure

The diagnosis of blood pressure disorders is facilitated by blood pressure measurements, which should be obtained with a well-calibrated sphygmomanometer. Accuracy of the measurements requires that persons taking the pressure are adequately trained in blood pressure measurement, the equipment is properly maintained, and the cuff bladder is appropriate for the arm size.[30] The width of the bladder should be at least 40% of arm circumference and the length at least 80% of arm circumference. Undercuffing (using a cuff with a bladder that is too small) can cause an overestimation of blood pressure.[31] This is because a cuff that is too small results in an uneven distribution of pressure across the arm, such that a greater cuff pressure is needed to occlude blood flow. Likewise, overcuffing (using a cuff with a bladder that is too large) can cause an underestimation of blood pressure. Readings should be taken after the person is relaxed and has rested for at least 5 minutes and has not smoked or ingested caffeine within 30 minutes. At least two measurements should be made on each occasion in the same arm while the person is seated in a chair (rather than on the examination table) with the feet on the floor and the arm supported at heart level.[31] Both the systolic and diastolic pressures should be recorded.

Hypertension

Hypertension, or high blood pressure, is probably the most common of all health problems in adults and is the leading risk factor for cardiovascular disorders. It affects approximately 50 million individuals in the United States and approximately 1 billion worldwide.[32] Hypertension is more common in younger men compared with younger women in the United States, in blacks compared with whites, in persons from lower socioeconomic groups, and in older persons. Men have higher blood pressures than women up until the time of menopause, at which point women quickly lose their protection. The prevalence of hypertension increases with age. Thus, the problem of hypertension can be expected to become even greater with the aging of the "baby-boomer" population.

Hypertension commonly is divided into the categories of primary and secondary hypertension. In primary, or *essential,* hypertension, the chronic elevation of blood pressure occurs without evidence of other disease conditions. Primary hypertension accounts for approximately 90% of all cases of hypertension.[33] In secondary hypertension, the elevation of blood pressure results from some other disorder, such as kidney disease.

Hypertension is diagnosed when the systolic pressure is consistently elevated above 140 mm Hg, or the diastolic blood pressure is 90 mm Hg or higher.[32] Hypertension is further divided into stages 1 and 2 based on

Hypertension

- Hypertension represents an elevation in systolic and/or diastolic blood pressure.
- Primary or essential hypertension is characterized by a chronic elevation in blood pressure that occurs without evidence of other disease, and secondary hypertension by an elevation of blood pressure that results from some other disorder, such as kidney disease.
- The pathogenesis of essential hypertension is thought to include constitutional and environmental factors involving the kidney and its role in regulating extracellular fluid volume through salt and water elimination, sympathetic nervous system hyperreactivity, renin-angiotensin system activity, or intracellular sodium and calcium levels. The medications that are used in the treatment of hypertension exert their effect through one or more of these mechanisms.
- Uncontrolled hypertension produces increased demands on the heart, resulting in left ventricular hypertrophy and heart failure, and on the vessels of the arterial system, leading to atherosclerosis, kidney disease, retinopathy, and stroke.

systolic and diastolic blood pressure measurements (Table 18-4). A systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg are normal, and systolic pressures between 120 and 139 mm Hg and diastolic pressures between 80 and 89 mm Hg are considered prehypertensive. For adults with diabetes mellitus, the blood pressure goal has been lowered to less than 130/80 mm Hg.[34] A single elevated blood pressure reading is not sufficient to make a diagnosis of hypertension. Rather, the diagnosis depends on a series of measurements, since readings can vary from time to time.

Systolic hypertension has been defined as a systolic pressure of 140 mm Hg or greater and a diastolic pressure of less than 90 mm Hg.[32] Historically, diastolic hypertension was thought to confer a greater risk for cardiovascular events than systolic hypertension. However, there is mounting evidence that elevated systolic blood pressure is at least as important, if not more so, than diastolic hypertension.[35] There are two aspects of systolic hypertension that confer increased risk for cardiovascular events—one is the actual elevation in systolic pressure and the other is the disproportionate rise in pulse pressure. Elevated pressures during systole favor the development of left ventricular hypertrophy, increased myocardial oxygen demands, and eventual left heart failure. At the same time, the absolute or relative lowering of diastolic pressure is a limiting factor in coronary perfusion because coronary perfusion is greatest during diastole. Elevated pulse pressures produce greater stretch of arteries, causing damage to the elastic elements of the vessel and thus predisposing to aneurysms and development of the intimal damage that leads to atherosclerosis and thrombosis.

Primary (Essential) Hypertension

Essential (primary) hypertension is the term applied to hypertension for which no cause for hypertension can be identified. Although the cause or causes of essential hypertension are largely unknown, both constitutional and lifestyle factors have been implicated, either singly or collectively, as contributing factors.

Constitutional Risk Factors. Constitutional or inborn risk factors include family history of hypertension, race, and age-related increases in blood pressure.[32,36] The

TABLE 18-4 Classification of Blood Pressure for Adults and Recommendations for Follow-up

Blood Pressure Classification	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Follow-up Recommendations for Initial Blood Pressure*†
Normal	<120	And <80	Recheck in 2 years
Prehypertensive	120–139	or 80–89	Recheck in 1 year‡
Stage 1 hypertension	140–159	or 90–99	Confirm within 2 months‡
Stage 2 hypertension	≥160	or ≥100	Evaluate or refer to source of care within 1 month. For those with higher pressure (e.g., >180/110 mm Hg), evaluate and treat immediately or within 1 week, depending on clinical situation and complications.

*Initial blood pressure: If systolic and diastolic categories are different, follow recommendations for shorter follow-up (e.g., 160/86 mm Hg should be evaluated or referred to source of care with 1 month).

†Follow-up blood pressure: Modify the scheduling of follow-up according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target-organ disease.

‡Provide advice about lifestyle modification.

Modified from the National Heart, Lung, and Blood Institute. (2003). *The seventh report of the National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.* NIH publication no. 03-5233. Bethesda, MD: National Institutes of Health.

inclusion of heredity as a contributing factor in the development of hypertension is supported by the fact that hypertension is seen most frequently among persons with a family history of hypertension. The inherited predisposition does not seem to rely on other risk factors, but when they are present, the risk apparently is additive. Hypertension not only is more prevalent in blacks than whites, but also is more severe, tends to occur earlier, and often is not treated early enough or aggressively enough.[37] Blacks also tend to experience greater cardiovascular and renal damage at any level of pressure.

Maturation and growth are known to cause predictable increases in blood pressure. For example, the arterial blood pressure in the newborn is approximately 50 mm Hg systolic and 40 mm Hg diastolic.[38] Sequentially, blood pressure increases with physical growth from a value of 78 mm Hg systolic at 10 days of age to 120 mm Hg at the end of adolescence. Diastolic pressure increases until 50 years of age and then declines from the sixth decade onward, whereas systolic blood pressure continues to rise with age.[38]

Another factor that is thought to contribute to hypertension is the insulin resistance and resultant hyperinsulinemia that occurs in persons with metabolic abnormalities such as prediabetes, type 2 diabetes, hyperlipidemia, and obesity.[39] This clustering of cardiovascular risk factors has been named the *insulin resistance syndrome, cardiometabolic syndrome,* or *metabolic syndrome* (see Chapter 33).

Lifestyle Risk Factors. Lifestyle factors can contribute to the development of hypertension by interacting with other risk factors. These lifestyle factors include high salt intake, excessive calorie intake and obesity, and excessive alcohol consumption. Although stress can raise blood pressure acutely, there is less evidence linking it to chronic elevations in blood pressure. Smoking and a diet high in saturated fats and cholesterol, although not identified as primary risk factors for hypertension, are independent risk factors for coronary heart disease and should be avoided.

Increased salt intake has long been suspected as an etiologic factor in the development of hypertension.[40,41] Just how increased salt intake contributes to the development of hypertension is still unclear. It may be that salt causes an elevation in blood volume, increases the sensitivity of cardiovascular or renal mechanisms to sympathetic nervous system influences, or exerts its effects through some other mechanism such as the renin-angiotensin-aldosterone system. Regardless of the mechanism, numerous studies have shown that a reduction in salt intake can lower blood pressure.

Excessive weight commonly is associated with hypertension. It has been suggested that fat distribution might be a more critical indicator of hypertension risk than actual overweight. The waist-to-hip ratio commonly is used to differentiate central or upper body obesity, with fat cells located in the abdomen and viscera, from peripheral or lower body obesity, with fat cell deposits in the buttocks and legs (see Chapter 10).[42] Abdominal or visceral fat seems to be more insulin resistant than fat deposited over the buttocks and legs. There is also an evolving understanding of the neuroendocrine effects of excess adipose tissue on blood pressure.[43] Recent evidence indicates that leptin, an adipocyte-derived hormone, may represent a link between adiposity and increased cardiovascular sympathetic activity. Besides its effect on appetite and metabolism, leptin is thought to act on the hypothalamus to increase blood pressure through activation of the sympathetic nervous system.[43] High levels of circulating free fatty acids in obese people also appear to participate in activation of the sympathetic nervous system. There is also research supporting activation of the renin-angiotensin-aldosterone system by adipocyte-derived angiotensinogen and the ability of adipose tissue to increase aldosterone levels through the production of factors that induce aldosterone production.[43]

Regular alcohol drinking plays a role in the development of hypertension.[44,45] The effect is seen with different types of alcoholic drinks, in men and women, and in a variety of ethnic groups. One of the first reports of a link between alcohol consumption and hypertension came from the Oakland–San Francisco Kaiser Permanente Medical Care Program study that correlated known drinking patterns and blood pressure levels of 84,000 persons.[45] This study revealed that the regular consumption of three or more drinks per day increases the risk for hypertension. Systolic pressures were more markedly affected than diastolic pressures. Blood pressure may improve or return to normal when alcohol consumption is decreased or eliminated.

Secondary Hypertension

Secondary hypertension, which describes an elevation in blood pressure due to another disease condition, accounts for 5% to 10% of hypertension cases.[46,47] Unlike essential hypertension, many of the conditions causing secondary hypertension can be corrected or cured by surgery or specific medical treatment. Secondary hypertension tends to be seen in persons younger than 30 and older than 50 years of age. Among the most common causes of secondary hypertension are kidney disease (i.e., renovascular hypertension), adrenal cortical disorders, pheochromocytoma, and coarctation of the aorta. Oral contraceptive agents are also implicated as a cause of secondary hypertension. Cocaine, amphetamines, and other illicit drugs can also cause significant hypertension, as can sympathomimetic agents (decongestants, anorectics), erythropoietin, and licorice (including some chewing tobaccos with licorice as an ingredient). Obstructive sleep apnea is an independent risk factor for secondary hypertension.

Renal Hypertension. With the dominant role that the kidney assumes in blood pressure regulation, it is not surprising that the largest single cause of secondary hypertension is renal disease. Most acute kidney disorders result in decreased urine formation, retention of salt and water, and hypertension. This includes acute glomerulonephritis, acute renal failure, and acute urinary tract obstruction. Hypertension also is common among persons with chronic pyelonephritis, polycystic kidney disease, diabetic nephropathy, and end-stage renal disease,

regardless of cause. In older persons, the sudden onset of secondary hypertension often is associated with atherosclerotic disease of the renal blood vessels.

Renovascular hypertension refers to hypertension caused by reduced renal blood flow and activation of the renin-angiotensin-aldosterone mechanism. It is the most common cause of secondary hypertension, accounting for 1% to 2% of all cases of hypertension.[48] The reduced renal blood flow that occurs with renovascular disease causes the affected kidney to release excessive amounts of renin, increasing circulating levels of angiotensin II. Angiotensin II, in turn, acts as a vasoconstrictor to increase peripheral vascular resistance and as a stimulus for increased aldosterone levels and sodium retention by the kidney. One or both of the kidneys may be affected. When the renal artery of only one kidney is involved, the unaffected kidney is subjected to the detrimental effects of the elevated blood pressure.

There are two major types of renovascular disease: atherosclerosis of the proximal renal artery and fibromuscular dysplasia, a noninflammatory vascular disease that affects the renal arteries and branch vessels. Atherosclerotic stenosis of the renal artery accounts for 70% to 90% of cases and is seen most often in older persons, particularly those with diabetes, aortoiliac occlusive disease, coronary artery disease, or hypertension.[48] Fibromuscular dysplasia is more common in women and tends to occur in younger age groups, often persons in their third decade.[49] Genetic factors may be involved, and the incidence tends to increase with risk factors such as smoking and hyperlipidemia.

Diagnostic tests for renovascular hypertension may include studies to assess overall renal function, physiologic studies to assess the renin-angiotensin system, perfusion studies to evaluate renal blood flow, and imaging studies to identify renal artery stenosis.[48] Renal arteriography remains the definitive test for identifying renal artery disease. Duplex ultrasonographic scanning, contrast-enhanced CT scans, and magnetic resonance angiography (MRA) are other tests that can be used to screen for renovascular hypertension.[48]

The goal of treatment for renal hypertension is to control the blood pressure and stabilize renal function. Angioplasty or revascularization has been shown to be an effective long-term treatment for the disorder. Angiotensin-converting enzyme (ACE) inhibitors may be used in medical management of renal stenosis. However, these agents must be used with caution because of their ability to produce marked hypotension and renal dysfunction.

Disorders of Adrenocortical Hormones. Increased levels of adrenocortical hormones also can give rise to hypertension. Primary hyperaldosteronism (excess production of aldosterone due to adrenocortical hyperplasia or adenoma) and excess levels of glucocorticoid (Cushing disease or syndrome) tend to raise the blood pressure[33,50] (see Chapter 32). These hormones facilitate salt and water retention by the kidney; the hypertension that accompanies excessive levels of either hormone probably is related to this factor. For patients with primary hyperaldosteronism, a salt-restricted diet often produces a reduction in blood pressure. Because aldosterone acts on the distal renal tubule to increase sodium absorption in exchange for potassium elimination in the urine, persons with hyperaldosteronism usually have decreased potassium levels. Screening tests for primary hyperaldosteronism involve the determination of plasma aldosterone concentration and plasma renin activity. CT and MRI scans are used to localize the lesion. Persons with solitary adenomas are usually treated surgically. Potassium-sparing diuretics, such as spironolactone, which is an aldosterone antagonist, often are used in the medical management of persons with bilateral hyperplasia.

Pheochromocytoma. A pheochromocytoma is a tumor of chromaffin tissue, which contains sympathetic nerve cells that stain with chromium salts. The tumor is most commonly located in the adrenal medulla but can arise in other sites, such as the sympathetic ganglia, where there is chromaffin tissue.[33,51] Although only 0.1% to 0.5% of persons with hypertension have an underlying pheochromocytoma, the disorder can cause serious hypertensive crises. The tumors are malignant 8% to 10% of the time.

Like adrenal medullary cells, the tumor cells of a pheochromocytoma produce and secrete the catecholamines epinephrine and norepinephrine. The hypertension that develops is a result of the massive release of these catecholamines. Their release may be paroxysmal rather than continuous, causing periodic episodes of headache, excessive sweating, and palpitations. Headache is the most common symptom and can be quite severe. Nervousness, tremor, facial pallor, weakness, fatigue, and weight loss occur less frequently. Marked variability in blood pressure between episodes is typical. Approximately 50% of persons with pheochromocytoma have paroxysmal episodes of hypertension, sometimes to dangerously high levels. The other 50% have sustained hypertension, and some even may be normotensive.[51]

Diagnostic methods include urinary and blood assays for catecholamines and their metabolites and CT and MRI studies to locate tumors and possible metastases. Surgical removal of the tumor or tumors is the treatment of choice. If the tumor is not resectable, treatment with drugs that block the action or synthesis of catecholamines can be used.

Coarctation of the Aorta. Coarctation represents a narrowing of the aorta. In the adult form of aortic coarctation, narrowing most commonly occurs just distal to the origin of the subclavian arteries[52] (see Chapter 19). The ejection of a large stroke volume into a narrowed aorta results in an increase in systolic blood pressure and blood flow to the upper part of the body. Blood pressure in the lower extremities may be normal, although it frequently is low. It has been suggested that the increase in cardiac output and maintenance of the blood pressure to the lower part of the body is achieved through the renin-angiotensin-aldosterone mechanism in response to a decrease in renal blood flow.

Coarctation of the aorta should be considered as a cause of secondary hypertension in young people with an elevation in blood pressure. Because the aortic capacity is diminished in coarctation of the aorta, there usually is a marked increase in pressure (measured in the arms) during exercise, when the stroke volume and heart rate are exaggerated. Pulse pressure in the legs almost always is narrowed, and the femoral pulses are weak. It is important that blood pressure be measured in both arms and one leg when coarctation of the aorta is suspected. A pressure in the arms 20 mm Hg or more higher than in the legs suggests coarctation of the aorta.

Treatment consists of surgical repair or balloon angioplasty. Although balloon angioplasty is a relatively recent form of treatment, it has been used in children and adults with good results. However, there are few data on long-term follow-up.

Oral Contraceptive Drugs. The use of oral contraceptive pills is probably the most common cause of secondary hypertension in young women. Women taking oral contraceptives should have their blood pressure taken regularly.[33] The cause of the increased blood pressure is largely unknown, although it has been suggested that the probable cause is volume expansion because both estrogens and synthetic progesterones used in oral contraceptive pills cause sodium retention. Various contraceptive drugs contain different amounts and combinations of estrogen and progestational agents, and these differences may contribute to the occurrence of hypertension in some women but not others. Fortunately, the hypertension associated with oral contraceptives usually disappears after the drug has been discontinued, although it may take as long as 3 months for this to happen. However, in some women the blood pressure may not return to normal, and they may be at risk for development of hypertension. The risk for hypertension-associated cardiovascular complications is found primarily in women older than 35 years of age and in those who smoke.

Target-Organ Damage

Hypertension is typically an asymptomatic disorder. When symptoms do occur, they are usually related to the long-term effects of hypertension on other organ systems, termed *target organs*, such as the kidneys, heart, eyes, and blood vessels[32] (Chart 18-2). The excess morbidity and mortality related to hypertension is progressive over the whole range of systolic and diastolic pressures, with target-organ damage varying markedly among persons with similar levels of hypertension.

Hypertension is a major risk factor for atherosclerosis; it predisposes to all major atherosclerotic cardiovascular disorders, including coronary heart disease, heart failure, stroke, and peripheral artery disease. The risk for coronary artery disease and stroke depends to a great extent on other risk factors, such as obesity, smoking, and elevated cholesterol levels. In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 30% to 40%; myocardial infarction, 20% to 25%; and heart failure, more than 50%.[32]

CHART 18-2 Target-Organ Damage

Heart
- Left ventricular hypertrophy
- Angina or prior myocardial infarction
- Prior coronary revascularization
- Heart failure

Brain
- Stroke or transient ischemic attack

Chronic kidney disease

Peripheral vascular disease

Retinopathy

From the National Heart, Lung, and Blood Institute. (2003). *The seventh report of the National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.* Publication no. 03–5233. Bethesda, MD: National Institutes of Health.

Hypertension increases the workload of the left ventricle by increasing the pressure against which the heart must pump as it ejects blood into the systemic circulation.[33] As the workload of the heart increases, the left ventricular wall hypertrophies to compensate for the increased pressure work. Despite its adaptive advantage, left ventricular hypertrophy is a major risk factor for coronary heart disease, cardiac arrhythmias, sudden death, and congestive heart failure. Hypertensive left ventricular hypertrophy regresses with therapy. Regression is most closely related to systolic pressure reduction and does not appear to reflect the particular type of medication used.

Chronic hypertension can lead to nephrosclerosis, a common cause of chronic kidney disease (see Chapter 25). Hypertensive kidney disease is more common in blacks than whites. Hypertension also plays an important role in accelerating the course of other types of kidney disease, particularly diabetic nephropathy. Because of the risk for diabetic nephropathy, the American Diabetes Association recommends that persons with diabetes maintain their blood pressure at levels less than 130/80 mm Hg[34] (see Chapter 33).

Dementia and cognitive impairment occur more commonly in persons with hypertension.[32] Hypertension, particularly systolic hypertension, is a major risk factor for ischemic stroke and intracerebral hemorrhage[33](see Chapter 37). Narrowing and sclerosis of small penetrating arteries in the subcortical regions of the brain are common findings on autopsy in persons with chronic hypertension.[32] These changes are thought to contribute to hypoperfusion, loss of autoregulation of blood flow, and impairment of the blood-brain barrier, ultimately leading to subcortical white matter demyelination. MRI studies have revealed more extensive white matter lesions and brain atrophy in hypertensive versus normotensive persons. Effective antihypertensive therapy strongly reduces the risk of development of significant white matter changes; however, existing white matter changes, once established, do not appear to be reversible.[32]

Diagnosis and Treatment

Unlike disorders of other body systems that are diagnosed by methods such as radiography and tissue examination, hypertension and other blood pressure disorders are determined by repeated blood pressure measurements. Laboratory tests, x-ray films, and other diagnostic tests usually are done to exclude secondary hypertension and determine the presence or extent of target-organ damage.

The increased availability of hypertensive screening clinics provides one of the best means for early detection. Because blood pressure in many individuals is highly variable, blood pressure should be measured on different occasions over a period of several months before a diagnosis of hypertension is made unless the pressure is extremely elevated or associated with symptoms.

Ambulatory and self/home measurement of blood pressure may provide valuable information outside the clinician's office regarding a person's blood pressure and response to treatment. Self/home measurement can help detect "white coat hypertension," a condition in which the blood pressure is consistently elevated in the health care provider's office but normal at other times; it can be used to assess the response to treatment methods for hypertension; it can motivate adherence to treatment regimens; and it can potentially reduce health care costs.[32,33]

The main objective for treatment of hypertension is to achieve and maintain arterial blood pressure below 140/90 mm Hg, with the goal of preventing morbidity and mortality. In persons with hypertension and diabetes or renal disease, the goal is below 130/80 mm Hg. Treatment methods include lifestyle modification and, when necessary, pharmacologic agents to achieve and maintain blood pressure within an optimal range.[32]

Lifestyle Modification. Lifestyle modification has been shown to reduce blood pressure, enhance the effects of antihypertensive drug therapy, and prevent cardiovascular risk. Major lifestyle modifications shown to lower blood pressure include weight reduction in persons who are overweight or obese, regular physical activity, reduction of dietary salt intake, and limitation of alcohol intake to no more than two drinks per day for most men and one drink for women and persons of lighter weight.[35,53] Although nicotine has not been associated with long-term elevations in blood pressure as in essential hypertension, it has been shown to increase the risk for heart disease. The fact that smoking and hypertension are major cardiovascular risk factors should be reason enough to encourage the hypertensive smoker to quit.

Pharmacologic Treatment. The decision to initiate pharmacologic treatment is based on the severity of the hypertension, the presence of target-organ disease, and the existence of other conditions and risk factors.[32,53] Drug selection is based on the stage of hypertension. Among the drugs used in the treatment of hypertension are diuretics, β-adrenergic receptor blockers, ACE inhibitors or angiotensin II receptor blockers, calcium channel blockers, central α_2-adrenergic agonists, α_1-adrenergic receptor blockers, and vasodilators.

The physiologic mechanisms whereby the different antihypertension drugs produce a reduction in blood pressure differ among agents. Diuretics lower blood pressure initially by decreasing vascular volume (by suppressing renal reabsorption of sodium and increasing sodium and water excretion) and cardiac output. With continued therapy, a reduction in peripheral resistance becomes a major mechanism of blood pressure reduction. The β-adrenergic blockers are effective in treating hypertension because they decrease heart rate, cardiac output, and renin release by the kidney. The ACE inhibitors act by inhibiting the conversion of angiotensin I to angiotensin II, thus decreasing angiotensin II levels and reducing its effect on vasoconstriction, aldosterone levels, intrarenal blood flow, and glomerular filtration rate. The calcium channel blockers decrease peripheral vascular resistance by inhibiting the movement of calcium into arterial smooth muscle cells. The centrally acting α_2-adrenergic agonists act in a negative-feedback manner to decrease sympathetic outflow from the central nervous system. The α_1-adrenergic receptor antagonists block α_1 receptors on vascular smooth muscle, causing vasodilatation and a reduction in peripheral vascular resistance. The direct-acting smooth muscle vasodilators promote a decrease in peripheral vascular resistance by producing relaxation of vascular smooth muscle, particularly of the arterioles.

Pharmacologic treatment of hypertension usually follows a stepwise approach.[32,53] It is usually initiated with a low dose of a single drug. The dose is slowly increased at a schedule dependent on the person's age, needs, and desired response. If the response to the initial drug is not adequate, one of three approaches can be used: the dose can be increased if the initial dose was below the maximum recommended; a drug with a different mode of action can be added; or the initial drug can be discontinued and another substituted. Combining drugs with different modes of action often allows smaller doses to be used to achieve blood pressure control while minimizing the dose-dependent side effects from any one drug.

Hypertensive Crisis

A small number of persons with hypertension develop an accelerated or severe form of hypertension.[33,54,55] Hypertensive crises are those situations in which a markedly elevated blood pressure is accompanied by progressive or impending target-organ damage. Severe hypertension and hypertensive crises are often associated with secondary hypertension, and many causes of secondary hypertension are known to result in blood pressure lability, further disposing to hypertensive crisis.

Hypertensive crisis is traditionally defined as an elevation in diastolic pressure greater than 120 mm Hg. This category includes persons who have severe hypertension, hypertensive urgency, and hypertensive emergency. *Severe hypertension* is usually defined as systolic blood pressure greater than 180 mm Hg and a diastolic pressure greater than 110 mm Hg; *hypertensive urgency* as an elevation in diastolic pressure greater than 110 mm

Hg and presence of significant symptoms such as severe headache or dyspnea; and *hypertensive emergency* as acute and rapidly evolving end-organ damage associated with significant hypertension, usually with a diastolic pressure greater than 120 mm Hg.[54,55] The major target organs in hypertensive emergency are the brain, heart and great vessels, kidney, and gravid uterus in pregnant women.

A persistent diastolic pressure exceeding 130 mm Hg is often associated with acute vascular damage; some persons may suffer vascular damage from lower levels of pressure, whereas others are able to withstand even higher levels without significant harm.[33] The rapidity of rise in the pressure may be more important than the actual level in producing vascular damage.

Hypertensive emergencies include intense arterial spasm of the cerebral arteries with hypertensive encephalopathy. Cerebral vasoconstriction probably is an exaggerated homeostatic response designed to protect the brain from excesses of blood pressure and flow. The regulatory mechanisms often are insufficient to protect the capillaries, and cerebral edema frequently develops. As it advances, papilledema (i.e., swelling of the optic nerve at its point of entrance into the eye) ensues, giving evidence of the effects of pressure on the optic nerve and retinal vessels. The person may have headache, restlessness, confusion, stupor, motor and sensory deficits, and visual disturbances. In severe cases, convulsions and coma follow.

The complications associated with a hypertensive crisis demand immediate and rigorous medical treatment in an intensive care unit with continuous monitoring of arterial blood pressure. Because chronic hypertension is associated with autoregulatory changes in coronary artery, cerebral artery, and kidney blood flow, care should be taken to avoid excessively rapid decreases in blood pressure, which can lead to hypoperfusion and ischemic injury. Therefore, the goal of initial treatment measures should be to obtain a partial reduction in blood pressure to a safer, less critical level, rather than to normotensive levels.[54]

Hypertension in Special Populations

High Blood Pressure in Pregnancy

Hypertensive disorders complicate 5% to 10% of pregnancies and remain a major cause of maternal and neonatal mortality and morbidity in the United States and worldwide.[56–59] In 2000, the National Institutes of Health Working Group on High Blood Pressure in Pregnancy published a revised classification system for high blood pressure in pregnancy that included preeclampsia–eclampsia, gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension[56] (Table 18-5). Most adverse events are attributable directly to the preeclampsia syndrome, characterized by new-onset hypertension with proteinuria that develops in the last half of pregnancy. Women with chronic hypertension can also manifest adverse events.

Preeclampsia–Eclampsia. Preeclampsia–eclampsia is a pregnancy-specific syndrome with both maternal and fetal manifestations.[56–60] It is defined as an elevation in blood pressure (systolic blood pressure >140 mm Hg or diastolic pressure >90 mm Hg) and proteinuria (≥300 mg in 24 hours) developing after 20 weeks of gestation. Edema, which previously was included in definitions of preeclampsia, was excluded from this most recent definition. The presence of a systolic blood pressure of 160 mm Hg or higher or a diastolic pressure of 110 mm Hg or higher, proteinuria greater than 2 g in 24 hours, serum creatinine greater than 1.2 mg/dL, platelet counts less than 100,000 cells/mm^3, elevated liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), persistent headache or cerebral or visual disturbances, and persistent epigastric pain serve to reinforce the diagnosis.[59] *Eclampsia* is the occurrence, in a woman with preeclampsia, of seizures that cannot be attributed to other causes. Preeclampsia occurs primarily during first pregnancies and during subsequent pregnancies in women with multiple fetuses, diabetes mellitus, collagen vascular disease, or underlying kidney disease.[56]

TABLE 18-5 Classification of High Blood Pressure in Pregnancy

Classification	Description
Preeclampsia–eclampsia	Pregnancy-specific syndrome of blood pressure elevation (blood pressure >140 mm Hg systolic or >90 mm Hg diastolic) that occurs after the first 20 weeks of pregnancy and is accompanied by proteinuria (urinary excretion of 0.3 g protein in a 24-hour specimen).
Gestational hypertension	Blood pressure elevation, without proteinuria, that is detected for the first time during mid-pregnancy and returns to normal by 12 weeks postpartum.
Chronic hypertension	Blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic that is present and observable before the 20th week of pregnancy. Hypertension that is diagnosed for the first time during pregnancy and does not resolve after pregnancy also is classified as chronic hypertension.
Preeclampsia superimposed on chronic hypertension	Chronic hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic before the 20th week of pregnancy) with superimposed proteinuria and with or without signs of the preeclampsia syndrome.

Developed using information from the National Institutes of Health. (2000). *Working group report on high blood pressure in pregnancy.* NIH publication no. 00-3029. Bethesda, MD: National Institutes of Health. Available: http://www.nhlbi.gov/health/prof/heart/hbp/hbp_preg.htm.

It is also associated with a condition called a *hydatidiform mole,* an abnormal mass of cysts that develop due to an abnormal pregnancy caused by a pathologic ovum. Women with chronic hypertension who become pregnant have an increased risk for preeclampsia and adverse neonatal outcomes, particularly when associated with proteinuria early in pregnancy.

The cause of pregnancy-induced hypertension is largely unknown. Considerable evidence suggests that the placenta is a key factor in all the manifestations because delivery is the only definitive cure for this disease. Pregnancy-induced hypertension is thought to involve a decrease in placental blood flow leading to the release of toxic mediators that alter the function of endothelial cells in blood vessels throughout the body, including those of the kidney, brain, liver, and heart. The endothelial changes result in signs and symptoms of preeclampsia and, in more severe cases, of intravascular clotting and hypoperfusion of vital organs. There is risk for development of disseminated intravascular coagulation (DIC; see Chapter 12), cerebral hemorrhage, hepatic failure, and acute renal failure. Thrombocytopenia is the most common hematologic complication of preeclampsia. The cause of thrombocytopenia has been ascribed to platelet deposition at the site of endothelial injury. The renal changes that occur with preeclampsia include a decrease in glomerular filtration rate and renal blood flow. Sodium excretion may be impaired, although this is variable. Edema may or may not be present. Some of the severest forms of preeclampsia occur in the absence of edema. Even when there is extensive edema, the plasma volume usually is lower than with a normal pregnancy. Liver damage, when it occurs, may range from mild hepatocellular necrosis with elevation of liver enzymes to the more ominous *h*emolysis, *e*levated *l*iver function test results, and *l*ow *p*latelet count (HELLP) syndrome that is associated with significant maternal mortality. Eclampsia, the convulsive stage of preeclampsia, is a significant cause of maternal mortality.

Gestational Hypertension. Gestational hypertension represents a blood pressure elevation without proteinuria that is detected for the first time after midpregnancy.[56] It includes women with preeclampsia syndrome who have not yet manifested proteinuria as well as women who do not have the syndrome. The hypertension may be accompanied by other signs of the syndrome. The final determination that a woman does not have the preeclampsia syndrome is made only postpartum. If preeclampsia has not developed and blood pressure has returned to normal by 12 weeks postpartum, the condition is considered to be gestational hypertension. If blood pressure elevation persists, a diagnosis of chronic hypertension is made.

Chronic Hypertension. Chronic hypertension is considered to be hypertension that is unrelated to the pregnancy. It is defined as a history of high blood pressure before pregnancy, identification of hypertension before 20 weeks of pregnancy, and hypertension that persists after pregnancy.[56] Hypertension that is diagnosed for the first time during pregnancy and does not resolve after pregnancy also is classified as chronic hypertension. In women with chronic hypertension, blood pressure often decreases in early pregnancy and increases during the last trimester (3 months) of pregnancy, resembling preeclampsia. Consequently, women with undiagnosed chronic hypertension who do not present for medical care until the later months of pregnancy may be incorrectly diagnosed as having preeclampsia.

Preeclampsia Superimposed on Chronic Hypertension. Women with chronic hypertension are at increased risk for the development of preeclampsia, in which case the prognosis for the mother and fetus tends to be worse than for either condition alone. Superimposed preeclampsia should be considered in women with hypertension before 20 weeks of gestation who develop new-onset proteinuria, women with hypertension and proteinuria before 20 weeks of gestation, women with previously well-controlled hypertension who experience a sudden increase in blood pressure, and women with chronic hypertension who develop thrombocytopenia or an increase in serum ALT or AST to abnormal levels.[56]

Diagnosis and Treatment. Early prenatal care is important in the detection of high blood pressure during pregnancy. It is recommended that all pregnant women, including those with hypertension, refrain from alcohol and tobacco use. Salt restriction usually is not recommended during pregnancy because pregnant women with hypertension tend to have lower plasma volumes than normotensive pregnant women and because the severity of hypertension may reflect the degree of volume contraction. The exception is women with preexisting hypertension who have been following a salt-restricted diet.

In women with preeclampsia, delivery of the fetus is curative. The timing of delivery becomes a difficult decision in preterm pregnancies because the welfare of both the mother and the infant must be taken into account. Bed rest is a traditional therapy. Antihypertensive medications, when required, must be carefully chosen because of their potential effects on uteroplacental blood flow and on the fetus. For example, the ACE inhibitors can cause injury and even death of the fetus when given during the second and third trimesters of pregnancy.

High Blood Pressure in Children and Adolescents

Until recently, the incidence of hypertension among children has been low, with a range of 1% to 3%.[61] Recent data, however, indicate that the prevalence and rate of diagnosis of hypertension in children and adolescents appear to be increasing.[61,62] This may be due in part to increasing prevalence of obesity and other lifestyle factors, such as decreased physical activity and increased intake of high-calorie, high-salt foods.

Blood pressure is known to increase from infancy to late adolescence. The average systolic pressure at 1 day of age is approximately 70 mm Hg and increases to approximately 85 mm Hg at 1 month of age.[63] Systolic

blood pressure continues to increase with physical growth to about 120 mm Hg at the end of adolescence. During the preschool years, blood pressure begins to follow a pattern that tends to be maintained as the child grows older. This pattern continues into adolescence and adulthood, suggesting that the roots of essential hypertension have their origin early in life. A familial influence on blood pressure often can be identified early in life. Children of parents with high blood pressure tend to have higher blood pressures than do children with normotensive parents.

Blood pressure norms for children are based on age-, height-, and gender-specific percentiles[63] (Table 18-6). The National High Blood Pressure Education Program (NHBPEP) first published its recommendations in 1977. The fourth task force report (published in 2004) recommended classification of blood pressure (systolic or diastolic) for age, height, and gender into four categories: normal (less than the 90th percentile), high normal (between the 90th and 95th percentiles), stage 1 hypertension (between the 95th and 99th percentiles plus 5 mm Hg), and stage 2 hypertension (greater than the 99th percentile plus 5 mm Hg).[63] The height percentile is determined by using the revised Centers for Disease Control and Prevention (CDC) growth charts.[64] As with the seventh report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) of the National Institutes of Health report, high normal is now considered to be "prehypertensive" and is an indication for lifestyle modification. Children and adolescents with hypertension should be evaluated for target-organ damage.[63]

Secondary hypertension is the most common form of high blood pressure in infants and children. In later childhood and adolescence, essential hypertension is more common. Approximately 75% to 80% of secondary hypertension in children is caused by kidney abnormalities.[65] Coarctation of the aorta is another cause of hypertension in children and adolescents. Endocrine causes of hypertension, such as pheochromocytoma and adrenal

TABLE 18-6 The 90th and 95th Percentiles of Systolic and Diastolic Blood Pressure for Boys and Girls 1 to 16 Years of Age by Percentiles for Height

Blood Pressure Percentile	Age (yrs)	Height Percentile for Boys				Height Percentile for Girls			
		5th	*25th*	*75th*	*95th*	*5th*	*25th*	*75th*	*95th*
Systolic Pressure									
90th	1	94	97	100	103	97	98	101	103
95th		98	101	104	106	100	102	105	107
90th	3	100	103	107	109	100	102	104	106
95th		104	107	110	113	104	105	108	110
90th	6	105	108	111	113	104	106	109	111
95th		109	112	115	117	108	110	113	115
90th	10	111	114	117	119	112	114	116	118
95th		115	117	121	123	116	117	120	122
90th	13	117	120	124	126	117	119	122	124
95th		121	124	128	130	121	123	126	128
90th	16	125	128	131	134	121	123	126	128
95th		129	132	135	137	125	127	130	132
Diastolic Pressure									
90th	1	49	51	53	54	52	53	55	56
95th		54	55	58	58	56	57	59	60
90th	3	59	60	62	63	61	62	64	65
95th		63	64	66	67	65	66	68	69
90th	6	68	69	71	72	68	69	70	72
95th		72	73	75	76	72	73	74	76
90th	10	73	74	76	78	73	73	75	76
95th		77	79	81	82	77	77	79	80
90th	13	75	76	78	79	76	76	78	79
95th		79	80	82	83	80	80	82	83
90th	16	78	79	81	82	78	79	81	82
95th		82	83	85	87	82	83	85	86

The height percentile is determined by using the newly revised CDC growth charts. Blood pressure levels are based on new data from the 1999–2000 National Health and Nutritional Examination Survey (NHANES) that have been added to the childhood BP database.

From the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adults. (2004). Fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114, 555–576. [Online] Available: www.pediatrics.org/cgi/content/full/114/S2/555.

cortical disorders, are rare. Hypertension in infants is associated most commonly with high umbilical catheterization and renal artery obstruction caused by thrombosis.[65] Most cases of essential hypertension are associated with obesity or a family history of hypertension.

A number of drugs of abuse, therapeutic agents, and toxins also may increase blood pressure.[65] Alcohol should be considered as a risk factor in adolescents. Oral contraceptives may be a cause of hypertension in adolescent girls. The nephrotoxicity of the drug cyclosporine, an immunosuppressant used in transplant therapy, may cause hypertension in children (and adults) after bone marrow, heart, kidney, or liver transplantation. The coadministration of corticosteroid drugs appears to increase the incidence of hypertension.

Diagnosis and Treatment. Children 3 years of age through adolescence should have their blood pressure taken once each year.[63] The auscultatory method using a cuff of an appropriate size for the child's upper arm is recommended.[63] Repeated measurements over time, rather than a single isolated determination, are required to establish consistent and significant observations. Children with high blood pressure should be referred for medical evaluation and treatment as indicated. Treatment includes nonpharmacologic methods and, if necessary, pharmacologic therapy.

High Blood Pressure in the Elderly

The prevalence of hypertension increases with advancing age to the extent that half of people aged 60 to 69 years and approximately three fourths of people 70 years and older are affected.[32] The age-related rise in systolic blood pressure is primarily responsible for the increase in hypertension that occurs with increasing age.

Among the aging processes that contribute to an increase in blood pressure are a stiffening of the large arteries, particularly the aorta; decreased baroreceptor sensitivity; increased peripheral vascular resistance; and decreased renal blood flow.[66] Systolic blood pressure rises almost linearly between 30 and 84 years of age, whereas diastolic pressure rises until 50 years of age and then levels off or decreases.[67] This rise in systolic pressure is thought to be related to increased stiffness of the large arteries. With aging, the elastin fibers in the walls of the arteries are gradually replaced by collagen fibers that render the vessels stiffer and less compliant.[66] Differences in the central and peripheral arteries relate to the fact that the larger vessels contain more elastin, whereas the peripheral resistance vessels have more smooth muscle and less elastin. Because of increased wall stiffness, the aorta and large arteries are less able to buffer the increase in systolic pressure that occurs as blood is ejected from the left heart, and they are less able to store the energy needed to maintain the diastolic pressure. As a result, the systolic pressure increases, the diastolic pressure remains unchanged or actually decreases, and the pulse pressure or difference between the systolic pressure and diastolic pressure widens.

Isolated systolic hypertension (systolic pressure ≥140 mm Hg and diastolic pressure <90 mm Hg) is recognized as an important risk factor for cardiovascular morbidity and mortality in older persons.[32] The treatment of hypertension in the elderly has beneficial effects in terms of reducing the incidence of cardiovascular events such as stroke. Studies have shown a reduction in stroke, coronary heart disease, and congestive heart failure in persons who were treated for hypertension compared with those who were not.[66]

Diagnosis and Treatment. The recommendations for measurement of blood pressure in the elderly are similar to those for the rest of the population.[68] Blood pressure variability is particularly prevalent among older persons, so it is especially important to obtain multiple measurements on different occasions to establish a diagnosis of hypertension. The effects of food, position, and other environmental factors also are exaggerated in older persons. Although sitting has been the standard position for blood pressure measurement, it is recommended that blood pressure also be taken in the supine and standing positions in the elderly. In some elderly persons with hypertension, a silent interval, called the *auscultatory gap*, may occur between the end of the first and beginning of the third phases of the Korotkoff sounds, providing the potential for underestimating the systolic pressure, sometimes by as much as 50 mm Hg. Because the gap occurs only with auscultation, it is recommended that a preliminary determination of systolic blood pressure be made by palpation and the cuff be inflated 30 mm Hg above this value for auscultatory measurement of blood pressure. In some older persons, the indirect measurement using a blood pressure cuff and the Korotkoff sounds has been shown to give falsely elevated readings compared with the direct intra-arterial method. This is because excessive cuff pressure is needed to compress the rigid vessels of some older persons. Pseudohypertension should be suspected in older persons with hypertension in whom the radial or brachial artery remains palpable but pulseless at higher cuff pressures.

The treatment of hypertension in the elderly is similar to that for younger people. However, blood pressure should be reduced slowly and cautiously. When possible, appropriate lifestyle modification measures should be tried first. Antihypertensive medications should be prescribed carefully because the older person may have impaired baroreflex sensitivity and renal function. Usually, medications are initiated at smaller doses, and doses are increased more gradually. There is also the danger of adverse drug interactions in older persons, who may be taking multiple medications, including over-the-counter drugs.

Orthostatic Hypotension

Orthostatic or postural hypotension is an abnormal drop in blood pressure on assumption of the standing position.[69–71] After the assumption of the upright posture from the supine position, approximately 500 to 700 mL of blood is momentarily shifted to the lower part of the

body, with an accompanying decrease in central blood volume and arterial pressure.[69] Normally, this decrease in blood pressure is transient, lasting through several cardiac cycles, because the baroreceptors located in the thorax and carotid sinus area sense the decreased pressure and initiate reflex constriction of the veins and arterioles and an increase in heart rate, which brings the blood pressure back to normal. Within a few minutes of a change to the standing position, blood levels of the sympathetic neuromediators and antidiuretic hormone increase as a secondary means of ensuring maintenance of normal blood pressure in the standing position. Muscle movement in the lower extremities also aids venous return to the heart by pumping blood out of the legs.

When the standing position is assumed in the absence of normal circulatory reflexes or blood volume, blood pools in the lower part of the body; cardiac output falls, blood pressure drops, and blood flow to the brain is inadequate (Fig. 18-16). Dizziness, syncope (i.e., fainting), or both may occur. Although there is no firm agreement on the definition of orthostatic hypotension, many authorities consider a drop in systolic pressure of 20 mm Hg or more or a drop in diastolic pressure of 10 mm Hg or more as diagnostic of the condition.[71] Some authorities regard the presence of orthostatic symptoms (e.g., dizziness, syncope) as being more relevant than the numeric decrease in blood pressure.

Causes

A wide variety of conditions, acute and chronic, are associated with orthostatic hypotension. These include reduced blood volume, drug-induced hypotension, altered vascular responses associated with aging, bed rest, and autonomic nervous system dysfunction.

Reduced Blood Volume. Orthostatic hypotension often is an early sign of reduced blood volume or fluid deficit. When blood volume is decreased, the vascular compartment is only partially filled; although cardiac output may be adequate when a person is in the recumbent position, it often decreases to the point of causing weakness and fainting when the person assumes the standing position. Common causes of orthostatic hypotension related to hypovolemia are excessive use of diuretics, excessive diaphoresis, loss of gastrointestinal fluids through vomiting and diarrhea, and loss of fluid volume associated with prolonged bed rest.

Drug-Induced Hypotension. Antihypertensive drugs and psychotropic drugs are a common cause of chronic orthostatic hypotension. In most cases, the orthostatic hypotension is well tolerated. If postural hypotension is severe enough to cause light-headedness or dizziness, it is recommended that the dosage of the drug be reduced or a different drug be used.

Aging. Weakness and dizziness on standing are common complaints of elderly persons. Orthostatic tolerance is usually well maintained until the age of 70 years, after which there is an increasing tendency toward arterial

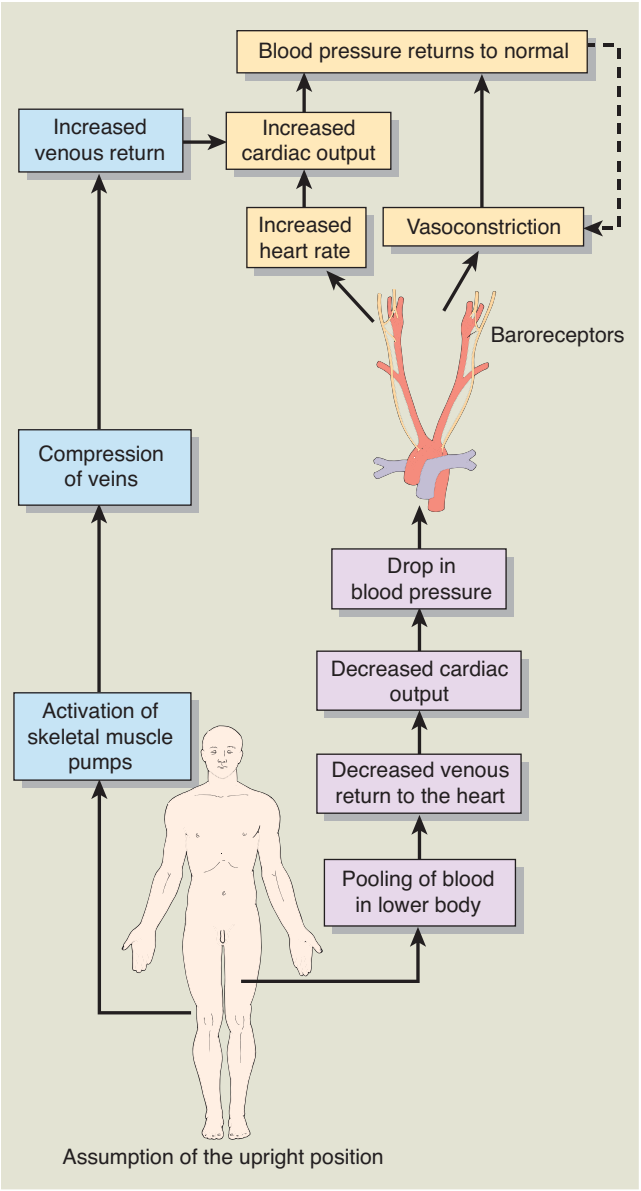


FIGURE 18-16. Mechanisms of blood control on immediate assumption of the upright position.

pressure instability and postural hypotension. Although orthostatic hypotension may be either systolic or diastolic, that associated with aging seems more often to be systolic.[70,72] Several deficiencies in the circulatory response may predispose to this problem in the elderly, including diminished ability to produce an adequate increase in the heart rate, ventricular stroke volume, or peripheral vascular resistance; decreased function of the skeletal muscle pumps; and decreased blood volume. Because cerebral blood flow primarily depends on systolic pressure, patients with impaired cerebral circulation may experience symptoms of weakness, ataxia, dizziness, and syncope when their arterial pressure falls even slightly. This may occur in older persons who are immobilized for even brief periods or whose blood volume is decreased owing to inadequate fluid intake or overzealous use of diuretics.

Postprandial blood pressure often decreases in elderly persons.[73] The greatest postprandial changes occur after a high-carbohydrate meal. Although the mechanism responsible for these changes is not fully understood, it is thought to result from glucose-mediated impairment of baroreflex sensitivity and increased splanchnic blood flow mediated by insulin and vasoactive gastrointestinal hormones.

Bed Rest and Immobility. Prolonged bed rest promotes a reduction in plasma volume, a decrease in venous tone, failure of peripheral vasoconstriction, and weakness of the skeletal muscles that support the veins and assist in returning blood to the heart. Physical deconditioning follows even short periods of bed rest. After 3 to 4 days, the blood volume is decreased. Loss of vascular and skeletal muscle tone is less predictable but probably becomes maximal after approximately 2 weeks of bed rest. Orthostatic intolerance is a recognized problem of space flight—a potential risk after reentry into the earth's gravitational field.

Disorders of Autonomic Nervous System Function. The sympathetic nervous system plays an essential role in adjustment to the upright position. Sympathetic stimulation increases heart rate and cardiac contractility and causes constriction of peripheral veins and arterioles. Orthostatic hypotension caused by altered ANS function is common in peripheral neuropathies associated with diabetes mellitus, after injury or disease of the spinal cord, or as the result of a cerebral vascular accident in which sympathetic outflow from the brain stem is disrupted. The American Autonomic Society and the American Academy of Neurology have distinguished three forms of primary ANS dysfunction: (1) pure autonomic failure, which is defined as a sporadic, idiopathic cause of persistent orthostatic hypotension and other manifestations of autonomic failure such as urinary retention, impotence, or decreased sweating; (2) Parkinson disease with autonomic failure; and (3) multiple-system atrophy (Shy-Drager syndrome).[74] The Shy-Drager syndrome usually develops in middle to late life as orthostatic hypotension associated with uncoordinated movements, urinary incontinence, constipation, and other signs of neurologic deficits referable to the corticospinal, extrapyramidal, corticobulbar, and cerebellar systems.

Diagnosis and Treatment

Orthostatic hypotension can be assessed with the auscultatory method of blood pressure measurement. A reading should be made when the patient is supine, immediately after assumption of the seated or upright position, and 2 to 3 minutes after assumption of the standing position. A tilt table also can be used for this purpose. With a tilt table, the recumbent patient can be moved to a head-up position without voluntary movement when the table is tilted. The tilt table also has the advantage of rapidly and safely returning persons with a profound postural drop in blood pressure to the horizontal position. Persons with a drop in blood pressure to orthostatic levels should be evaluated to determine the cause and seriousness of the condition. A history should be taken to elicit information about symptoms, particularly dizziness and history of syncope and falls; medical conditions, particularly those such as diabetes mellitus that predispose to orthostatic hypotension; use of prescription and over-the-counter drugs; and symptoms of ANS dysfunction, such as impotence or bladder dysfunction. A physical examination should document blood pressure in both arms and the heart rate while the patient is in the supine, sitting, and standing positions and should note the occurrence of symptoms. Noninvasive, 24-hour ambulatory blood pressure monitoring may be used to determine blood pressure responses to other stimuli of daily life, such as food ingestion and exertion.

Treatment of orthostatic hypotension usually is directed toward alleviating the cause, or if this is not possible, toward helping the person learn to cope with the disorder and prevent falls and injuries. Medications that predispose to postural hypotension should be avoided. Correcting the fluid deficit and trying a different antihypertensive medication are examples of measures designed to correct the cause. Measures designed to help persons prevent symptomatic orthostatic drops in blood pressure include gradual ambulation to allow the circulatory system to adjust (i.e., sitting on the edge of the bed for several minutes and moving the legs to initiate skeletal muscle pump function before standing); avoidance of situations that encourage excessive vasodilation (e.g., drinking alcohol, exercising vigorously in a warm environment); and avoidance of excess diuresis (e.g., use of diuretics), diaphoresis, or loss of body fluids. Tight-fitting elastic support hose or an abdominal support garment may help prevent pooling of blood in the lower extremities and abdomen.

Pharmacologic treatment may be used when nonpharmacologic methods are unsuccessful. A number of types of drugs can be used for this purpose.[70,72] Mineralocorticoids (e.g., fludrocortisone) can be used to reduce salt and water loss and probably increase α-adrenergic sensitivity. Vasopressin-2–receptor agonists (desmopressin as a nasal spray) may be used to reduce nocturnal polyuria. Sympathomimetic drugs that act directly on the resistance vessels (e.g., phenylephrine, clonidine) or on the capacitance vessels (e.g., dihydroergotamine) may be used. Many of these agents have undesirable side effects.

In summary, hypertension (systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg) is one of the most common cardiovascular disorders. It may occur as a primary disorder (i.e., essential hypertension) or as a symptom of some other disease (i.e., secondary hypertension). The incidence of essential hypertension increases with age; the condition is seen more frequently among blacks, and it may be associated with a family history of high blood pressure, metabolic

syndrome, obesity, and increased sodium intake. Causes of secondary hypertension include kidney disease and adrenal cortical disorders (hyperaldosteronism and Cushing disease), which increase sodium and water retention; pheochromocytomas, which increase catecholamine levels; and coarctation of the aorta, which produces an increase in blood flow and systolic blood pressure in the arms and a decrease in blood flow and systolic pressure in the legs.

Unlike disorders of other body systems that are diagnosed by methods such as radiography and tissue examination, hypertension and other blood pressure disorders are determined by repeated blood pressure measurements. Uncontrolled hypertension increases the risk of heart disease, renal complications, retinopathy, and stroke. Treatment of essential hypertension focuses on nonpharmacologic methods such as weight reduction, reduction of sodium intake, regular physical activity, and modification of alcohol intake. Among the drugs used in the treatment of hypertension are diuretics, β-adrenergic blocking agents, ACE inhibitors, calcium channel blocking agents, α_1-adrenergic blocking agents, centrally acting α_2 agonists, and vasodilating drugs.

Hypertension among special populations includes hypertension that occurs during pregnancy, in children and adolescents, and in the elderly. Hypertension that occurs during pregnancy can be divided into four categories: preeclampsia–eclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia–eclampsia. Preeclampsia–eclampsia is hypertension that develops after 20 weeks' gestation and is accompanied by proteinuria, posing a particular threat to the mother and the fetus. Chronic hypertension is hypertension that is present before 20 weeks' gestation. Secondary hypertension is the most common form of high blood pressure in infants and children. In later childhood and adolescence, essential hypertension is more common. Isolated systolic hypertension, the most common type of hypertension in the elderly, represents the effects of aging on the distensibility of the aorta and its ability to stretch and accommodate blood being ejected from the left heart during systole. Untreated systolic hypertension is recognized as an important risk factor for stroke and other cardiovascular morbidity and mortality in older persons.

Orthostatic hypotension refers to an abnormal decrease in systolic and diastolic blood pressures that occurs on assumption of the upright position. An important consideration in orthostatic hypotension is the occurrence of dizziness and syncope. Among the factors that contribute to its occurrence are decreased fluid volume, medications, aging, defective function of the ANS, and the effects of immobility. Diagnosis of orthostatic hypotension relies on blood pressure measurements in the supine and upright positions and a history of symptomatology, medication use, and disease conditions that contribute to a postural drop in blood pressure. Treatment includes correcting the reversible causes and assisting the person to compensate for the disorder and prevent falls and injuries.

Disorders of the Venous Circulation

Veins are low-pressure, thin-walled vessels that rely on the ancillary action of skeletal muscle pumps and changes in abdominal and intrathoracic pressure to return blood to the heart. Unlike the arterial system, the venous system is equipped with valves that prevent retrograde flow of blood (see Chapter 17). Although its structure enables the venous system to serve as a storage area for blood, it also renders the system susceptible to problems related to stasis and venous insufficiency. This section focuses on three common problems of the venous system: varicose veins, venous insufficiency, and venous thrombosis.

Venous Circulation of the Lower Extremities

The venous system in the legs consists of two components: the superficial veins (i.e., saphenous vein and its tributaries) and the deep venous channels (Fig. 18-17A). Perforating or communicating veins connect these two systems. Blood from the skin and subcutaneous tissues in the leg collects in the superficial veins and is then transported across the communicating veins into the deeper venous channels for return to the heart. Venous

Disorders of the Venous Circulation

- Veins are thin-walled, distensible vessels that collect blood from the tissues and return it to the heart. The venous system is a low-pressure system that relies on the pumping action of the skeletal muscles to move blood forward and the presence of venous valves to prevent retrograde flow.
- Disorders of the venous system produce congestion of the affected tissues and predispose to clot formation because of stagnation of flow and activation of the clotting system.
- Varicose veins are dilated and tortuous veins that result from a sustained increase in pressure that causes the venous valves to become incompetent, allowing for reflux of blood and vein engorgement.
- Thrombophlebitis refers to thrombus formation in a vein and the accompanying inflammatory response in the vessel wall as a result of conditions that obstruct or slow blood flow, increase the activity of the coagulation system, or cause vessel injury. Deep vein thrombosis may be a precursor to pulmonary embolism.

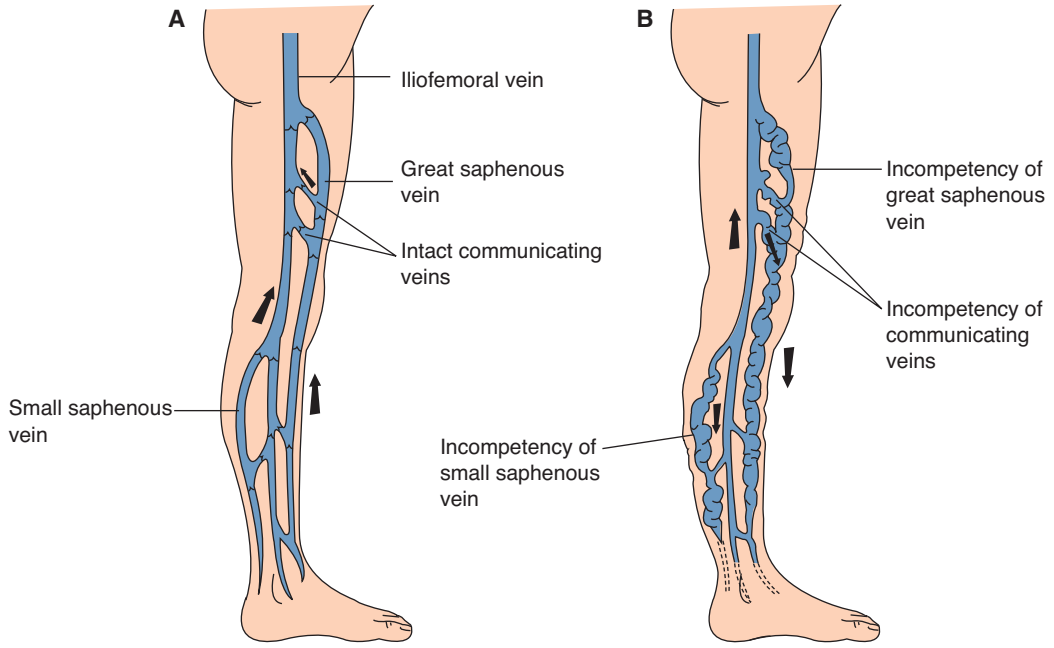


FIGURE 18-17. Superficial and deep venous channels of the leg. **(A)** Normal venous structures and flow patterns. **(B)** Varicosities in the superficial venous system are the result of incompetent valves in the communicating veins. The *arrows* in both views indicate the direction of blood flow. (Modified from Abramson D.I. [1974]. *Vascular disorders of the extremities* [2nd ed.]. New York: Harper & Row.)

valves prevent the retrograde flow of blood and play an important role in the function of the venous system. Although these valves are irregularly located along the length of the veins, they almost always are found at junctions where the communicating veins merge with the larger deep veins and where two veins meet. The number of venous valves differs somewhat from one person to another, as does their structural competence, factors that may help explain the familial predisposition to development of varicose veins.

The action of the leg muscles assists in moving venous blood from the lower extremities back to the heart. When a person walks, the action of the leg muscles serves to increase flow in the deep venous channels and return venous blood to the heart (Fig. 18-18). The function of the so-called *muscle pump,* located in the gastrocnemius and soleus muscles of the lower extremities, can be compared with the pumping action of the heart.[75] During muscle contraction, which is similar to systole, valves in the communicating channels close to prevent backward flow of blood into the superficial system, as blood in the deep veins is moved forward by the action of the contracting muscles. During muscle relaxation, which is similar to diastole, the communicating valves open, allowing blood from the superficial veins to move into the deep veins.

Varicose Veins

Varicose, or dilated, tortuous veins of the lower extremities are common and often lead to secondary problems of venous insufficiency[76,77] (see Fig. 18-17B). The prevalence of varicose veins in Western populations is about 25% to 30% in women and 10% to 20% in men. The condition is more common after 50 years of age and in obese persons, and it occurs more often in women, probably because of venous stasis caused by pregnancy.[2]

Varicose veins are described as being primary or secondary. Primary varicose veins originate in the superficial saphenous veins, and secondary varicose veins result

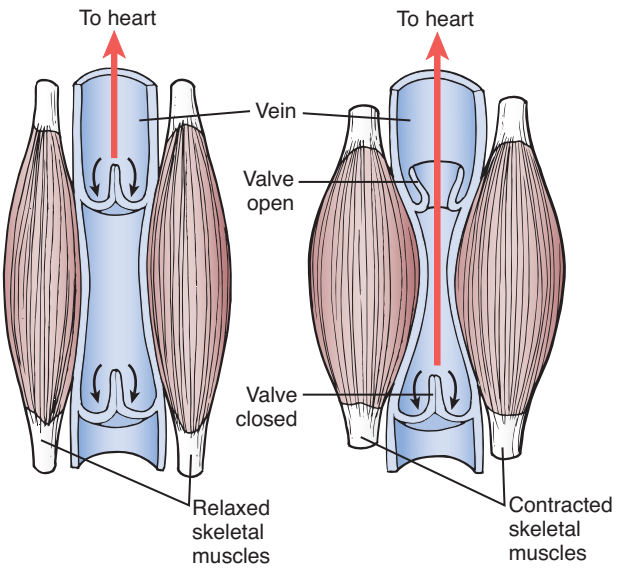


FIGURE 18-18. The skeletal muscle pumps and their function in promoting blood flow in the deep and superficial calf vessels of the leg.

from impaired flow in the deep venous channels. Approximately 80% to 90% of venous blood from the lower extremities is transported through the deep channels. The development of secondary varicose veins becomes inevitable when flow in these deep channels is impaired or blocked. The most common cause of secondary varicose veins is deep vein thrombosis. Other causes include congenital or acquired arteriovenous fistulas, congenital venous malformations, and pressure on the abdominal veins caused by pregnancy or a tumor.

Prolonged standing and increased intra-abdominal pressure are important contributing factors in the development of primary varicose veins. Because there are no valves in the inferior vena cava or common iliac veins, blood in the abdominal veins must be supported by the valves located in the external iliac or femoral veins. When intra-abdominal pressure increases, as it does during pregnancy, or when the valves in these two veins are absent or defective, the stress on the saphenofemoral junction is increased. The high incidence of varicose veins in women who have been pregnant also suggests a hormonal effect on venous smooth muscle contributing to venous dilation and valvular incompetence. Lifting also increases intra-abdominal pressure and decreases flow of blood through the abdominal veins. Occupations that require repeated heavy lifting predispose to development of varicose veins.

Prolonged exposure to increased pressure causes the venous valves to become incompetent so they no longer close properly. When this happens, the reflux of blood causes further venous enlargement, pulling the valve leaflet apart and causing more valvular incompetence in sections of adjacent distal veins. Another consideration in the development of varicose veins is the fact that the superficial veins have only subcutaneous fat and superficial fascia for support, whereas the deep venous channels are supported by muscle, bone, and connective tissue. Obesity reduces the support provided by the superficial fascia and tissues, increasing the risk for development of varicose veins.

The signs and symptoms associated with primary varicose veins vary. Most women with superficial varicose veins complain of their unsightly appearance. In many cases, aching in the lower extremities and edema, especially after long periods of standing, may occur. The edema usually subsides at night when the legs are elevated. When the communicating veins are incompetent, symptoms are more common.

The diagnosis of varicose veins often can be made after physical inspection. Primary varicose veins should be differentiated from those secondary to chronic venous insufficiency, retroperitoneal venous obstruction, or congenital venous malformations. The Doppler ultrasonic flow probe also may be used to assess flow in the large vessels. Angiographic studies using a radiopaque contrast medium also are used to assess venous function.

Treatment measures for varicose veins focus on improving venous flow and preventing tissue injury. When correctly fitted, elastic support stockings or leggings compress the superficial veins and prevent distention. The most precise control is afforded by prescription stockings, measured to fit properly. These stockings should be applied before the standing position is assumed, when the leg veins are empty. Sclerotherapy, which often is used in the treatment of small residual varicosities, involves the injection of a sclerosing agent into the collapsed superficial veins to produce fibrosis of the vessel lumen. Surgical treatment consists of removing the varicosities and the incompetent perforating veins, but it is limited to persons with patent deep venous channels.

Chronic Venous Insufficiency

Chronic venous disease of the lower extremities is manifested by venous hypertension and a range of signs, the most obvious of which are varicose veins and venous ulcers due to venous insufficiency.[75,78] Venous hypertension represents a sustained increase in venous blood pressures. It is most commonly caused by reflux through incompetent veins, but other causes include venous outflow obstruction and impaired function of the skeletal muscle pumps. Pressure in the veins of the legs is determined by two components: a *hydrostatic component* related to the weight of a column of blood below the level of the heart and a *hydrodynamic component* related to the action of the skeletal muscle pump. Prolonged standing increases venous pressure and causes dilation and stretching of the vessel wall. When a person is in the erect position, the full weight of the venous columns of blood is transmitted to the leg veins. The effects of gravity are compounded in persons who stand for long periods without using their leg muscles to assist in pumping blood back to the heart.

Chronic venous insufficiency is characterized by signs and symptoms associated with impaired blood flow. In contrast to the ischemia caused by arterial insufficiency, venous insufficiency leads to tissue congestion, edema, and eventual impairment of tissue nutrition. The edema is exacerbated by long periods of standing. Necrosis of subcutaneous fat deposits occurs, followed by skin atrophy. Brown pigmentation of the skin caused by hemosiderin deposits resulting from the breakdown of red blood cells is common. Secondary lymphatic insufficiency occurs, with progressive sclerosis of the lymph channels in the face of increased demand for clearance of interstitial fluid.

In advanced venous insufficiency, impaired tissue nutrition causes stasis dermatitis and the development of stasis or venous ulcers (Fig. 18-19). Stasis dermatitis is characterized by the presence of thin, shiny, bluish brown, irregularly pigmented desquamative skin that lacks the support of the underlying subcutaneous tissues. Minor injury leads to relatively painless ulcerations that are difficult to heal. The lower part of the leg is particularly prone to development of stasis dermatitis and venous ulcers. Most lesions are located medially over the ankle and lower leg, with the highest frequency just above the medial malleolus.

Treatment of venous ulcers includes compression therapy with dressings and inelastic or elastic bandages. Occasionally skin grafting is required for large or slow-healing venous ulcers. Growth factors (which are

FIGURE 18-19. Varicose veins of the legs. Severe varicosities of the superficial leg veins have led to stasis dermatitis and secondary ulcerations. [From Gotlieb A.I. [2008] Blood vessels. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 423]. Philadelphia: Lippincott Williams & Wilkins.)

administered topically or by perilesional injection) may also be warranted.[79]

Venous Thrombosis

The term *venous thrombosis,* or *thrombophlebitis,* describes the presence of thrombus in a vein and the accompanying inflammatory response in the vessel wall.[80,81] Thrombi can develop in the superficial or the deep veins. Deep venous thrombosis (DVT) most commonly occurs in the lower extremities. DVT of the lower extremity is a serious disorder, complicated by pulmonary embolism (see Chapter 23), recurrent episodes of DVT, and development of chronic venous insufficiency. Isolated calf thrombi often are asymptomatic. If left untreated, they may extend to the larger, more proximal veins, with an increased risk of pulmonary emboli (up to 50% risk from proximal DVTs).

In 1846, Virchow described the triad that has come to be associated with venous thrombosis: stasis of blood, increased blood coagulability, and vessel wall injury.[82] Risk factors for venous thrombosis are summarized in Chart 18-3. Stasis of blood occurs with immobility of an extremity or the entire body. Bed rest and immobilization are associated with decreased blood flow, venous pooling in the lower extremities, and increased risk of DVT. Persons who are immobilized by a hip fracture, joint replacement, or spinal cord injury are particularly vulnerable to DVT. The risk of DVT is increased in situations of impaired cardiac function. This may account for the relatively high incidence in persons with acute myocardial infarction and congestive heart failure. Elderly persons are more susceptible than younger persons, probably because disorders that produce venous stasis occur more frequently in older persons. Long airplane travel poses a particular threat in persons predisposed to DVT because of prolonged sitting and increased blood viscosity due to dehydration.[83]

Hypercoagulability is a homeostatic mechanism designed to increase clot formation, and conditions that increase the concentration or activation of clotting factors predispose to DVT. Thrombosis also can be caused by inherited or acquired deficiencies in certain plasma proteins that normally inhibit thrombus formation, such as antithrombin III, protein C, and protein S. However, the most common inherited risk factors are the factor V Leiden and prothrombin gene mutations (see Chapter 12). The postpartum state is associated with increased levels of fibrinogen, prothrombin, and other coagulation factors. The use of oral contraceptives and hormone replacement therapy appears to increase coagulability and predispose to venous thrombosis, a risk that is further increased in women who smoke. Certain cancers are associated with increased clotting tendencies, and although the reason for this is largely unknown, substances that promote blood coagulation may be produced by the tumor cells or

CHART 18-3 Risk Factors Associated with Venous Thrombosis*

Venous Stasis
Bed rest
Immobility
Spinal cord injury
Acute myocardial infarction
Congestive heart failure
Shock
Venous obstruction

Hyperreactivity of Blood Coagulation
Genetic factors
Stress and trauma
Pregnancy
Childbirth
Oral contraceptive and hormone replacement use
Dehydration
Cancer
Antiphospholipid syndrome
Hyperhomocystinemia

Vascular Trauma
Indwelling venous catheters
Surgery
Massive trauma or infection
Fractured hip
Orthopedic surgery

*Many of these disorders involve more than one mechanism.

released from the surrounding tissues in response to the cancerous growth. Immune interactions with cancer cells can result in the release of cytokines that can cause endothelial damage and predispose to thrombosis. When body fluid is lost because of injury or disease, the resulting hemoconcentration causes clotting factors to become more concentrated. Other important risk factors include the antiphospholipid syndrome (discussed in Chapter 12) and hyperhomocysteinemia.

Vessel injury can result from a trauma situation or from surgical intervention. It also may occur secondary to infection or inflammation of the vessel wall. Persons undergoing hip surgery and total hip replacement are at particular risk because of trauma to the femoral and iliac veins and, in the case of hip replacement, thermal damage from heat generated by the polymerization of the acrylic cement that is used in the procedure. Venous catheters are another source of vascular injury.

Many persons with venous thrombosis are asymptomatic, probably because the vein is not totally occluded or because of collateral circulation.[84] When present, the most common signs and symptoms of venous thrombosis are those related to the inflammatory process: pain, swelling, and deep muscle tenderness. Fever, general malaise, and an elevated white blood cell count and erythrocyte sedimentation rate are accompanying indications of inflammation. There may be tenderness and pain along the vein. Swelling may vary from minimal to maximal. As much as 50% of persons with DVT are asymptomatic.

The site of thrombus formation determines the location of the physical findings. The most common site is in the venous sinuses in the soleus muscle and posterior tibial and peroneal veins. Swelling in these cases involves the foot and ankle, although it may be slight or absent. Calf pain and tenderness are common. Femoral vein thrombosis produces pain and tenderness in the distal thigh and popliteal area. Thrombi in ileofemoral veins produce the most profound manifestations, with swelling, pain, and tenderness of the entire extremity. With DVT in the calf veins, active dorsiflexion produces calf pain (i.e., Homans sign).

The risk of pulmonary embolism emphasizes the need for early detection and treatment of DVT. Several tests are useful for this purpose: ascending venography, ultrasonography (e.g., real time, B mode, duplex), and plasma D-dimer (a degradation product of fibrin) assessment[84] (see Chapter 23).

Whenever possible, venous thrombosis should be prevented in preference to being treated. Early ambulation after childbirth and surgery is one measure that decreases the risk of thrombus formation. Exercising the legs and wearing support stockings improve venous flow. A further precautionary measure is to avoid assuming body positions that favor venous pooling. Antiembolism stockings of the proper fit and length should be used routinely in persons at risk for DVT. Another strategy used for immobile persons at risk for development of DVT is a sequential pneumatic compression device. This consists of a plastic sleeve that encircles the legs and provides alternating periods of compression on the lower extremity. When properly used, these devices enhance venous emptying to augment flow and reduce stasis.

The objectives of treatment of venous thrombosis are to prevent the formation of additional thrombi, prevent extension and embolization of existing thrombi, and minimize venous valve damage.[85] Anticoagulation therapy (i.e., warfarin and low-molecular-weight warfarin) is used to treat and prevent venous thrombosis (see Chapter 12). A 15- to 20-degree elevation of the legs prevents stasis. It is important that the entire lower extremity or extremities be carefully extended to avoid acute flexion of the knee or hip. Heat often is applied to the leg to relieve venospasm and to aid in the resolution of the inflammatory process. Bed rest usually is maintained until local tenderness and swelling have subsided. Gradual ambulation with elastic support is then permitted. Standing and sitting increase venous pressure and are to be avoided. Elastic support is needed for 3 to 6 months to permit recanalization and collateralization and to prevent venous insufficiency.

In summary, the storage function of the venous system renders it susceptible to venous insufficiency, stasis, and thrombus formation. Varicose veins occur with prolonged distention and stretching of the superficial veins owing to venous insufficiency. Varicosities can arise because of defects in the superficial veins (i.e., primary varicose veins) or because of impaired blood flow in the deep venous channels (i.e., secondary varicose veins). Venous insufficiency reflects chronic venous stasis resulting from valvular incompetence. It is associated with stasis dermatitis and stasis or venous ulcers. Venous thrombosis describes the presence of thrombus in a vein and the accompanying inflammatory response in the vessel wall. It is associated with vessel injury, stasis of venous flow, and hypercoagulability states. Thrombi can develop in the superficial or the deep veins (i.e., DVT). Thrombus formation in deep veins is a precursor to venous insufficiency and embolus formation.

REVIEW EXERCISES

1. The Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recommends that a person's HDL should be above 40 mg/dL.

A. Explain the role of HDL in prevention of atherosclerosis.

2. A 55-year-old man presents at the emergency department of his local hospital with complaints of excruciating, "ripping" pain in his upper back. He has a history of poorly controlled hypertension. His radial pulse and blood pressure, which on admission were 92 and 140/80 mm Hg, respectively, become unobtainable in both arms. A transesophageal echocardiogram reveals a dissection of

the descending aorta. Aggressive blood pressure control is initiated with the goal of reducing the systolic pressure and pulsatile blood flow (pulse pressure).

A. Explain how aortic dissection differs from a thoracic aorta aneurysm.
B. Explain the role of poorly controlled hypertension as an etiologic factor in dissecting aneurysms.
C. Why did his radial pulse and blood pressure become unobtainable?
D. Explain the need for aggressive control of aortic pressure and pulsatile blood flow.

3. A 34-year-old, otherwise healthy woman complains of episodes lasting several hours in which her fingers become pale and numb. This is followed by a period during which the fingers become red, throbbing, and painful.

A. What do you think is causing this woman's problem?
B. She relates that the episodes often occur when her fingers become cold or when she becomes upset. Explain the possible underlying mechanisms.
C. What types of measures could be used to treat this woman?

4. A 47-year-old black man who is an executive in a law firm has his blood pressure taken at a screening program and is told that his pressure is 142/90 mm Hg. His father and older brother have hypertension, and his paternal grandparents had a history of stroke and myocardial infarction. The patient enjoys salty foods and routinely uses a salt shaker to add salt to meals his wife prepares, drinks about four beers while watching television in the evening, and gained 15 pounds in the past year. Although his family has encouraged him to engage in physical activities with them, he states he is either too busy or too tired.

A. According to the JNC 7 guidelines, into what category does the patient's blood pressure fall?
B. What are his risk factors for hypertension?
C. Explain how an increased salt intake might contribute to his increase in blood pressure.
D. What lifestyle changes would you suggest to the patient? Explain the rationale for your suggestions.

5. A 36-year-old woman enters the clinic complaining of headache and not feeling well. Her blood pressure is 175/90 mm Hg. Her renal test results are abnormal, and follow-up tests confirm that she has a stricture of the left renal artery.

A. Would this woman's hypertension be classified as primary or secondary?
B. Explain the physiologic mechanisms underlying her blood pressure elevation.

6. A 75-year-old woman residing in an extended care facility has multiple health problems, including diabetes, hypertension, and heart failure. Lately, she has been feeling dizzy when she stands up, and she has almost fallen on several occasions. Her family is concerned and wants to know why this is happening and what they can do to prevent her from falling and breaking her hip.

A. How would you go about assessing this woman for orthostatic hypotension?
B. What are the causes of orthostatic hypotension in elderly persons?
C. How might this woman's medical conditions and their treatment contribute to her orthostatic hypotension?
D. The woman tells you that she feels particularly dizzy after she has eaten, yet staff members insist that she sit up and socialize with the other residents even though she would rather lie down and rest until the dizziness goes away. Explain the possible reason for her dizziness and what measures might be used to counteract the dizziness.
E. The woman recently had an episode of vomiting and diarrhea on an extremely hot day. She told her family that she was so dizzy that she was sure she would fall. Explain why her dizziness was more severe under these conditions and what might be done to alleviate the situation.

REFERENCES

1. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., 147–149, 487–520). Philadelphia: Saunders Elsevier.
2. Gottlieb A.I. (2008). Blood vessels. In Rubin R., Strayer D.S., et al. (Eds.), *Pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 387–426). Philadelphia: Lippincott Williams & Wilkins.
3. Deanfield J.E., Halcox J.P., Rabelink T.J. (2007). Endothelial function and dysfunction. *Circulation* 115, 1285–1295.
4. Hadi A.R., Carr C.S., Suwaldi A.S. (2005). Endothelial dysfunction: Cardiovascular risk factors, therapy, and outcome. *Vascular Health and Risk Management* 1(3), 183–198.
5. Guay A.T. (2007). ED2: Erectile dysfunction = endothelial dysfunction. *Endocrinology and Metabolic Clinics of North America* 36(2), 453–463.
6. Ridker P.M., Libby P. (2008). Risk factors for atherosclerotic disease. In Libby L., Bonow R.O., Mann D.L., et al. (Eds.), *Braunwald's heart disease* (8th ed., pp. 1003–1027). Philadelphia: Saunders Elsevier.
7. Smith C., Marks A.D., Lieberman M. (2005). *Basic medical biochemistry* (2nd ed., pp. 579–593, 619–653). Philadelphia: Lippincott Williams & Wilkins.
8. Moore K.J. (2006). Scavenger receptors in atherosclerosis: Beyond lipid uptake. *Atherosclerosis, Thrombosis, and Vascular Biology* 26, 1702–1711.
9. Oram J.F. (2002). ATP-binding cassette transporter A1 and cholesterol trafficking. *Current Opinions in Lipidology* 13, 373–381.
10. National Institute of Health Expert Panel. (2001). *Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood*

Cholesterol in Adults (Adult Treatment Panel III). NIH publication no. 01-3670. Bethesda, MD: National Institutes of Health.
11. Baron R.B. (2009). Lipid disorders. In: McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 1095–1106). New York: McGraw-Hill Medical.
12. Lau J.F., Smith D.A. (2008). Advanced lipoprotein testing: Recommendations based on current evidence. *Endocrinology and Metabolic Clinics of North America* 38, 1–21.
13. Fletcher B., Berra K., Ades P. (2005). Managing abnormal blood lipids. *Circulation* 112, 3184–3209.
14. Grundy S.M., Cleeman J.I., Merz C.N., et al. (2004). Implications of recent clinical trials for the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines. *Circulation* 110, 227–239.
15. Hansson G. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England of Medicine* 352(16), 1685–1695.
16. Lonn E., Yusuf S., Arnold M.J., et al. (2006). Homocysteine lowering with folic acid and B vitamins in vascular disease. *New England Journal of Medicine* 354, 1567–1577.
17. Libby P. (2008). The vascular pathology of atherosclerosis. In Libby L., Bonow R.O., Mann D.L., et al. (Eds.), *Braunwald's heart disease* (8th ed., pp. 985–1002). Philadelphia: Saunders Elsevier.
18. Insult W., Jr. (2009). The pathology of atherosclerosis: Plaque development and plaque responses to treatment. *American Journal of Medicine* 122, S3–S14.
19. Guillevin L., Dörner T. (2007). Vasculitis: Mechanisms involved and clinical manifestations. *Arthritis Research & Therapy* 9(suppl 2), 2–9.
20. Seo P., Stone J.H. (2007). Small-vessel and medium-vessel vasculitis. *Arthritis & Rheumatism* 57(9), 1552–1539.
21. Sontheimer D.L. (2006). Peripheral vascular disease: Diagnosis and treatment. *American Family Physician* 73, 1971–1976.
22. White C. (2007). Intermittent claudication. *New England Journal of Medicine* 356, 1241–1250.
23. Olin J.W. (2000). Thromboangiitis obliterans (Buerger's disease). *New England Journal of Medicine* 343, 864–869.
24. Bakst R., Merola J.E., Franks A.G., et al. (2008). Raynaud's phenomenon. *Journal American Academy of Dermatology* 59, 633–653.
25. Block J.A., Sequeira W. (2001). Raynaud's phenomenon. *Lancet* 357, 2042–2048.
26. Sakalihasen N. (2005). Abdominal aortic aneurysms. *Lancet* 365, 1577–1589.
27. Isselbacher E.M. (2005). Thoracic and abdominal aortic aneurysm. *Circulation* 111, 816–828.
28. Kamalakannan D., Rosman H.S., Eagle K.A. (2007). Acute aortic dissection. *Critical Care Clinics* 23, 779–800.
29. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 204–231). Philadelphia: Elsevier Saunders.
30. Grim C.E., Grim C.M. (2001). Accurate and reliable blood pressure measurement in the clinic and home: The key to hypertension control. In Hollenberg N. (Ed.), *Hypertension: Mechanisms and management* (3rd ed., pp. 315–324). Philadelphia: Current Medicine.
31. O'Brien E. (1996). Review: A century of confusion; which bladder for accurate blood pressure measurement? *Journal of Human Hypertension* 10, 565–572.
32. National Heart, Lung, and Blood Institute. (2003). *The seventh report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.* U.S. Department of Health and Human Services (NIH publication 03-5233). [Online] Available: www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf. Accessed June 25, 2009.
33. Victor R.G., Kaplan N.M. (2008). Systemic hypertension: Mechanisms and diagnosis. In Libby L., Bonow R. Mann D.L., et al. (Eds.), *Braunwald's heart disease* (8th ed., pp. 1027–1048). Philadelphia: Saunders Elsevier.
34. American Diabetes Association. (2009). Standards of medical care in diabetes: 2009. *Diabetes Care* 32(suppl 1), 28.
35. Griffith T.F., Klassen P.S., Franklin S.S. (2005). Systolic hypertension: An overview. *American Heart Journal* 149, 769–775.
36. Staesen J.A., Wang J., Bianchi G., et al. (2003). Essential hypertension. *Lancet* 361, 1629–1641.
37. Gadegbeku C.A., Lea J.P. (2005). Update on disparities in the pathophysiology and management of hypertension: Focus on African Americans. *Medical Clinics of North America* 89, 921–933.
38. Burt V.L., Whelton P., Rocella E.J., et al. (1995). Prevalence of hypertension in the US population: Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 25, 305–313.
39. Natali A., Ferrannini E. (2004). Hypertension, insulin resistance, and the metabolic syndrome. *Endocrine and Metabolic Clinics of North America* 33, 417–429.
40. Rodriguez-Iturbe B., Romero F., Johnson R.J. (2007). Pathophysiologic mechanisms of salt-dependent hypertension. *American Journal of Kidney Disease* 50(4), 655–672.
41. Katori M., Majima M. (2006). A missing link between high salt intake and blood pressure increase. *Journal of Pharmacological Sciences* 100, 370–390.
42. Mathieu P., Poirier P., Pibarot P., et al. (2009). Visceral obesity: The link among inflammation, hypertension, and cardiovascular disease. *Circulation* 53, 577–584.
43. Rahmouni K., Correla M.L.G., Haynes W.G., et al. (2005). Obesity-associated hypertension: New insights into mechanisms. *Hypertension* 45, 9–14.
44. Beilin L.J., Puddey I.B. (2006). Alcohol and hypertension: An update. *Hypertension* 47, 1035–1038.
45. Klatsky A.L., Freidman G.D., Siegelaub A.B. (1977). Alcohol consumption and blood pressure. *New England Journal of Medicine* 296, 1194–1200.
46. Onusko E. (2003). Diagnosing secondary hypertension. *American Family Physician* 67, 67–74.
47. Taler S.J. (2008). Secondary causes of hypertension. *Primary Care Clinics in Office Practice* 35, 489–500.
48. Safian R.D., Textor S.C. (2001). Renal-artery stenosis. *New England Journal of Medicine* 344, 431–444.
49. Prisant L.M., Szerlip H.M., Mulloy L.L. (2006). Fibromuscular dysplasia: An uncommon cause of secondary hypertension. *Journal of Clinical Hypertension* 81, 894–898.
50. Stern N., Tuck M. (2003). Pathology of adrenal cortical hypertension. In Izzo J.L., Black H.R. (Eds.), *Hypertension primer* (3rd ed., pp. 144–148). Dallas: American Heart Association.
51. Yu R., Nissen N.N., Chopra P., et al. (2009). Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007. *American Journal of Medicine* 122, 85–95.
52. Roa P.S. (1995). Coarctation of the aorta. *Seminars in Nephrology* 15, 87–105.
53. Kaplan N.M. (2008). Systemic hypertension: Therapy. In Libby L., Bonow R.O., Mann D.L., et al. (Eds.), *Braunwald's heart disease* (8th ed., pp. 1049–1070). Philadelphia: Elsevier Saunders.
54. Flanigan J.S., Vitberg D. (2006). Hypertensive emergency and severe hypertension: What to treat, who to treat, and how to treat. *Medical Clinics of North America* 90, 439–451.
55. Hebert C.J., Vidt D.G. (2008). Hypertensive crises. *Primary Care Clinics of Office Practice* 35, 475–487.
56. Gifford R.W., Jr. (Chair). (2000). *National High Blood Pressure Working Group report on high blood pressure in pregnancy.* NIH publication no. 00-3029. Bethesda, MD: National Institutes of Health.
57. Leeman L., Fontaine P. (2008). Hypertension in pregnancy. *American Family Physician* 78(1), 93–100.
58. Roberts J.M., Pearson G., Cutler J., et al. (2003). Summary of NHLBI working group on research on hypertension during pregnancy. *Hypertension* 41, 437–445.

59. Sibai B., Dekker G., Kupfemic M. (2005). Pre-eclampsia. *Lancet* 365, 785–799.
60. Solomon C.G., Seely E.W. (2006). Hypertension in pregnancy. *Endocrinology and Metabolism Clinics* 35, 157–171.
61. Luma G.B., Spiotta R.T. (2006). Hypertension in children and adolescents. *American Family Physician* 73, 1158–1168.
62. Mitsnefes M.M. (2006). Hypertension in children and adolescents. *Pediatric Clinics of North America* 53, 493–512.
63. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. (2004). The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114, 555–576.
64. National Center for Health Statistics. (2000). *2000 CDC growth charts: United States*. [Online] Available: www.cdc.gov/growthcharts. Accessed June 25, 2009.
65. Bernstein D. (2007). Systemic hypertension. In Behrman R.E., Kliegman R.M., Arvin A.M. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1988–1995). Philadelphia: Saunders Elsevier.
66. Maddens M., Imam K., Ashkar A. (2005). Hypertension in the elderly. *Primary Care Clinics in Office Practice* 32, 723–753.
67. Chobanian A.V. (2007). Isolated systolic hypertension in the elderly. *New England Journal of Medicine* 357(8), 789–796.
68. Dickerson L.M., Gibson M.V. (2005). Management of hypertension in older persons. *American Family Physician* 71, 469–476.
69. Smith J.J., Porth C.J.M. (1990). Age and the response to orthostatic stress. In Smith J.J. (Ed.), *Circulatory response to the upright posture* (pp. 121–138). Boca Raton, FL: CRC Press.
70. Mukai S., Lipsitz L.A. (2002). Orthostatic hypotension. *Clinics in Geriatric Medicine* 19, 253–268.
71. Bradley J.G., Davis K.A. (2003). Orthostatic hypotension. *American Family Physician* 68, 2393–2398.
72. Gupta V., Lipsitz L.A. (2007). Orthostatic hypotension in the elderly: Diagnosis and treatment. *American Journal of Medicine* 120, 841–847.
73. Jansen R.W.M.M., Lipsitz L.A. (1995). Postprandial hypotension: Epidemiology, pathophysiology, and clinical management. *Annals of Internal Medicine* 122, 286–295.
74. American Autonomic Society and American Academy of Neurologists. (1996). Consensus statement of the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 46, 1470.
75. Bergen J.J., Schmid-Schönein G.W., Smith P.D.C., et al. (2006). Chronic venous disease. *New England Journal of Medicine* 355(5), 485–498.
76. Rapp J.H., Sarkar R., Chang C.K. (2009). Blood vessel and lymphatic disorders. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 416–422). New York: McGraw-Hill Medical.
77. Jones R.H., Carek P.J. (2008). Management of varicose veins. *American Family Physician* 78(11), 1289–1294.
78. Eberhardt R.T., Raffeno J.D. (2005). Chronic venous insufficiency. *Circulation* 111, 2398–2409.
79. Nelson E.A., Cullun N., Jones J. (2006). Venous leg ulcers. *Clinical Evidence Concise* 15, 657–660.
80. López J.A., Kearon C., Lee A.Y.Y. (2004). Deep venous thrombosis. *Hematology* 2004, 439–455.
81. Wakefield T.W., Myers D.D., Henke P.K. (2008). Mechanisms of venous thrombosis and resolution. *Arteriosclerosis Thrombosis and Vascular Biology* 28, 387–391.
82. Virchow R. (1846). Weinere Untersuchungen uber die Verstropfung der Lungenrarterie und ihre Folgen. *Beitrage zur Experimentelle Pathologie und Physiologie* 2, 21.
83. Schurr J.H., Machin S.J., Bailey-King S., et al. (2001). Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights. *Lancet* 357, 1485–1489.
84. Wells P.S., Owen C., Doucette S., et al. (2006). Does this patient have deep vein thrombosis? *Journal of the American Medical Association* 295, 199–207.
85. Merti G.J. (2008). Treatment of venous thromboembolism. *American Journal of Medicine* 121(11A), 52.

Disorders of the Pericardium
Acute Pericarditis
Pericardial Effusion and Cardiac Tamponade
Constrictive Pericarditis
Coronary Artery Disease
Coronary Circulation
Pathogenesis of Coronary Artery Disease
Plaque Disruption and Thrombus Formation
Acute Coronary Syndrome
Electrocardiographic and Serum Biomarker Changes
Unstable Angina/Non–ST Elevation Myocardial Infarction
ST Elevation Myocardial Infarction
Chronic Ischemic Heart Disease
Chronic Stable Angina
Silent Myocardial Ischemia
Variant (Vasospastic) Angina
Diagnosis and Treatment
Cardiomyopathies
Primary Cardiomyopathies
Genetic Cardiomyopathies
Mixed (Genetic and Nongenetic) Cardiomyopathies
Acquired Cardiomyopathies
Secondary Cardiomyopathies
Endocardial and Valvular Disorders
Disorders Affecting the Endocardium
Infective Endocarditis
Rheumatic Heart Disease
Valvular Heart Disease
Hemodynamic Derangements
Mitral Valve Disorders
Aortic Valve Disorders
Diagnosis and Treatment
Heart Disease in Infants and Children
Fetal and Perinatal Circulation
Congenital Heart Defects
Anatomic and Hemodynamic Effects
Manifestations and Treatment
Types of Defects
Kawasaki Disease
Manifestations and Clinical Course
Diagnosis and Treatment

Chapter 19

Disorders of Cardiac Function

Heart disease affects persons of all ages and all walks of life. It is the leading cause of death in the United States[1] as well as other developed nations of the world. It accounts for approximately 30% of deaths worldwide including nearly 40% in high-income countries and about 28% in low- and middle-income countries.[2] Because of economic advances, social structures, and demographics, it is predicted that heart disease will become the leading cause of death worldwide by 2020, surpassing infectious diseases.[2]

In an attempt to focus on common heart problems that affect persons in all age groups, this chapter is organized into five sections: disorders of the pericardium, coronary artery disease, cardiomyopathies, endocardial and valvular disorders, and heart disease in infants and children.

Disorders of the Pericardium

The pericardium, sometimes referred to as the *pericardial sac,* is a double-layered fibroserous membrane that isolates the heart from other thoracic structures, maintains its position in the thorax, prevents it from overfilling, and serves as a barrier to infection. The pericardium consists of two layers: a thin inner layer, called the *visceral pericardium,* that adheres to the epicardium, and an outer fibrous layer, called the *parietal pericardium,* that is attached to the great vessels that enter and leave the heart (see Chapter 17, Fig. 17-15). The two layers of the pericardium are separated by a thin layer of serous fluid, which prevents frictional forces from developing as the heart contracts and relaxes. Although the fibrous tissue in the pericardium allows for moderate changes in cardiac size, it cannot stretch sufficiently to accommodate rapid dilation of the heart or accumulation of pericardial fluid without increasing pericardial and intracardiac pressures.

The pericardium is subject to many of the same pathologic processes (e.g., congenital disorders, infections, trauma, and immune mechanisms) that affect other structures of the body. Pericardial disorders frequently are associated with other diseases in the heart or surrounding structures (Chart 19-1).

CHART 19-1 Classification of Disorders of the Pericardium

Inflammation

Acute inflammatory pericarditis
- Infectious
  - Viral (echovirus, coxsackievirus, and others)
  - Bacterial (e.g., tuberculosis, *Staphylococcus, Streptococcus*)
  - Fungal
- Immune and collagen disorders
  - Rheumatic fever
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
- Metabolic disorders
  - Uremia and dialysis
  - Myxedema
- Ischemia and tissue injury
  - Myocardial infarction
  - Cardiac surgery
  - Chest trauma
- Physical and chemical agents
  - Radiation therapy
  - Untoward reactions to drugs, such as hydralazine, procainamide, and anticoagulants

Chronic inflammatory pericarditis
- Can be associated with most of the agents causing an acute inflammatory response

Neoplastic Disease
- Primary
- Secondary (e.g., carcinoma of the lung or breast, lymphoma)

Congenital Disorders
- Complete or partial absence of the pericardium
- Congenital pericardial cysts

Acute Pericarditis

Pericarditis is an inflammatory process of the pericardium. *Acute pericarditis*, defined as signs and symptoms resulting from a pericardial inflammation of less than 2 weeks' duration, may be infectious in origin or occur as the result of systemic disease. Viral infections (especially infections with coxsackieviruses and echoviruses) are the most common cause of pericarditis and probably are responsible for many cases of idiopathic or pericarditis of unknown etiology. Other causes of acute pericarditis include bacterial or mycobacterial infections, connective tissue diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), uremia, postcardiac surgery, neoplastic invasion of the pericardium, radiation, trauma, drug toxicity, and contiguous inflammatory processes of the myocardium or lung.[3,4]

As an inflammatory condition, acute pericarditis often is associated with increased capillary permeability. The capillaries that supply the serous pericardium become permeable, allowing plasma proteins, including fibrinogen, to leave the capillaries and enter the pericardial space. This results in an exudate that varies in type and amount according to the causative agent. Acute pericarditis frequently is associated with a fibrinous (fibrin-containing) exudate and heals by resolution or progresses to deposition of scar tissue and formation of adhesions between the layers of the serous pericardium.

The manifestations of acute pericarditis include a triad of chest pain, an auscultatory pericardial friction rub, and electrocardiographic (ECG) changes. The clinical findings may vary according to the causative agent. Nearly all persons with acute pericarditis have chest pain. The pain usually is sharp and abrupt in onset, occurring in the precordial area, and may radiate to the neck, back, abdomen, or side. Pain in the scapular area may be due to irritation of the phrenic nerve. The pain typically is worse with deep breathing, coughing, swallowing, and postural changes because of changes in venous return and cardiac filling. It is important that chest pain from pericarditis (which can be relieved by sitting and leaning forward) be differentiated from that of acute myocardial infarction or pulmonary embolism. A pericardial friction rub (heard through a stethoscope), often described as "leathery" or "close to the ear," results from the rubbing and friction between the inflamed pericardial surfaces.[4]

Diagnosis of acute pericarditis is based on clinical manifestations, ECG, chest radiography, and echocardiography. Treatment depends on the cause. When infection is present, antibiotics specific for the causative agent usually are prescribed. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may be given to minimize the inflammatory response and the accompanying undesirable effects.

Recurrent pericarditis can occur in up to 30% of persons with acute pericarditis who responded satisfactorily to treatment.[3] A minority of these develop recurrent bouts of pericardial pain, which can sometimes be chronic and debilitating. The process commonly is associated with autoimmune disorders, such as lupus erythematosus, rheumatoid arthritis, scleroderma, and myxedema, but may also occur following viral pericarditis. Treatment includes the use of anti-inflammatory medications such as NSAIDs, corticosteroids, or colchicine.

Pericardial Effusion and Cardiac Tamponade

Pericardial effusion refers to the accumulation of fluid in the pericardial cavity, usually as a result of an inflammatory or infectious process. It may also develop as the result of neoplasms, cardiac surgery, or trauma. Its major effect is compression of the heart chambers. The amount of fluid, the rapidity with which it accumulates, and the elasticity of the pericardium determine the effect that the effusion has on cardiac function. Small pericardial effusions may produce no symptoms or abnormal clinical findings. Even a large effusion that develops slowly may cause few or no symptoms, provided the pericardium is able to stretch and avoid compressing the heart. However, a sudden accumulation of even 200 mL may raise

intracardiac pressure to levels that seriously limit venous return of blood to the heart. Symptoms of cardiac compression also may occur with relatively small accumulations of fluid if the pericardium has become thickened by scar tissue or neoplastic infiltrations.

Pericardial effusion can lead to a condition called *cardiac tamponade,* in which there is compression of the heart due to the accumulation of fluid or blood in the pericardial sac. This life-threatening condition can be caused by bleeding into the pericardial sac after blunt or penetrating trauma, by rupture of the heart following myocardial infarction, as a complication of percutaneous cardiac procedures or device placement, or from retrograde bleeding during aortic dissection.[3,4] Cardiac tamponade results in increased intracardiac pressure, progressive limitation of ventricular diastolic filling, and reductions in stroke volume and cardiac output. The severity of the condition depends on the amount of fluid present and the rate at which it accumulates. The rapid accumulation of fluid results in an elevated central venous pressure, jugular vein distention, a fall in systolic blood pressure, narrowed pulse pressure, and signs of circulatory shock. The heart sounds may become difficult to hear because of the insulating effects of the pericardial fluid and reduced cardiac function. Persons with slowly developing cardiac tamponade usually appear acutely ill, but not to the extreme seen in those with rapidly developing tamponade.

A significant accumulation of fluid in the pericardium results in increased sympathetic nervous system stimulation, which leads to tachycardia and increased cardiac contractility. A key diagnostic finding in cardiac tamponade is *pulsus paradoxus,* or an exaggeration of the normal variation in the systolic blood pressure, commonly defined as a 10-mm Hg or more fall in the systolic blood pressure, that occurs with respiration.[3,4] Normally, the decrease in intrathoracic pressure that occurs during inspiration accelerates venous flow, increasing right atrial and right ventricular filling. This causes the interventricular septum to bulge to the left, producing a slight decrease in left ventricular filling, stroke volume output, and systolic blood pressure. In cardiac tamponade, the left ventricle is compressed from within by movement of the interventricular septum and from without by fluid in the pericardium (Fig. 19-1). This produces a marked decrease in left ventricular filling and left ventricular stroke volume output, often within a beat of the beginning of inspiration.

The echocardiogram is a rapid, accurate, and widely used method of evaluating pericardial effusion. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful adjuncts to echocardiography in cardiac tamponade. The ECG often reveals nonspecific T-wave changes and low QRS voltage. Usually only moderate to large effusions can be detected by chest radiography.

Treatment of pericardial effusions depends on the progression to cardiac tamponade. In small pericardial effusions or mild cardiac tamponade, NSAIDs, colchicine, or corticosteroids may minimize fluid accumulation. Pericardiocentesis, or removal of fluid from the pericardial sac, often with the aid of echocardiography, is the initial

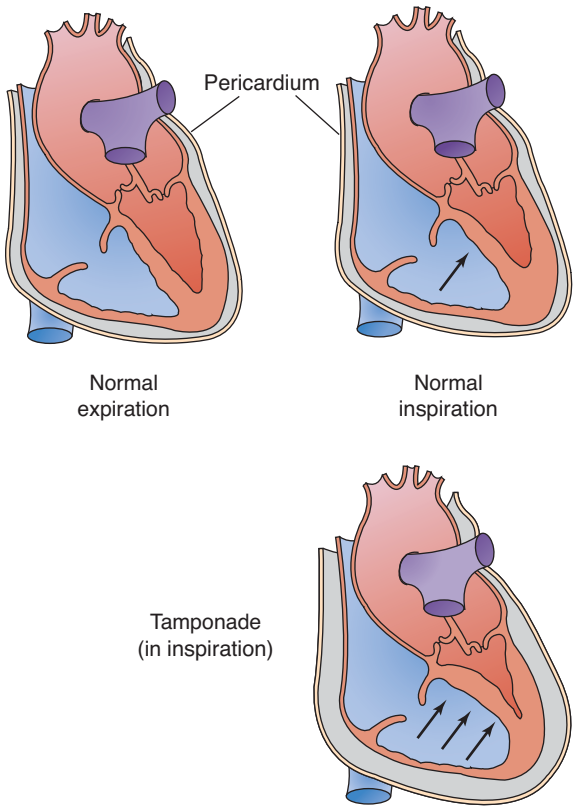


FIGURE 19-1. Effects of respiration and cardiac tamponade on ventricular filling and cardiac output. During inspiration, venous flow into the right heart increases, causing the interventricular septum to bulge into the left ventricle. This produces a decrease in left ventricular volume, with a subsequent decrease in stroke volume output. In cardiac tamponade, the fluid in the pericardial sac produces further compression of the left ventricle, causing an exaggeration of the normal inspiratory decrease in stroke volume and systolic blood pressure.

treatment of choice. Closed pericardiocentesis, which is performed with a needle inserted through the chest wall, may be an emergency lifesaving measure in severe cardiac tamponade. Open pericardiocentesis may be used for recurrent or loculated effusions (i.e., those confined to one or more pockets in the pleural space), during which biopsies can be obtained and pericardial windows created. Aspiration and laboratory evaluation of the pericardial fluid may be used to identify the causative agent.

Constrictive Pericarditis

In constrictive pericarditis, fibrous scar tissue develops between the visceral and parietal layers of the serous pericardium. In time, the scar tissue contracts and interferes with diastolic filling of the heart, at which point cardiac output and cardiac reserve become fixed. It is most commonly associated with inflammation resulting from infections, mediastinal radiation, or cardiac surgical trauma.

The condition is characterized by high venous pressure, low cardiac output, small pulse pressure, and fluid retention.[5] Ascites is a prominent early finding and may be accompanied by pedal edema, dyspnea on exertion,

and fatigue. The jugular veins also are distended. The Kussmaul sign is an inspiratory distention of the jugular veins caused by the inability of the right atrium, encased in its rigid pericardium, to accommodate the increase in venous return that occurs with inspiration. Exercise intolerance, muscle wasting, and weight loss develop in end-stage constrictive pericarditis. Surgical removal or resection of the pericardium (i.e., pericardiectomy) is often the treatment of choice.

In summary, disorders of the pericardium include acute and chronic pericarditis, pericardial effusion and cardiac tamponade, and constrictive pericarditis. The major threat of pericardial disease is compression of the heart chambers. Acute pericarditis may be infectious in origin or it may be due to systemic diseases. It is characterized by chest pain, ECG changes, and pericardial friction rub. Recurrent pericarditis is usually associated with autoimmune disorders, and symptoms may be minimal. Pericardial effusion, either acute or chronic, refers to the presence of an exudate in the pericardial cavity. It can increase intracardiac pressure, compress the heart, and interfere with venous return to the heart. The amount of exudate, the rapidity with which it accumulates, and the elasticity of the pericardium determine the effect the effusion has on cardiac function. Cardiac tamponade represents a life-threatening compression of the heart resulting from excess fluid in the pericardial sac. In constrictive pericarditis, scar tissue develops between the visceral and parietal layers of the serous pericardium. In time, the scar tissue contracts and interferes with cardiac filling.

Coronary Artery Disease

The term *coronary artery disease* (CAD) describes heart disease caused by impaired coronary blood flow. Diseases of the coronary arteries can cause a spectrum of disorders ranging from myocardial ischemia and angina to myocardial infarction or heart attack, conduction defects, heart failure, and sudden death.

Coronary Circulation

The blood vessels of the heart comprise the coronary arteries and coronary veins, which carry blood to and from most of the myocardium (Fig. 19-2). The blood vessels of the heart, normally embedded in fat, travel across the surface of the heart just under the epicardium. There are two main coronary arteries, the left and the right, which arise from the coronary sinus just above the aortic valve.[6–8] The left coronary artery extends for approximately 3.5 cm as the *left main coronary artery* and then divides into the left anterior descending and circumflex branches. The *left anterior descending artery* passes down through the groove between the two ventricles, giving off diagonal branches, which supply the anterior wall of the left ventricle, and perforating branches, which supply the anterior portion of the interventricular septum and the anterior papillary muscle of the left ventricle. The *circumflex branch* of the left coronary artery passes to the left and moves posteriorly in the groove that separates the left atrium and ventricle, giving off branches that supply the left lateral wall of the left ventricle. The *right coronary artery* lies in the right atrioventricular groove, and its branches supply the right ventricle. The right coronary artery usually moves to the back of the heart, where it

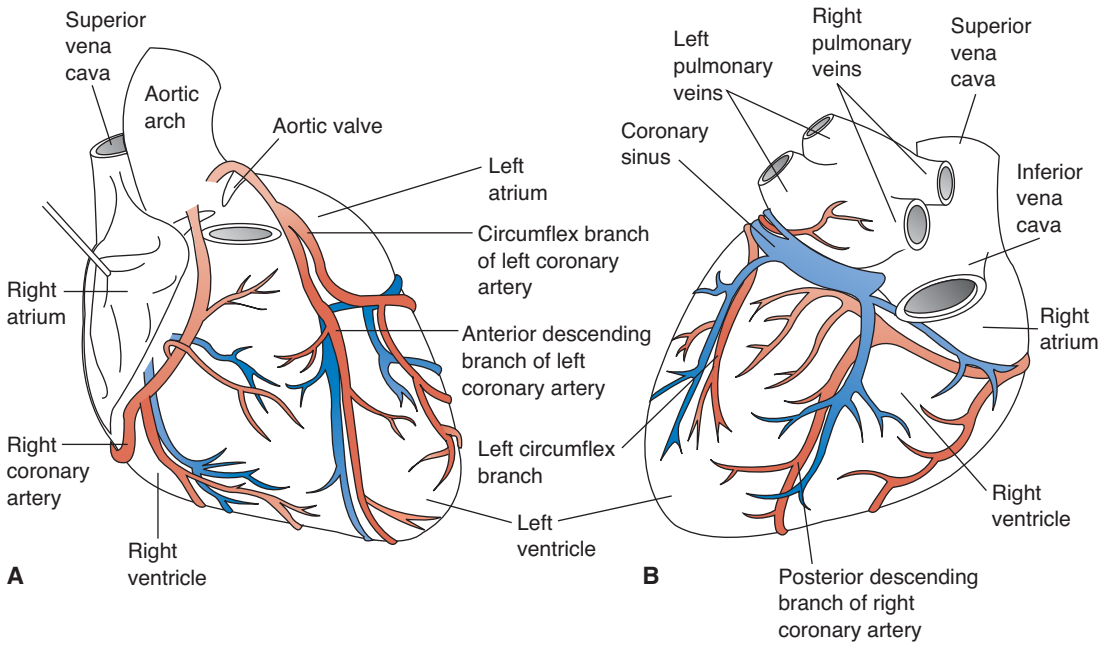


FIGURE 19-2. Coronary circulation. **(A)** Anterior view of the coronary arteries. **(B)** Posterior view of the coronary arteries and coronary sinus veins.

forms the *posterior descending artery,* which normally supplies the posterior portion of the heart, interventricular septum, sinoatrial (SA) and atrioventricular (AV) nodes, and posterior papillary muscle.

The large epicardial coronary arteries lie on the surface of the heart, with smaller intramyocardial arteries branching and penetrating the myocardium before merging with a network or plexus of subendocardial vessels. Although there are no connections between the large coronary arteries, there are anastomotic channels that join the small arteries. With gradual occlusion of the larger vessels, the smaller collateral vessels increase in size and provide alternative channels for blood flow. One of the reasons CAD does not produce symptoms until it is far advanced is that the collateral channels develop at the same time the atherosclerotic changes are occurring.

Blood flow in the coronary arteries is largely controlled by physical, metabolic, and neural factors. The openings for the coronary arteries originate in the root of the aorta just outside the aortic valve. Thus, the main factor controlling the perfusion pressure in the coronary arteries is the aortic blood pressure, which is generated by the heart itself. Myocardial blood flow, in turn, is largely regulated by the metabolic activity of the myocardium and autoregulatory mechanisms that control vessel dilation. In addition to generating the aortic pressure that moves blood through the coronary vessels, the contracting heart muscle influences its own blood supply by compressing the intramyocardial and subendocardial blood vessels during systole.

Coronary blood flow is usually regulated by the need of the cardiac muscle for oxygen. Even under normal resting conditions, the heart extracts and uses 60% to 80% of oxygen in blood flowing through the coronary arteries, compared with the 25% to 30% extracted by skeletal muscle.[6] Because there is little oxygen reserve in the blood, the coronary arteries must increase their flow to meet the metabolic needs of the myocardium during periods of increased activity. One of the major determinants of coronary blood flow is the metabolic activity of the heart muscle. Numerous substances, referred to as *metabolites,* are thought to act as mediators for the vasodilation that accompanies increased cardiac work. These substances, which include potassium ions, lactic acid, carbon dioxide, and adenosine, are released from working myocardial cells. Of these substances, adenosine appears to have the greatest vasodilator effect and is perhaps the critical mediator of local blood flow.[6]

The endothelial cells that line blood vessels, including the coronaries, play an active role in the control of blood flow. They function as a selective permeability barrier, which allows for the movement of small and large molecules from the blood to the tissues and from the tissues to the blood. They also synthesize several substances that, when released, can affect relaxation or constriction of the smooth muscle in the arterial wall. Potent vasodilators produced by the endothelium include nitric oxide, prostacyclin, and endothelium-dependent hyperpolarizing factor (EDHF). The most important of these is nitric oxide (see Chapter 18). Most vasodilators and vasodilating stimuli exert their effects through nitric oxide. Products from aggregating platelets, thrombin, the products of mast cells, and increased shear force, which is responsible for so-called flow-mediated vasodilation, stimulate the synthesis and release of nitric oxide.[7] The endothelium also is the source of endothelium-dependent constricting factors, the best known of which are the endothelins.

Pathogenesis of Coronary Artery Disease

Atherosclerosis (discussed in Chapter 18) is by far the most common cause of CAD. Atherosclerosis can affect one or all three of the major epicardial coronary arteries and their branches. Clinically significant lesions may be located anywhere in these vessels, but tend to predominate in the first several centimeters of the left anterior descending and left circumflex or the entire length of the right coronary artery.[8] Sometimes the major secondary branches also are involved.

Coronary heart disease is commonly divided into two types of disorders: the acute coronary syndromes and chronic ischemic heart disease. The acute coronary syndromes represent the spectrum of acute CAD ranging from unstable angina to myocardial infarction that is caused by acute plaque disruption, whereas chronic ischemic heart disease is caused by atherosclerotic or vasospastic obstruction of the coronary arteries.

Plaque Disruption and Thrombus Formation

Stable Versus Unstable Plaques. There are two types of atherosclerotic lesions: (1) the *fixed* or *stable plaque*, which obstructs blood flow, and (2) the *unstable* or *vulnerable plaque*, which can rupture and cause platelet adhesion and thrombus formation. The fixed or stable plaque is commonly implicated in stable angina and the unstable plaque in unstable angina and myocardial infarction (MI). In most cases the myocardial ischemia underlying unstable angina and acute MI is precipitated by plaque disruption, followed by thrombosis. The major determinants of plaque vulnerability to disruption include the size of its lipid-rich core, lack of stabilizing smooth muscle cells, presence of inflammation with plaque degradation, and stability and thickness of its fibrous cap[8,9] (Fig. 19-3). Plaques with a thin fibrous cap overlying a large lipid core are at high risk of rupture.

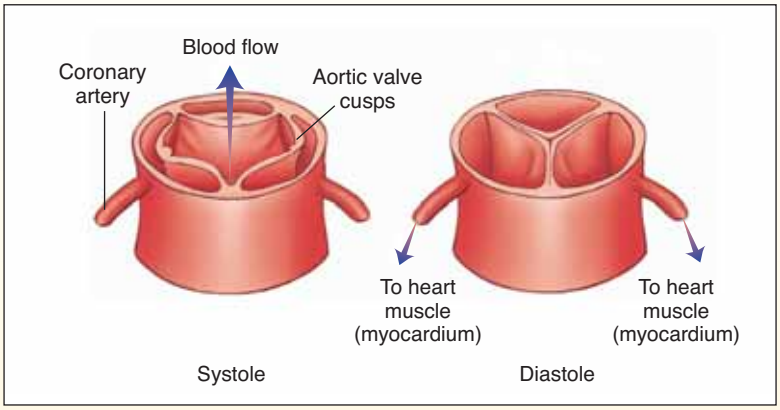
Although plaque disruption may occur spontaneously, it is often triggered by hemodynamic factors such as blood flow characteristics and vessel tension. For example, a sudden surge of sympathetic activity with an increase in blood pressure, heart rate, force of cardiac contraction, and coronary blood flow is thought to increase the risk of plaque disruption.[8] Indeed, many people with myocardial infarction report a trigger event, most often emotional stress or physical activity. Plaque disruption also has a diurnal variation, occurring most frequently during the first hour after arising, suggesting that physiologic factors such as surges in coronary artery tone and blood pressure may promote atherosclerotic

UNDERSTANDING → Myocardial Blood Flow

Blood flow in the coronary vessels that supply the myocardium is influenced by (1) the aortic pressure, (2) autoregulatory mechanisms, and (3) compression of the intramyocardial vessels by the contracting heart muscle.

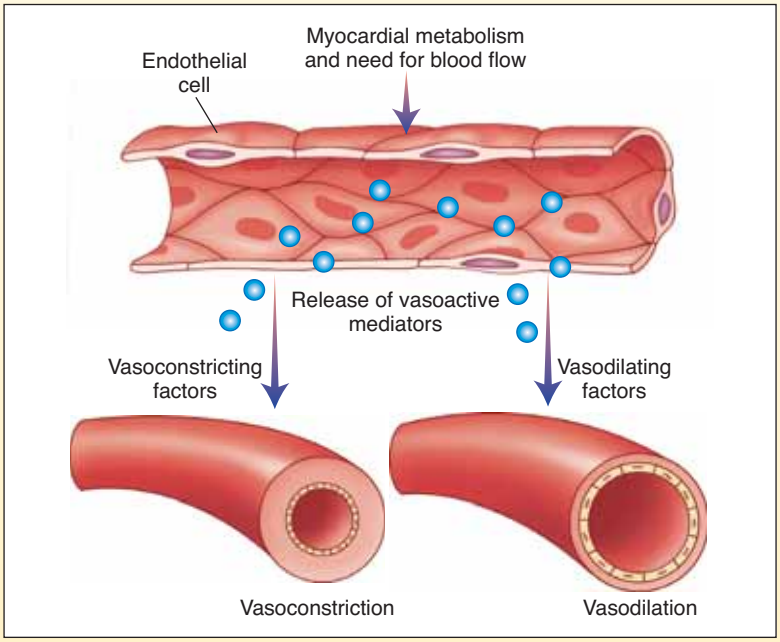
1

Aortic Pressure. The two main coronary arteries that supply blood flow to the myocardium arise in the sinuses behind the two cusps of the aortic valve. Because of their location, the pressure and flow of blood in the coronary arteries reflects that of the aorta. During systole, when the aortic valve is open, the velocity of blood flow and position of the valve cusps cause the blood to move rapidly past the coronary artery inlets, and during diastole, when the aortic valve is closed, blood flow and the aortic pressure are transmitted directly into the coronary arteries.



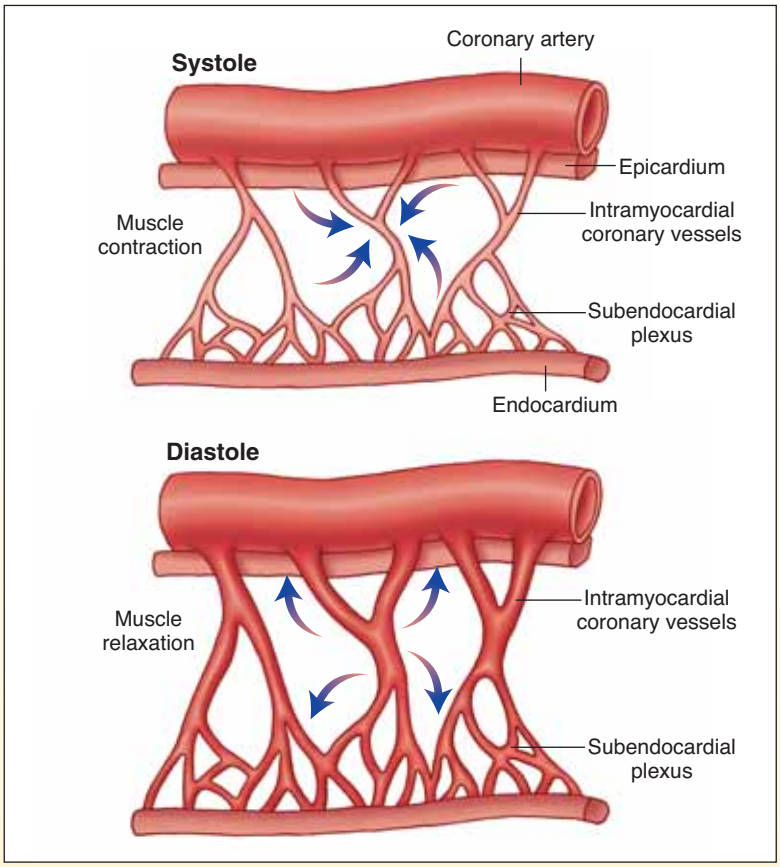
2

Autoregulatory Mechanisms. The heart normally extracts 60% to 80% of the oxygen in the blood delivered to it, leaving little in reserve. Accordingly, oxygen delivery during periods of increased metabolic demand depends on autoregulatory mechanisms that regulate blood flow through a change in vessel tone and diameter. During increased metabolic demand, vasodilation produces an increase in blood flow; during decreased demand, vasoconstriction or return of vessel tone to normal produces a reduction in flow. The mechanisms that link the metabolic activity of the heart to changes in vessel tone result from vasoactive mediators released from myocardial cells and the vascular endothelium.



3

Vessel Compression. The large coronary arteries lie on the epicardial surface of the heart, with the smaller intramyocardial vessels branching off and moving through the myocardium before merging with a plexus of vessels that supply the subendocardial muscle with blood. During systole, the contracting cardiac muscle has a squeezing effect on the intramyocardial vessels while at the same time producing an increase in intraventricular pressure that pushes against and compresses the subendocardial vessels. As a result, blood flow to the subendocardial muscle is greatest during diastole. Because the time spent in diastole becomes shortened as the heart rate increases, myocardial blood flow can be greatly reduced during sustained periods of tachycardia.



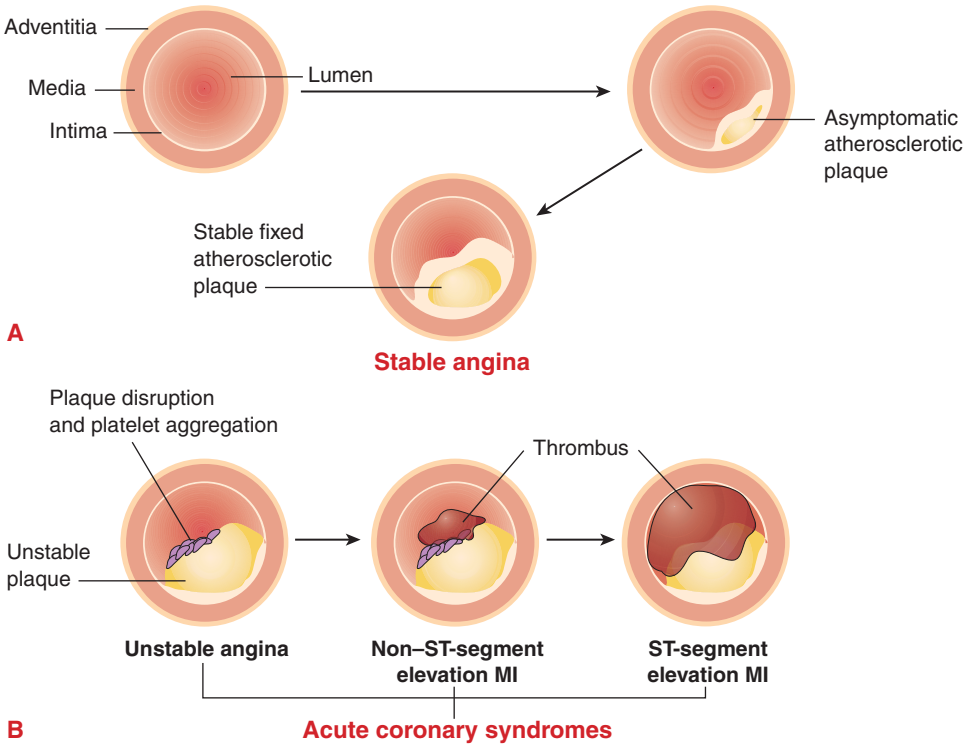


FIGURE 19-3. Atherosclerotic plaque. **(A)** Stable fixed atherosclerotic plaque in stable angina and **(B)** unstable plaque with plaque disruption and platelet aggregation in the acute coronary syndromes.

Coronary Artery Disease

- The term *coronary artery disease* refers to disorders of myocardial blood flow due to stable or unstable coronary atherosclerotic plaques.
- Unstable atherosclerotic plaques tend to fissure or rupture, causing platelet aggregation and potential for thrombus formation with production of a spectrum of acute coronary syndromes of increasing severity, ranging from unstable angina, to non–ST-segment elevation myocardial infarction, to ST-segment elevation myocardial infarction.
- Stable atherosclerotic plaques produce fixed obstruction of coronary blood flow with myocardial ischemia occurring during periods of increased metabolic need, such as in stable angina.

plaque disruption and subsequent platelet deposition.[8] It has been suggested that the sympathetic nervous system is activated on arising, resulting in changes in platelet aggregation and fibrinolytic activity that tend to favor plaque disruption and thrombosis.

Thrombosis and Vessel Occlusion. Local thrombosis occurring after plaque disruption results from a complex interaction among its lipid core, smooth muscle cells, macrophages, and collagen. The lipid core provides a stimulus for platelet aggregation and thrombus formation.[8] Both smooth muscle and foam cells in the lipid core contribute to the expression of tissue factor in unstable plaques. Once exposed to blood, tissue factor initiates the extrinsic coagulation pathway, resulting in the local generation of thrombin and deposition of fibrin (see Chapter 12).

Platelets play an important role in linking plaque disruption to acute CAD. As a part of the response to plaque disruption, platelets adhere to the endothelium and release substances (i.e., adenosine diphosphate [ADP], thromboxane A_2, and thrombin) that promote further aggregation of platelets and thrombus formation. The platelet membrane, which contains glycoprotein receptors that bind fibrinogen and link platelets together, contributes to thrombus formation. Platelet adhesion and aggregation occurs in several steps. First, release of ADP, thromboxane A_2, and thrombin initiates the aggregation process. Second, glycoprotein IIb/IIIa receptors on the platelet surface are activated. Third, fibrinogen binds to the activated glycoprotein receptors, forming bridges between adjacent platelets.

Acute Coronary Syndrome

The acute coronary syndromes (ACSs) represent a spectrum of acute ischemic heart diseases ranging from unstable ischemia to acute MI. Acute coronary syndromes are classified based on the presence or absence of an ST-segment elevation on the ECG.[10–12] This allows for immediate classification of risk and guides whether a person should be considered for acute reperfusion therapy. The evaluation of serum biomarkers is then used to determine whether MI has occurred.

Electrocardiographic and Serum Biomarker Changes

Electrocardiographic Changes. The classic ECG changes that occur with ACS include T-wave inversion, ST-segment elevation, and development of an abnormal Q wave[10–12] (Fig. 19-4). These changes may not be present immediately after the onset of symptoms and vary considerably depending on the duration of the ischemic event (acute versus evolving), its extent (subendocardial versus transmural), and its location (anterior versus inferior posterior). Because these changes usually occur over time and are seen on the ECG leads that view the involved area of the myocardium, provision for continuous and serial 12-lead ECG monitoring is indicated.

The T wave and ST segment, which represent the repolarization phase of the cardiac action potential on the ECG, are usually the first to be involved during myocardial ischemia and injury.[13] As the involved area becomes ischemic, myocardial repolarization is altered, causing changes in the T wave. This is usually represented by T-wave inversion. ST-segment changes occur with ischemic myocardial injury. Normally, the ST segment of the ECG is nearly isoelectric (e.g., flat along the baseline) because all healthy myocardial cells attain the same potential during early repolarization. Acute severe ischemia reduces the resting membrane potential and shortens the duration of the action potential in the ischemic area. These changes create a voltage difference between the normal and ischemic areas of the myocardium that leads to a so-called "current of injury" between these regions. It is these currents of injury that are represented as a deviation of the ST segment on the ECG. When the acute injury is transmural, the overall ST vector is shifted in the direction of the outer epicardium, resulting in an elevation of the ST segment (see Fig. 19-5). When the injury is confined primarily to the subendocardium, the ST vector is shifted toward the inner ventricular layer, resulting in an overall depression of the ST segment.

Additional ventricular depolarization (QRS) changes may follow the T-wave and ST-segment abnormalities.[10,13] With actual infarction, depolarization (QRS) changes often follow the T-wave and ST-segment abnormalities. With Q-wave infarction, abnormal Q waves develop because there is no depolarizing current conduction from the necrotic tissue.

Serum Biomarkers. Serum biomarkers for ACS include cardiac-specific troponin I (TnI) and troponin T (TnT), myoglobin, and creatine kinase MB (CK-MB).[11,12] As the myocardial cells become necrotic, their intracellular contents begin to diffuse into the surrounding interstitium and then into the blood. The rate at which the enzymes appear in the blood depends on their intracellular location, their

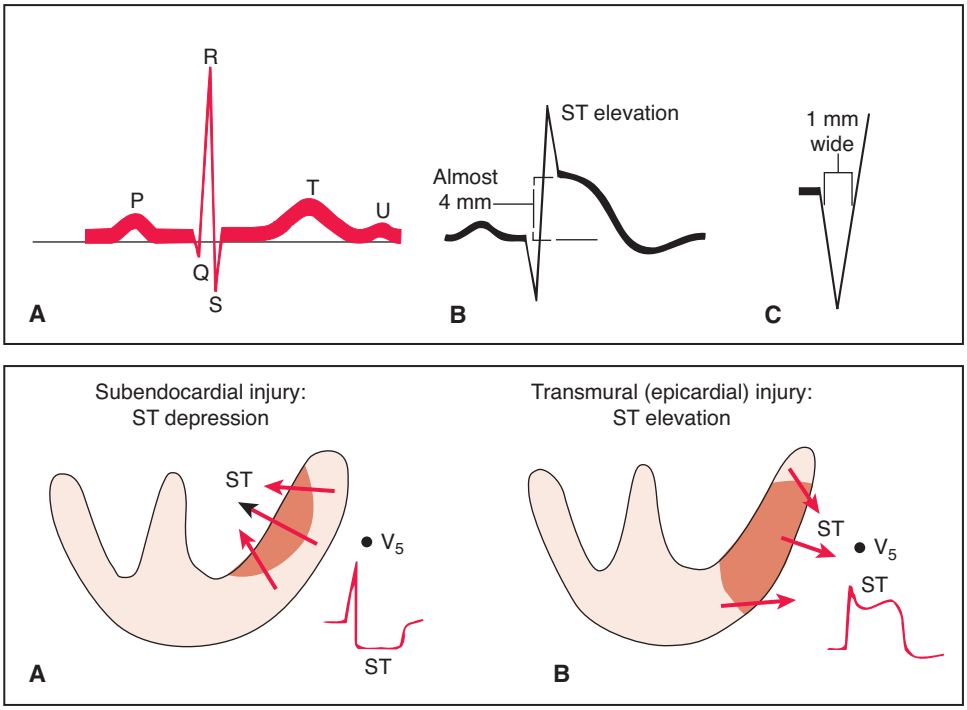


FIGURE 19-4. (*Top*) **(A)** Electrocardiogram tracing showing normal P, Q, R, S, and T waves. **(B)** ST-segment elevation with acute ischemia. **(C)** Q wave with acute myocardial infarction. (*Bottom*) Current-of-injury patterns with acute ischemia. **(A)** With predominant subendocardial ischemia, the resultant ST segment is directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore record ST-segment depression. **(B)** With ischemia involving the outer ventricular layer (transmural or epicardial injury), the ST vector is directed outward. Overlying leads record ST-segment elevation. (*Bottom* from Zipes D.P., Bonow R.O., Mann D.L., et al. [Eds.]. [2008]. *Heart disease: A textbook of cardiovascular medicine* [8th ed., p. 174]. Philadelphia: Saunders Elsevier.)

molecular weight, and local blood flow. For example, they may appear at an earlier-than-predicted time in patients who have undergone successful reperfusion therapy.

The *troponin assays* have high specificity for myocardial tissue and have become the primary biomarker tests for the diagnosis of MI. The troponin complex, which is part of the actin filament, consists of three subunits (i.e., TnC, TnT, and TnI) that regulate the calcium-mediated actin–myosin contractile process in striated muscle (see Chapter 1, Fig. 1-19). TnI and TnT, which are present in cardiac muscle, begin to rise within 3 hours after the onset of myocardial infarction and may remain elevated

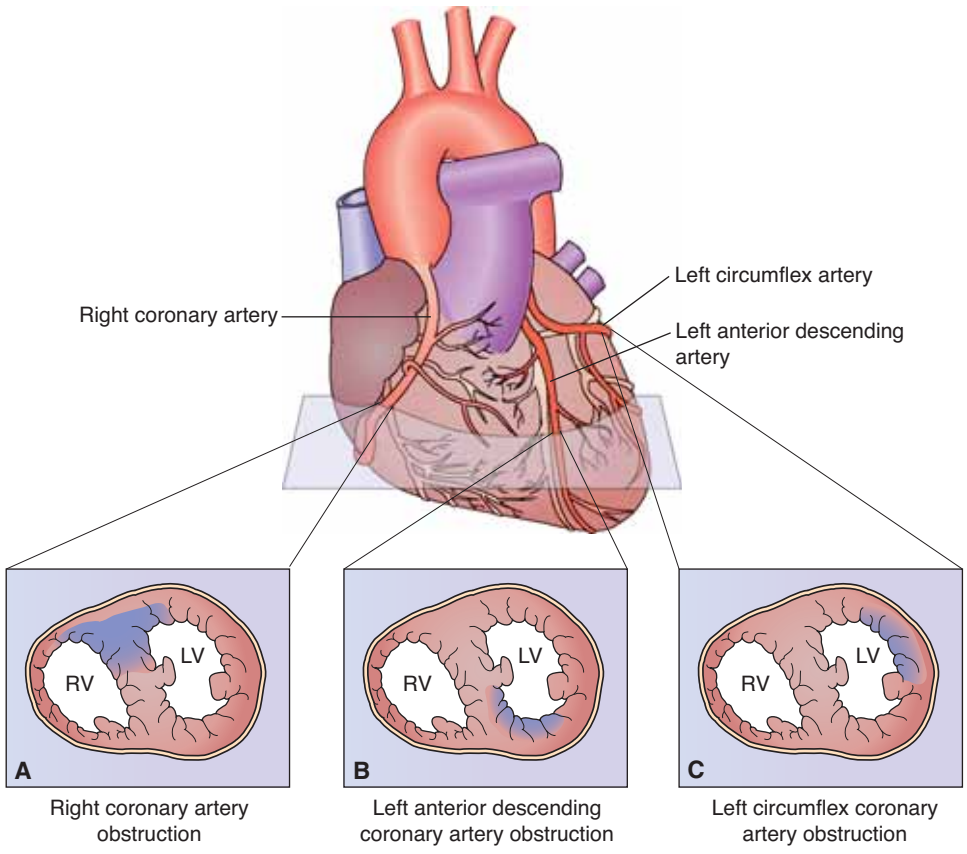


FIGURE 19-5. Areas of the heart affected by occlusion of the **(A)** right coronary artery, **(B)** left anterior descending coronary artery, and **(C)** left circumflex coronary artery. LV, left ventricle; RV, right ventricle.

for 7 to 10 days after the event. This is especially useful in the late diagnosis of MI.[11]

Creatine kinase is an intracellular enzyme found in muscle cells. There are three isoenzymes of CK, with the MB isoenzyme being highly specific for injury to myocardial tissue. Serum levels of CK-MB exceed normal ranges within 4 to 8 hours of myocardial injury and decline to normal within 2 to 3 days.[11] *Myoglobin* is an oxygen-carrying protein, similar to hemoglobin, that is normally present in cardiac and skeletal muscle. It is a small molecule that is released quickly from infarcted myocardial tissue and becomes elevated within 1 hour after myocardial cell death, with peak levels reached within 4 to 8 hours.[11] Because myoglobin is present in both cardiac and skeletal muscle, it is not cardiac specific.

Unstable Angina/Non–ST Elevation Myocardial Infarction

Unstable angina/non–ST elevation myocardial infarction (UA/NSTEMI) is considered to be a clinical syndrome of myocardial ischemia ranging from angina to myocardial infarction.[12,14] Typically, unstable angina and NSTEMI differ in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of serum cardiac markers. Persons who have no evidence of serum markers for myocardial damage are considered to have unstable angina, whereas a diagnosis of NSTEMI is indicated if a serum marker of myocardial injury is present.

The pain associated with unstable angina typically has a persistent and severe course and is characterized by at least one of three features: (1) it occurs at rest (or with minimal exertion), usually lasting more than 20 minutes (if not interrupted by nitroglycerin); (2) it is severe and described as frank pain and of new onset (i.e., within 1 month); and (3) it is more severe, prolonged, or frequent than previously experienced.[14]

Unstable angina/NSTEMI is classified as low, intermediate, or high risk for acute MI, based on the clinical history, ECG pattern, and serum biomarkers. The ECG pattern in NSTEMI may demonstrate normal or ST-segment depression (or transient ST-segment elevation) and T-wave changes. The degree of ST-segment deviation has been shown to be an important measure of ischemia and prognosis.

ST Elevation Myocardial Infarction

Acute ST elevation MI (STEMI), also known as *heart attack*, is characterized by the ischemic death of myocardial tissue associated with atherosclerotic disease of the coronary arteries. The area of infarction is determined by the coronary artery that is affected and by its distribution of blood flow (Fig. 19-5).

The onset of STEMI usually is abrupt, with chest pain as the significant symptom. The pain typically is severe and crushing, often described as being constricting, suffocating, or like "someone sitting on my chest." It usually is substernal, radiating to the left arm, neck, or jaw, although it may be experienced in other areas of the chest. Unlike that of angina, the pain associated with MI is more prolonged and not relieved by rest or nitroglycerin, and narcotics frequently are required. Some persons may not describe it as "pain," but as "discomfort." Women often experience atypical ischemic-type chest pain, whereas the elderly may complain of shortness of breath more frequently than chest pain.[15]

Gastrointestinal complaints are common with acute MI. There may be a sensation of epigastric distress; nausea and vomiting may occur. These symptoms are thought to be related to the severity of the pain and vagal stimulation. The epigastric distress may be mistaken for indigestion, and the person may seek relief with antacids or other home remedies, which only delays getting medical attention. Complaints of fatigue and weakness, especially of the arms and legs, are common. Pain and sympathetic stimulation combine to give rise to tachycardia, anxiety, restlessness, and feelings of impending doom. The skin often is pale, cool, and moist. Impairment of myocardial function may lead to hypotension and shock.

Sudden death from acute MI is death that occurs within 1 hour of symptom onset.[16] It usually is attributed to fatal arrhythmias, which may occur without evidence of infarction. Early hospitalization after onset of symptoms greatly improves the chances of averting sudden death because appropriate resuscitation facilities are immediately available should ventricular arrhythmia occur. The recent distribution of automatic external defibrillators in multiple public arenas highlights the importance of early defibrillation in the survival of patients with STEMI.

Pathologic Changes. The size and pattern of the infarct depends on the location and extent of occlusion, amount of heart tissue supplied by the vessel, duration of the occlusion, metabolic needs of the affected tissue, extent of collateral circulation, and other factors such as heart rate, blood pressure, and cardiac rhythm. An infarct may involve the endocardium, myocardium, epicardium, or a combination of these.[8] Transmural infarcts involve the full thickness of the ventricular wall and most commonly occur when there is obstruction of a single artery (Fig. 19-6). Subendocardial infarcts involve the inner one third to one half of the ventricular wall and occur more frequently in the presence of severely narrowed but still patent arteries.

The principal biochemical consequence of MI is the conversion from aerobic to anaerobic metabolism with inadequate production of energy to sustain normal myocardial function.[8] As a result, a striking loss of contractile function occurs within 60 seconds of onset.[8] Changes in cell structure (i.e., glycogen depletion and mitochondrial swelling) develop within several minutes. These early changes are reversible if blood flow is restored. Although gross tissue changes are not apparent for hours after the onset of MI, the ischemic area ceases to function within a matter of minutes, and damage to cells occurs in approximately 40 minutes. Irreversible myocardial cell death (necrosis) occurs after 20 to 40 minutes of severe ischemia.[8] The term *reperfusion* refers to the reestablishment of blood flow through

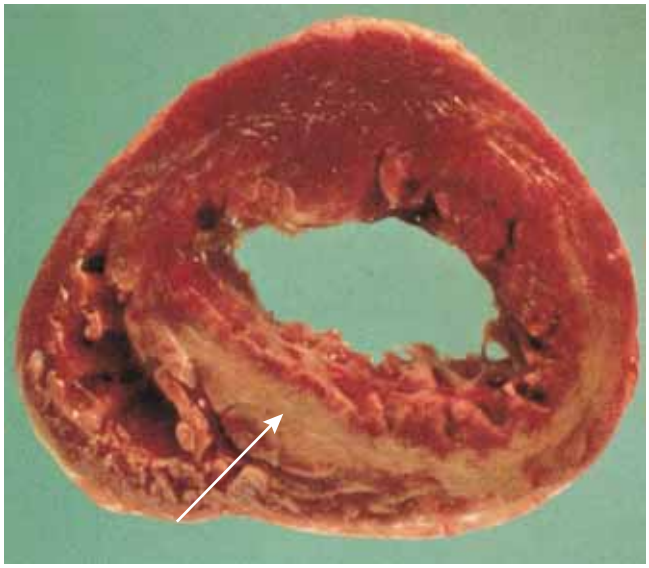


FIGURE 19-6. Acute myocardial infarct. A cross-section of the ventricles of a man who died a few days after the onset of severe chest pain shows a transmural infarct in the posterior and septal regions of the left ventricle. The necrotic myocardium is soft, yellowish, and sharply demarcated. (From Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 558]. Philadelphia: Lippincott Williams & Wilkins.)

the use of fibrinolytic therapy or revascularization procedures. Early reperfusion after onset of occlusion can prevent necrosis and improve myocardial perfusion in the infarct zone. Reperfusion after a longer interval can salvage some of the myocardial cells that would have died owing to longer periods of ischemia. It also may prevent the microvascular injury that occurs over a longer period. Even though much of the viable myocardium existing at the time of reflow, or reperfusion, ultimately recovers, critical abnormalities in biochemical function may persist, causing impaired ventricular function. The recovering area of the heart is often referred to as a *stunned myocardium*. Because myocardial function is lost before cell death occurs, a stunned myocardium may not be capable of sustaining life, and persons with large areas of dysfunctional myocardium may require life support until the stunned regions regain their function.[8]

Diagnosis and Treatment. Because the specific diagnosis of STEMI often is difficult to make at the time of entry into the health care system, the immediate management of unstable angina/NSTEMI and STEMI is generally the same.[11,12] The prognosis in ACS is largely related to the occurrences of two general complications—arrhythmias and mechanical complications (pump failure). The majority of deaths from ACS are due to the sudden development of ventricular fibrillation. Therefore, the major elements in management of persons with ACS are recognition of symptoms and prompt seeking of medical care; the prompt deployment of an emergency medical team capable of resuscitation procedures, including defibrillation; expeditious transport to a hospital equipped for managing arrhythmias and providing advanced cardiac life support; and expeditious implementation of reperfusion therapy.[16]

The emergency department goals for management of ACS include identification of persons who are candidates for reperfusion therapy. Evaluation of the person's chief complaint, typically chest pain, along with other associated symptoms is essential in differentiating ACS from other diagnoses. For any person presenting with symptoms of ACS, ECG monitoring should be instituted, and a 12-lead ECG performed. Commonly indicated treatment regimens include administration of oxygen, aspirin, nitrates, pain medications, antiplatelet and anticoagulant therapy, β-adrenergic blocking agents (beta blockers), and an angiotensin-converting enzyme (ACE) inhibitor.[12,16]

The administration of oxygen augments the oxygen content of inspired air and increases the oxygen saturation of hemoglobin. Arterial oxygen levels may fall precipitously after acute MI, and oxygen administration helps to maintain the oxygen content of the blood perfusing the myocardial tissue. Platelets play a major role in the thrombotic response to atherosclerotic plaque disruption; therefore, inhibition of platelet aggregation is an important aspect in the early treatment of both unstable angina/NSTEMI and STEMI. Aspirin (i.e., acetylsalicylic acid) is the preferred antiplatelet agent for preventing platelet aggregation in persons with ACS. Aspirin, which acts by inhibiting synthesis of the prostaglandin thromboxane A_2, is thought to promote reperfusion and reduce the likelihood of rethrombosis. For patients who are unable to take aspirin because of hypersensitivity or gastrointestinal intolerance, clopidogrel may be prescribed. Clopidogrel exerts its effects by inhibiting the ADP pathway in platelets (see Chapter 12).

The severe pain of acute MI gives rise to anxiety and recruitment of autonomic nervous system responses, both of which increase the work demands on the heart.[16] Control of pain in acute MI is accomplished through a combination of nitrates, analgesics (e.g., morphine), and beta-blocking agents.[16] Nitroglycerin is given because of its vasodilating effect and ability to relieve coronary pain. The vasodilating effects of the drug decrease venous return (i.e., reduce preload) and arterial blood pressure (i.e., reduce afterload), thereby reducing oxygen consumption. Although a number of analgesic agents have been used to treat the pain of acute MI, morphine is usually the drug of choice.[10] It is commonly given intravenously because of the rapid onset of action. Beta blockers act as antagonists to β-receptor–mediated functions of the sympathetic nervous system and thus decrease myocardial oxygen demand by reducing heart rate, cardiac contractility, and systemic arterial blood pressure.

Immediate reperfusion therapy, through use of pharmacologic agents (fibrinolytic therapy), percutaneous coronary intervention, or coronary artery bypass grafting is usually indicated for persons with ECG evidence of STEMI. *Fibrinolytic drugs* dissolve blood and platelet clots and are used to reduce mortality, limit infarct size, encourage infarct healing and myocardial remodeling, and reduce the potential for life-threatening arrhythmias.[16] These agents interact with plasminogen to generate plasmin, which lyses fibrin clots and digests clotting factors V

and VIII, prothrombin, and fibrinogen (see Chapter 12). The person must be a low-risk candidate for complications caused by bleeding, with no intracranial hemorrhage or significant trauma within the last 3 months.[12]

Percutaneous coronary intervention (PCI) is indicated as an early invasive procedure for patients with unstable angina/NSTEMI.[17] PCI includes percutaneous transluminal coronary angioplasty (PTCA) and stent implantation. *Balloon PTCA* involves dilatation of a vessel containing a stenotic atherosclerotic plaque with an inflatable balloon (Fig. 19-7). The procedure is done under local anesthesia in the cardiac catheterization laboratory. This procedure is usually used in conjunction with the placement of stents and is now rarely used alone. The use of *coronary stenting* has been shown to improve short- and long-term outcomes compared with PTCA alone. Persons undergoing stent procedures are treated with antiplatelet and anticoagulant drugs to prevent thrombosis, which is a major risk of the procedure. The self-expanding wire mesh stents that were used initially had high thrombosis rates and have largely been replaced by balloon-expandable stents. Drug-eluting stents that provide sustained delivery of an antiproliferative pharmacologic agent may be used to decrease the risk of restenosis.[17]

Coronary artery bypass grafting (CABG) may be the treatment of choice for people with significant CAD who do not respond to medical treatment and who are not suitable candidates for PCI. It may also be indicated as an emergent treatment for STEMI, in which case the surgery should be done within 4 to 6 hours of symptom onset if possible. The procedure involves revascularization of the affected myocardium by placing a saphenous vein graft between the aorta and the affected coronary artery distal to the site of occlusion, or by using the internal mammary artery to revascularize the left anterior descending artery or its branches (Fig. 19-8). One to five distal anastomoses commonly are done. Emergent or urgent CABG, as a reperfusion strategy, is indicated in situations such as failed PCI with persistent pain or hemodynamic instability, or for patients who are not candidates for PCI or fibrinolytic therapy.[18]

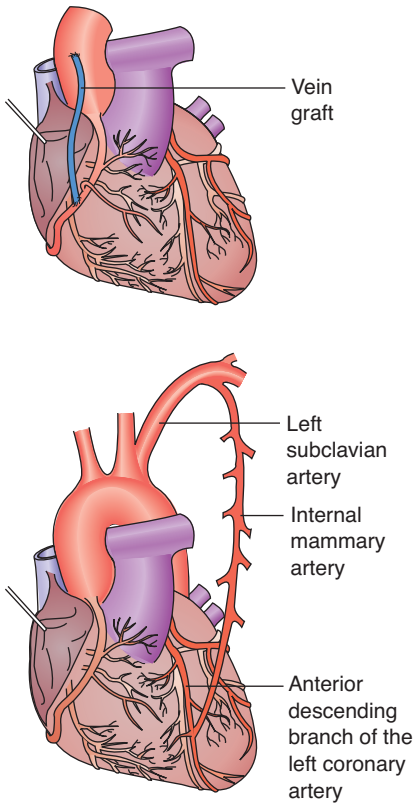


FIGURE 19-8. Coronary artery revascularization. (*Top*) Saphenous vein bypass graft. The vein segment is sutured to the ascending aorta and the right coronary artery at a point distal to the occluding lesion. (*Bottom*) Mammary artery bypass graft. The mammary artery is anastomosed to the anterior descending branch of the left coronary artery, bypassing the obstructing lesion.

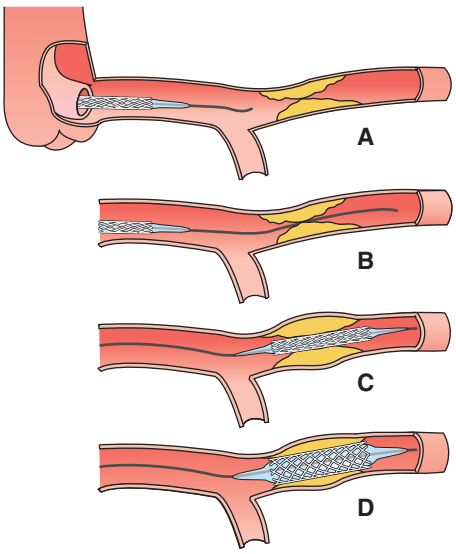


FIGURE 19-7. Balloon-expandable stent insertion. **(A)** Insertion of a guide catheter with a collapsed balloon-expandable stent mounted over a guide wire into a coronary artery. **(B)** Advancement of guide wire across the coronary lesion. **(C)** Positioning of the balloon-expandable stent across the lesion. **(D)** Balloon inflation with expansion of the stent. Once the stent is expanded, the balloon system is removed.

Myocardial Postinfarction Recovery Period. After a MI, there usually are three zones of tissue damage: a zone of myocardial tissue that becomes necrotic because of an absolute lack of blood flow; a surrounding zone of injured cells, some of which will recover; and an outer zone in which cells are ischemic and can be salvaged if blood flow can be reestablished. The boundaries of these zones may change with time after the infarction and with the success of treatment measures to reestablish blood flow. If blood flow can be restored within the 20- to 40-minute time frame, loss of cell viability does not occur or is minimal.[8] The progression of ischemic necrosis usually begins in the subendocardial area of the heart and extends through the myocardium to involve progressively more of the transmural thickness of the ischemic zone.

Myocardial cells that undergo necrosis are gradually replaced with scar tissue. An acute inflammatory response develops in the area of necrosis approximately 2 to 3 days

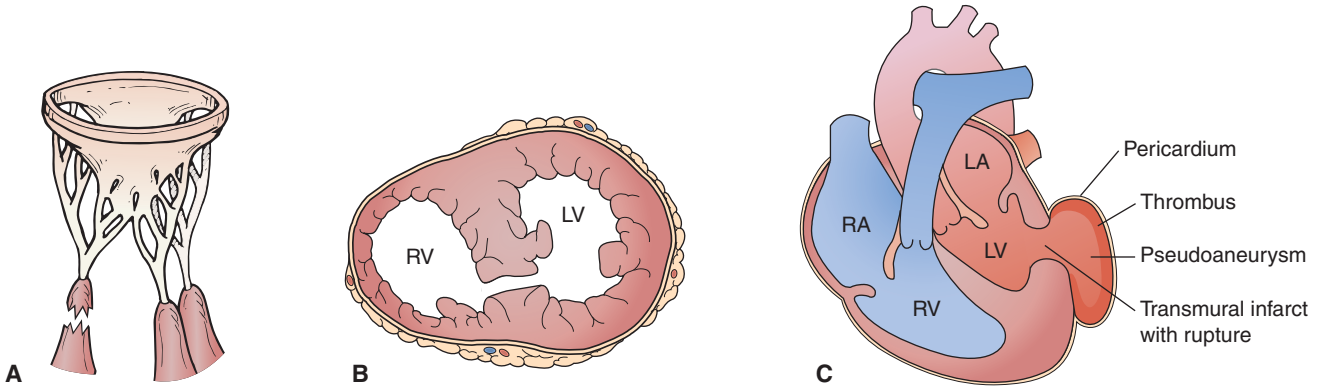


FIGURE 19-9. Acute mechanical complications of myocardial infarction. **(A)** Papillary muscle rupture. **(B)** Interventricular septum rupture. **(C)** Rupture of the free wall of the left ventricle with pseudoaneurysm formation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

after infarction.[8] Thereafter, macrophages begin removing the necrotic tissue; the damaged area is gradually replaced with an ingrowth of highly vascularized granulation tissue, which gradually becomes less vascular and more fibrous in composition. At approximately 3 to 7 days, the center of the infarcted area is soft and yellow; if rupture of the ventricle, interventricular septum, or valve structures occurs, it usually happens at this time. Replacement of the necrotic myocardial tissue usually is complete by the seventh week. Areas of the myocardium that have been replaced with scar tissue lack the ability to contract and initiate or conduct action potentials.

The stages of recovery from STEMI are closely related to the size of the infarct and the changes that have taken place in the infarcted area. Fibrous scar tissue lacks the contractile, elastic, and conductive properties of normal myocardial cells; the residual effects and the complications are determined essentially by the extent and location of the injury. Among the complications of STEMI are life-threatening arrhythmias, pericarditis, stroke, thromboemboli, and mechanical defects (e.g., mitral valve regurgitation, ventricular septal rupture, left ventricular wall rupture, and left ventricular aneurysm). Depending on its severity, MI has the potential for compromising the pumping action of the heart. Heart failure and cardiogenic shock are dreaded complications of MI (see Chapter 20).

Pericarditis tends to occur in patients with large infarcts, a lower ejection fraction, and a higher occurrence of heart failure. It may appear as early as the second or third day postinfarction or up to several weeks later.[16] This late complication, called *Dressler syndrome,* occurs weeks to months after MI and is thought to be an autoimmune response. In contrast to the pain associated with MI, the pain with pericarditis is sharp and stabbing and aggravated by deep inspiration and positional changes. Because of reperfusion therapy, this complication has been greatly reduced.

Mechanical defects result from changes that occur in the necrotic and subsequently inflamed myocardium and include rupture of the ventricular septum, papillary muscle, or free ventricular wall[8,16] (Fig. 19-9). Partial or complete rupture of a papillary muscle is a rare but often fatal complication of transmural myocardial infarction. It is detected by the presence of a new systolic murmur and clinical deterioration, often with pulmonary edema. More frequently, postinfarction mitral valve regurgitation results from early ischemic dysfunction of the papillary muscle and underlying myocardium. Ventricular septal rupture occurs less frequently than in the past because of the use of reperfusion therapy. Previously thought to require surgical intervention only in symptomatic patients, surgical repair is now recommended for all patients with ventricular septal rupture. Complete rupture of the free wall of the infarcted ventricle occurs in up to 10% of patients and usually results in immediate death.[16] It usually occurs 3 to 7 days postinfarction, usually involves the anterior wall, and is more frequent in older women.[8]

A left ventricular aneurysm is a sharply delineated area of scar tissue that bulges paradoxically during systole[8,16] (Fig. 19-10). This section of the myocardium does

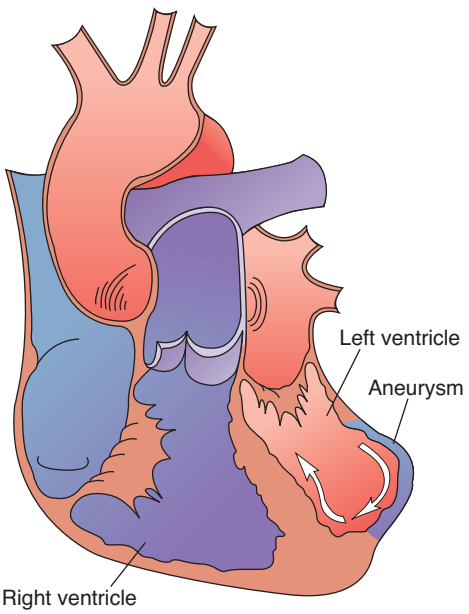


FIGURE 19-10. Paradoxical movement of a left ventricular aneurysm during systole.

not contract with the rest of the ventricle during systole. Instead, it diminishes the pumping efficiency of the heart and increases the work of the left ventricle, predisposing the patient to heart failure. Ischemia in the surrounding area predisposes the patient to development of arrhythmias, and stasis of blood in the aneurysm can lead to thrombus formation. Surgical resection may be performed to prevent these complications when other treatment measures fail.[16]

Chronic Ischemic Heart Disease

Myocardial ischemia occurs when the ability of the coronary arteries to supply blood is inadequate to meet the metabolic demands of the heart. Limitations in coronary blood flow most commonly are the result of atherosclerosis, but vasospasm may serve as an initiating or contributing factor.[18] There are three types of chronic ischemic coronary artery disease: chronic stable angina, silent myocardial ischemia, and variant or vasospastic angina.

Chronic Stable Angina

Angina pectoris is a symptomatic paroxysmal chest pain or pressure sensation associated with transient myocardial ischemia. Chronic stable angina is associated with a fixed coronary obstruction that produces a disparity between coronary blood flow and metabolic demands of the myocardium. Stable angina is the initial manifestation of ischemic heart disease in approximately half of persons with CAD.[19] Although most persons with stable angina have atherosclerotic heart disease, angina does not develop in a considerable number of persons with advanced coronary atherosclerosis. This probably is because of their sedentary lifestyle, the development of adequate collateral circulation, or the inability of these persons to perceive pain. In many instances, myocardial infarction occurs without a history of angina.

Angina pectoris usually is precipitated by situations that increase the work demands of the heart, such as physical exertion, exposure to cold, and emotional stress. The pain typically is described as a constricting, squeezing, or suffocating sensation. It usually is steady, increasing in intensity only at the onset and end of the attack. The pain of angina commonly is located in the precordial or substernal area of the chest; it is similar to myocardial infarction in that it may radiate to the left shoulder, jaw, arm, or other areas of the chest (Fig. 19-11). In some persons, the arm or shoulder pain may be confused with arthritis; in others, epigastric pain is confused with indigestion. Angina commonly is categorized according to whether it occurs with exercise, occurs during rest, is of new onset, or is of increasing severity.

Typically, chronic stable angina is provoked by exertion or emotional stress and relieved within minutes by rest or the use of nitroglycerin. A delay of more than 5 to 10 minutes before relief is obtained suggests that the symptoms are not due to ischemia or that they are due to severe ischemia. Angina that occurs at rest, is of new onset, or is increasing in intensity or duration denotes an increased risk for myocardial infarction and should be evaluated using the criteria for ACS.

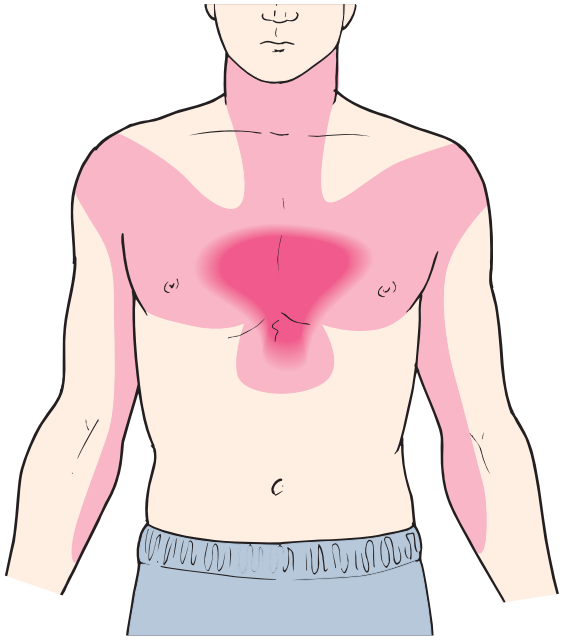


FIGURE 19-11. Areas of pain due to angina.

Silent Myocardial Ischemia

Silent myocardial ischemia occurs in the absence of anginal pain. The factors that cause silent myocardial ischemia appear to be the same as those responsible for angina: impaired blood flow from the effects of coronary atherosclerosis or vasospasm. Silent myocardial ischemia affects three populations—persons who are asymptomatic without other evidence of CAD, persons who have had a myocardial infarct and continue to have episodes of silent ischemia, and persons with angina who also have episodes of silent ischemia.[18] The reason for the painless episodes of ischemia is unclear. The ischemic episodes may be shorter and involve less myocardial tissue than those producing pain. Another explanation is that persons with silent angina have defects in pain threshold or pain transmission, or autonomic neuropathy with sensory denervation. There is evidence of an increased incidence of silent myocardial ischemia in persons with diabetes mellitus, probably the result of autonomic neuropathy, which is a common complication of diabetes.[18] Silent myocardial ischemia makes up a significant proportion of all STEMIs in the elderly.

Variant (Vasospastic) Angina

Variant angina, also known as *vasospastic* or *Prinzmetal angina,* is caused by coronory artery spasm. The causes of variant angina are not completely understood, but a combination of pathologic processes may be responsible. It has been suggested that it may result from endothelial dysfunction, hyperactive sympathetic nervous system responses, defective handling of calcium by vascular

smooth muscle, or altered nitric oxide production.[18] In some persons it is associated with hypercontractility of vascular smooth muscle and is associated with migraine headaches or Raynaud phenomenon. Unlike stable angina that occurs with exertion or stress, variant angina usually occurs during rest or with minimal exercise and frequently occurs nocturnally (between midnight and 8 AM).

Arrhythmias often occur when the pain is severe, and most persons are aware of their presence during an attack. ECG changes are significant if recorded during an attack. These abnormalities include ST-segment elevation or depression, T-wave peaking, inversion of U waves, and rhythm disturbances. Persons with variant angina who have serious arrhythmias during spontaneous episodes of pain are at a higher risk of sudden death.

Diagnosis and Treatment

The diagnosis of chronic ischemic heart disease is based on a detailed pain history, the presence of risk factors, invasive and noninvasive studies, and laboratory studies. Noncoronary causes of chest pain, such as esophageal reflux or musculoskeletal disorders, are ruled out. Noninvasive testing for chronic stable angina includes ECG, echocardiography, exercise stress testing, nuclear imaging studies, CT, and possibly cardiac MRI. Because the resting ECG is often normal, exercise testing is often used in evaluating persons with angina. Although noninvasive testing is valuable in the diagnosis of chronic stable angina, cardiac catheterization and coronary arteriography are often needed for a definitive diagnosis.[18]

The treatment goals for stable angina are directed toward symptom reduction and prevention of myocardial infarction through nonpharmacologic strategies, pharmacologic therapy, and coronary interventions. Nonpharmacologic methods are aimed at symptom control and lifestyle modifications to reduce risk factors for coronary disease. They include smoking cessation in persons who smoke, stress reduction, a regular exercise program, limiting dietary intake of cholesterol and saturated fats, weight reduction if obesity is present, and avoidance of cold or other stresses that produce vasoconstriction. Immediate cessation of activity often is sufficient to abort an angina attack. Sitting down or standing quietly may be preferable to lying down because these positions decrease preload by producing pooling of blood in the lower extremities.

Pharmacologic agents used in the treatment of chronic stable angina include nitrates, beta blockers, and calcium channel blockers.[19] Nitrates, both short- and long-acting, are vasodilators used in the treatment of chronic stable angina and in silent myocardial ischemia. Nitrates exert their effect mainly through a decrease in venous return to the heart with a resultant decrease in intraventricular volume. Arterial pressure also decreases. Decreased intraventricular pressure and volume are associated with decreased wall tension and myocardial oxygen requirement. Although they are not vasodilators, beta blockers are extremely useful in management of angina associated with effort. The benefits of beta blockers are due primarily to their hemodynamic effects—decreased heart rate, blood pressure, and myocardial contractility—which decrease myocardial oxygen requirements at rest and during exercise. The calcium channel–blocking agents, also called *calcium antagonists*, block activated and inactivated L-type calcium channels in cardiac and smooth muscle. The therapeutic effects of the calcium channel blockers result from coronary and peripheral artery dilation and from decreased myocardial metabolism associated with the decrease in myocardial contractility. PCI relieves symptoms for patients with chronic stable angina, but does not appear to extend the life span. CABG is usually indicated in patients with double- or triple-vessel disease.[19]

In summary, coronary artery disease is a disorder of impaired coronary blood flow, usually caused by atherosclerosis. The ACSs include unstable angina/NSTEMI and STEMI, which differ in terms of the extent of thrombotic coronary artery occlusion. Unstable angina/NSTEMI is an accelerated form of angina that is caused by subtotal or intermittent coronary occlusion. STEMI refers to the ischemic death of myocardial tissue associated with obstructed blood flow in the coronary arteries due to plaque disruption and occlusion of blood flow. The complications of STEMI can include potentially fatal arrhythmias, heart failure and cardiogenic shock, pericarditis, thromboemboli, rupture of cardiac structures, and ventricular aneurysms. Diagnostic methods include the use of ECG monitoring and serum cardiac biomarkers. Treatment goals focus on reestablishment of myocardial blood flow through rapid reperfusion of the occluded coronary artery, prevention of clot extension through use of aspirin and other antiplatelet and antithrombotic agents, alleviation of pain, administration of oxygen, and the use of vasodilators (nitroglycerin) and beta blockers to reduce the work demands on the heart.

The chronic ischemic heart diseases include chronic stable angina, variant (vasospastic) angina, and silent myocardial ischemia. Chronic stable angina is associated with a fixed atherosclerotic obstruction and pain that is precipitated by increased work demands on the heart and relieved by rest. Variant angina can result from spasms of the coronary arteries or other dysfunctions. Silent myocardial ischemia occurs without symptoms.

Cardiomyopathies

Cardiomyopathies are disorders of the heart muscle and are usually associated with disorders of myocardial performance, which may be mechanical (e.g., heart failure) or electrical (e.g., life-threatening arrhythmias). The definition and classification of the cardiomyopathies have evolved tremendously with the advance of molecular genetics. In 2006, the definition and classification of cardiomyopathies were updated in an American Heart

Association scientific statement incorporating not only the advances in cardiac molecular genetics, but also other newly diagnosed diseases.[20] The classification system divides the cardiomyopathies into two major groups: primary cardiomyopathies, which are confined to the myocardium, and secondary cardiomyopathies, which are associated with other disease conditions.

Primary Cardiomyopathies

The primary cardiomyopathies are classified as genetic, mixed, or acquired, based on their etiology.[20] The genetic cardiomyopathies include hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. The mixed cardiomyopathies, which include dilated and restrictive cardiomyopathy, are of both genetic and nongenetic origin. Acquired cardiomyopathies include those that have their origin in the inflammatory process (e.g., myocarditis), pregnancy (peripartum cardiomyopathy), and stress (takotsubo cardiomyopathy). In many cases the cause is unknown, in which case it is referred to as an *idiopathic cardiomyopathy.*

Genetic Cardiomyopathies

Hypertrophic Cardiomyopathy. Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy with disproportionate thickening of the ventricular septum, abnormal diastolic filling, cardiac arrhythmias, and, in some cases, intermittent left ventricular outflow obstruction[21] (Fig. 19-12). It is one of the most common types of cardiomyopathy, occurring in approximately 1 out of 500 persons in the general population.[21] HCM is the most common cause of sudden cardiac death in young athletes.

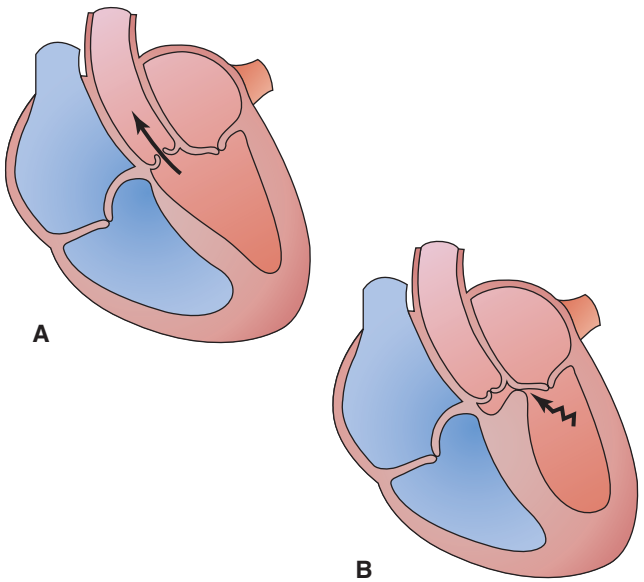


FIGURE 19-12. Vertical section of the heart showing **(A)** normal heart and **(B)** a heart with hypertrophic cardiomyopathy in which disproportionate thickening of the intraventricular septum causes intermittent left ventricular outflow obstruction.

HCM is an autosomal dominant disorder caused by mutations in genes encoding proteins of the cardiac sarcomere (i.e., muscle fibers). Histologically, HCM appears as myocyte hypertrophy with myofibril disarray and increased cardiac fibrosis. More than 400 mutations have been identified in 11 sarcomeric genes.[21,22] Although HCM is inherited, it may present at any time from early childhood to late adulthood with a broad category of manifestations and variable clinical course.

Clinically, HCM is characterized by a massively hypertrophied left ventricle with a reduced chamber size and a paradoxical decrease in stroke volume that results from impaired diastolic filling; in about 25% of cases, dynamic obstruction of left ventricular outflow occurs due to a disproportionate thickening of the interventricular septum.[8] HCM is frequently associated with the development of left ventricular outflow obstruction that is caused by systolic anterior motion of the mitral valve and midsystolic contact with the ventricular septum. The obstruction is worsened by factors that increase myocardial contraction (e.g., sympathetic stimulation) or decrease left ventricular filling (e.g., Valsalva maneuver, peripheral vasodilation).

Clinical manifestations are highly variable and may progress to end-stage heart failure with left ventricular remodeling and systolic dysfunction. The most frequent symptoms of HCM are dyspnea and chest pain. Syncope (fainting) is also common and is typically postexertional, when diastolic filling diminishes and outflow obstruction increases. Atrial fibrillation can occur as a long-term consequence of elevated left atrial pressures. Ventricular arrhythmias are also common, and sudden death may occur, often in athletes after extensive exertion.

Diagnosis of HCM is frequently established with two-dimensional (2-D) echocardiography, ECG, and continuous ambulatory monitoring. Cardiac MRI can also be helpful. Genetic testing, through bidirectional deoxyribonucleic acid (DNA) sequence analysis, provides accurate diagnosis and precise identification of gene mutations, although with some limitations.[23]

Medical management of HCM is primarily focused on symptom management. The first-line approach to relief of symptoms is pharmacologic therapy designed to block the effects of catecholamines that exacerbate outflow obstruction and to slow the heart rate to enhance diastolic filling. Beta blockers are generally the initial choice for persons with symptomatic HCM. Calcium channel blockers, especially verapamil, can also be used. They can, however, exacerbate left ventricular outflow obstruction and are not recommended for persons with severe outflow obstruction and pronounced symptoms. Dual-chamber and biventricular pacing may be used to prevent progression of hypertrophy and obstruction. In obstructive HCM that is refractory to drug therapy, septal myotomy-myectomy (surgical excision of part of the outflow myocardial septum) or alcohol ablation of the interventricular septum can be used. An implantable cardioverter–defibrillator should be considered for persons with HCM who have sustained ventricular tachycardia or ventricular fibrillation and are receiving optimal medical therapy.[21]

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a heart muscle disease that affects primarily the right ventricle, causing right-sided heart failure and various rhythm disturbances, particularly ventricular tachycardia.[24] It ranks second, after HCM, as the leading cause of sudden cardiac death in young athletes. The incidence of ARVC/D varies from about 1 in 2000 to 1 in 5000, affecting men more frequently than women.[24] ARVC/D is inherited as an autosomal dominant trait in greater than 50% of cases, although often with incomplete penetrance and variable expression. Although a gene mutation was recently located on chromosome 14, the pathogenesis of the disorder remains unclear.

The disorder is characterized by progressive loss of myocytes, with partial or complete replacement of the right ventricular muscle with fatty or fibrofatty tissue. These changes are associated with reentrant ventricular tachyarrhythmias of right ventricular origin that are often precipitated by exercise-induced discharge of catecholamines. Clinical manifestations include palpitations, syncope, or cardiac arrest, usually in young or middle-aged men. Other symptoms may include abdominal pain and mental confusion.

Diagnosis of ARVC/D is based on clinical, ECG, echocardiographic, and histologic findings. Personal and family history, including first- and second-degree relatives, is important. Treatment for ARVC/D is aimed at prevention of sudden cardiac death. Although ARVC/D cannot be cured, the goal of treatment is to control the arrhythmias with antiarrhythmic agents.[24] Combinations of various antiarrhythmic agents are often used. Radiofrequency ablation may be used in drug-refractory cases, although it is completely successful in only 30% to 65% of cases, with multiple ablations sometimes needed. An implantable cardioverter–defibrillator is also indicated for drug-refractory cases and for those who have survived a sudden cardiac death episode. Final options for treatment include ventriculotomy and heart transplantation.[24]

Mixed (Genetic and Nongenetic) Cardiomyopathies

Dilated Cardiomyopathy. Dilated cardiomyopathy (DCM) is a common cause of heart failure and the leading indication for heart transplantation. Up to 35% of cases of dilated cardiomyopathy are reported as familial; that proportion may be even higher because incomplete penetrance often makes it difficult to identify early or latent disease in family members.[8,25] Most familial cases appear to be transmitted as an autosomal dominant trait, but autosomal recessive, X-linked recessive, and mitochondrial inheritance patterns have been identified. Other causes include infections (i.e., viral, bacterial, fungal, mycobacterial, parasitic), toxins, alcoholism, chemotherapeutic agents, metals, and multiple other disorders. Often no cause is found, in which case it is often referred to as *idiopathic DCM*.

DCM is characterized by progressive cardiac dilation and contractile (systolic) dysfunction, usually with concurrent hypertrophy.[8,25] The heart is enlarged (two to three times its normal weight) and flabby with dilation of all four chambers (Fig. 19-13). Because of wall thinning that accompanies dilation, the ventricular thickness may be less than, equal to, or greater than normal. The histologic abnormalities in DCM are nonspecific. Microscopically, most myocytes are hypertrophied with enlarged nuclei, but many are thinned, stretched, and irregular.

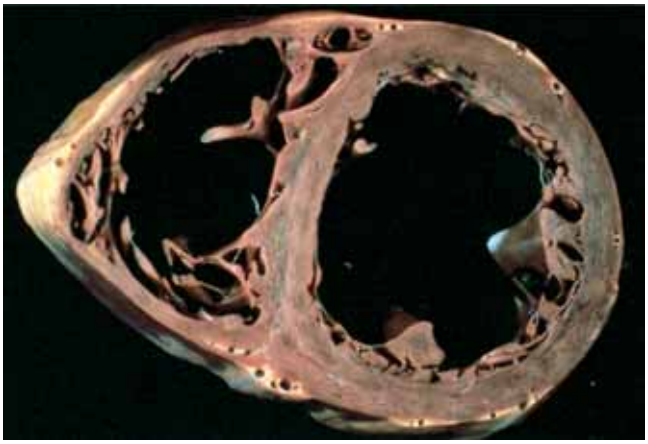


FIGURE 19-13. Idiopathic dilated cardiomyopathy. A transverse section of the enlarged heart reveals conspicuous dilation of both ventricles. Although the ventricular wall appears thinned, the increased mass of the heart indicates considerable hypertrophy. (From Saffitz J.E. [2008]. The heart. In Rubin E., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 470]. Philadelphia: Lippincott Williams & Wilkins.)

The most common clinical manifestations of dilated cardiomyopathy are those related to heart failure, such as dyspnea, orthopnea, and reduced exercise capacity. In the end stages, persons with DCM often have ejection fractions of less than 25% (normal, 50% to 65% or greater).[8] As the disease progresses, stasis of blood in the walls of the heart chambers can lead to thrombus formation and systemic emboli. Secondary mitral valve regurgitation and abnormal cardiac rhythms are common. Death is usually due to heart failure or arrhythmias and can occur suddenly.

The treatment of DCM is directed toward relieving the symptoms of heart failure and reducing the work of the heart. Pharmacologic agents include diuretics to reduce preload, beta blockers to reduce heart rate and myocardial oxygen demand, afterload-reducing agents to improve contractility and decrease left ventricular filling pressures, and ACE inhibitors to prevent vasoconstriction. Anticoagulant and antiarrhythmic drugs may also be used. Other treatments may include a biventricular pacemaker, an implantable cardioverter–defibrillator, and, in cases that are refractory to treatment, cardiac transplantation. Removing or avoiding causative agents (if identified); avoiding myocardial depressants, including alcohol; and pacing rest with asymptomatic levels of exercise or activity are also important.

Primary Restrictive Cardiomyopathy. Restrictive cardiomyopathy is a rare form of heart muscle disease in

which ventricular filling is restricted because of excessive rigidity of the ventricular walls, although the contractile properties of the heart remain relatively normal.[8] Restrictive cardiomyopathy can be idiopathic or associated with other conditions that affect the myocardium, principally radiation fibrosis, amyloidosis, sarcoidosis, or metastatic tumors. Genetics may also play a role because familial forms of restrictive cardiomyopathy have been reported.[20]

Symptoms of restrictive cardiomyopathy include dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, ascites, fatigue, and weakness. The manifestations of restrictive cardiomyopathy resemble those of constrictive pericarditis. In the advanced form of the disease, all the signs of heart failure are present except cardiomegaly.

Acquired Cardiomyopathies

Myocarditis. Myocarditis, or inflammatory cardiomyopathy, can be defined as "an inflammation of the heart."[8,25] The clinical spectrum of the disease is broad: at one end, the disease is asymptomatic with full recovery, and at the other end is it has a precipitous onset of heart failure or arrhythmias, occasionally with sudden cardiac death.

Although there are a number of etiologies associated with myocarditis, it is usually caused by a viral infection, most commonly an enterovirus (coxsackievirus group B).[8,26–28] Adenovirus and parvovirus in young children have also been identified as causative agents. Other etiologies include bacterial or fungal infections, hypersensitivity to certain drugs, and autoimmune diseases, such as systemic lupus erythematosus. Myocarditis is a frequent pathologic cardiac finding in persons with acquired immunodeficiency syndrome (AIDS), although it is unclear whether it is due to the human immunodeficiency virus infection itself or to a secondary infection.

The pathogenesis of myocarditis is one of cardiac injury, followed by an immunologic response. Myocardial injury due to infectious agents is thought to result from necrosis caused by direct invasion of the offending organism, toxic effects of exotoxins or endotoxins produced by a systemic pathogen, or destruction of cardiac tissue by immunologic mechanisms initiated by the infectious agent. The immunologic response may be directed at foreign antigens of the infectious agent that share molecular characteristics with those of the host cardiac myocytes (i.e., molecular mimicry; see Chapter 16), providing a continuous stimulus for the immune response even after the infectious agent has been cleared from the body.

The signs and symptoms of myocarditis vary from person to person.[27] Some persons may present with fever, chills, nausea, vomiting, arthralgia, and myalgia, occurring up to 6 weeks before the diagnosis of myocarditis. Other persons may present with heart failure without antecedent symptoms. The onset of heart failure may be gradual or abrupt and fulminant. Emboli may occur because of the procoagulant effect of inflammatory cytokines combined with decreased myocardial contractility. At times, the presentation may mimic ACS, with ST-segment and T-wave changes, positive serum cardiac biomarkers, and regional wall motion abnormalities despite normal coronary arteries. Viral myocarditis in children or young adults is often nonspecific, with symptoms such as fever and poor eating.

The diagnosis of myocarditis can be suggested by clinical manifestations. Methods used in confirming the diagnosis include the ECG, chest radiography, serum cardiac biomarkers (i.e., creatinine phosphokinase, troponin I), and echocardiography. Endomyocardial biopsy findings, obtained through cardiac catheterization, remain the gold standard for establishing the diagnosis of acute myocarditis, despite limited accuracy.[26–28]

Many cases of myocarditis are mild and self-limiting, so first-line treatment remains largely supportive.[26–28] Initial treatments include supplemental oxygen, bed rest, and antibiotics, if needed. In persons with more severe myocarditis, arrhythmia suppression and hemodynamic support with vasopressors and positive inotropic agents may be needed. Persons with severe fulminant myocarditis may require aggressive short-term support with an intra-aortic balloon pump or left ventricular assist devices.[26] Immunosuppressive therapy continues to be investigated as a treatment for myocarditis. Although treatment of myocarditis is successful in many persons, some progress to congestive heart failure and can expect only a limited life span. For these persons, heart transplantation becomes an alternative.

Peripartum Cardiomyopathy. Peripartum cardiomyopathy is a dilated cardiomyopathy that occurs in the last month of pregnancy or within 5 months after delivery.[29] It is manifested by signs of systolic dysfunction and heart failure for which there is no identifiable cause of heart failure or evidence of it before the last month of pregnancy.[29–31] The incidence is greater in black, multiparous, or older women, and in women with twin fetuses, preeclampsia, or use of tocolytic therapy to prevent premature labor and delivery.[30,31] Although the etiology of peripartum cardiomyopathy is unknown, several causes have been proposed, including infectious, immunologic, nutritional, drug-induced, and genetic factors. Some women exhibit inflammatory cells in heart biopsies taken during the symptomatic phase of the disorder, suggesting a disordered immune response.

Management of peripartum cardiomyopathy includes standard therapy for heart failure. However, potential teratogenic effects and excretion of drugs during breastfeeding need to be considered. Prognosis depends on resolution of the heart failure. About half of women with peripartum cardiomyopathy spontaneously recover normal cardiac function; the other half are left with persistent left ventricular dysfunction or progress to overt heart failure and early death.[31]

Stress or "Takotsubo" Cardiomyopathy. First described in Japan in 1991, *takotsubo-like left ventricular dysfunction* is named after the fishing pot used to trap octopus that has a narrow neck and wide base, a shape similar to that of the affected ventricle.[20,32] The term *transient left ventricular apical ballooning* has also been used to describe this syndrome.

Stress or takotsubo cardiomyopathy has been identified in the clinical setting as a transient, reversible left ventricular dysfunction in response to profound psychological or emotional stress. The syndrome occurs primarily in middle-aged women who present with acute STEMI but who, on cardiac catheterization, have no evidence of CAD. There is, however, impaired myocardial contractility characterized by left ventricular apical ballooning with hypercontractility of the basal left ventricle.

The mechanism for myocardial stunning in stress cardiomyopathy is unclear, although some theories suggest ischemia from coronary artery spasm, microvascular spasm, or direct myocyte injury. When catecholamine levels return to normal, the interventricular gradient resolves and left ventricular function recovers.[33] Treatment of takotsubo cardiomyopathy is the same as that for heart failure, and most patients demonstrate rapid improvement and an excellent prognosis.

Secondary Cardiomyopathies

Secondary cardiomyopathy is a heart muscle disease in the presence of a multisystem disorder. There are numerous conditions reported to involve the myocardium (Chart 19-2). Some of these disorders produce accumulation of abnormal substances between myocytes (extracellular), whereas others produce accumulation of abnormal substances within myocytes (intracellular).

Almost 100 distinct myocardial diseases can result in the clinical features of DCM. They include cardiomyopathies associated with drugs, diabetes mellitus, muscular dystrophy, autoimmune disorders, and cancer treatment agents (radiation and cancer drugs).[20] Alcoholic cardiomyopathy is the single most common identifiable cause of DCM in the United States and Europe. Doxorubicin (Adriamycin) and other anthracycline drugs, used in the treatment of cancer, are potent agents whose usefulness is limited by cumulative dose-dependent cardiac toxicity. Another cancer chemotherapeutic agent with cardiotoxic potential is cyclophosphamide (Cytoxan). Unlike the primary myocyte injury that occurs with doxorubicin, the principal insult with cyclophosphamide appears to be vascular, leading to myocardial hemorrhage.

CHART 19-2 Conditions Associated with Secondary Cardiomyopathies*

Autoimmune Disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Polyarteritis nodosa

Endocrine Disorders
Acromegaly
Diabetes mellitus
Hypothyroidism and hyperthyroidism
Hyperparathyroidism

Familial Storage Diseases
Glycogen storage disease
Mucopolysaccharidoses
Hemochromatosis

Infiltrative Disorders
Amyloidosis
Sarcoidosis
Radiation-induced fibrosis

Neuromuscular/Neurologic Disorders
Friedreich ataxia
Muscular dystrophy
Neurofibromatosis

Nutritional Deficiencies
Thiamine (beriberi)
Protein (kwashiorkor)

Toxins
Alcohol and its metabolites
Arsenic
Cancer chemotherapeutic agents (anthracyclines [doxorubicin, daunorubicin], cyclophosphamide)
Catecholamines
Hydrocarbons

*Not intended to be inclusive.

In summary, the cardiomyopathies involve both mechanical and electrical etiologies of myocardial dysfunction. They are currently identified as either primary or secondary cardiomyopathies, based on genetic or other organ system involvement. Symptoms related to most cardiomyopathies, whether primary or secondary, are those associated with heart failure and sudden cardiac death. Treatment focuses on symptom management and prevention of lethal arrhythmias.

The primary cardiomyopathies include genetic, mixed, or acquired types. The genetic cardiomyopathies include hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. The mixed cardiomyopathies, which include dilated and restrictive cardiomyopathies, are of both genetic and acquired origin. Acquired cardiomyopathies include those that have their origin in the inflammatory process (e.g., myocarditis), stress (takotsubo cardiomyopathy), or pregnancy (peripartum cardiomyopathy). In many cases the cause is unknown, in which case it is referred to as an *idiopathic cardiomyopathy.*

The secondary cardiomyopathies are heart diseases in which myocardial involvement occurs as part of a multisystem disorder. They include cardiomyopathies associated with drugs, diabetes mellitus, muscular dystrophy, autoimmune disorders, and cancer treatment agents (radiation and chemotherapeutic drugs).

Endocardial and Valvular Disorders

The endocardium, which lines the heart and covers the heart valves, is continuous with the tunica intima of the blood vessels entering and leaving the heart. It is composed of an inner endothelium, consisting of endothelium and subendothelial connective tissue; a middle layer of connective tissue and smooth muscle cells; and a deeper layer of loose connective tissue, called the *subendocardial layer,* which is continuous with the connective tissue of the myocardium. The subendocardium contains small blood vessels, nerves, and Purkinje fibers from the cardiac conduction system. Among the disorders that affect the endocardium are infective endocarditis, rheumatic fever, and valvular heart disorders.

Disorders Affecting the Endocardium

Infective Endocarditis

Infective endocarditis (IE) is a serious and potentially life-threatening infection of the inner surface of the heart. It is characterized by colonization or invasion of the heart valves and the mural endocardium by a microbial agent, leading to the formation of bulky, friable vegetations and destruction of underlying cardiac tissues.[8] Although other microorganisms such as fungi and chlamydiae can cause endocarditis, the vast majority of cases are caused by bacteria.

Infective endocarditis is commonly classified into acute or subacute–chronic forms, depending on the onset, etiology, and severity of the disease.[34] The onset of acute IE is usually rapid and involves patients with normal cardiac valves who are healthy and perhaps have a history of intravenous drug abuse, whereas subacute or chronic IE evolves over months, usually in persons who have heart valve abnormalities.[35]

Etiology and Pathogenesis. Two factors contribute to the development of IE: a portal of entry by which the organism gains access to the circulatory system and a damaged endocardial surface. The portal of entry into the bloodstream may be an obvious infection, a dental or surgical procedure that causes transient bacteremia, injection of a contaminated substance directly into the blood by intravenous drug users, or an occult source in the oral cavity or gut, or a trivial injury.[8] Infective endocarditis can develop on previously normal heart valves, but the presence of cardiac abnormalities such as mitral valve prolapse or congenital heart disease can contribute to its development. Host factors such as neutropenia, immunodeficiency, malignancy, therapeutic immunosuppression, diabetes, and alcohol or intravenous drug use are predisposing factors.[8] A recently identified cause of IE is infection involving a variety of cardiovascular prostheses and devices, such as pacemakers, defibrillators, and left ventricular assist devices.

Staphylococcal infections have now emerged as the leading cause of IE, with streptococci and enterococci as the other two most common causes. Other bacterial agents include the so-called HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*), all commensals in the oral cavity.[8,34] Less commonly, gram-negative bacteria and fungi are involved. The causative agents differ somewhat in high-risk groups. For example, *Staphylococcus aureus* is the major offender in injection drug abusers, whereas prosthetic heart valve infective endocarditis tends to be caused by coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*).[8]

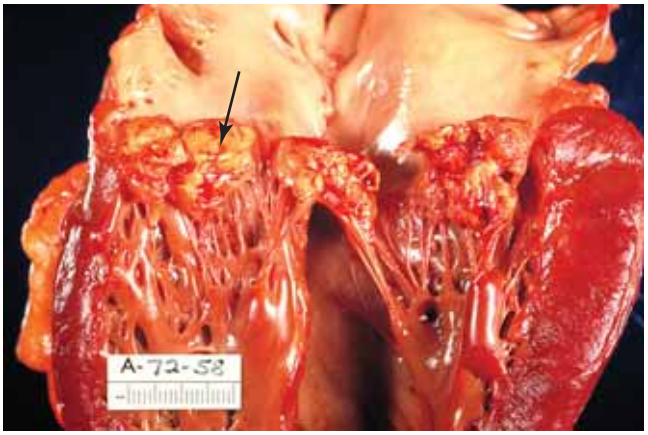


FIGURE 19-14. Gross pathology of subacute bacterial endocarditis involving the mitral valve. Left ventricle of the heart has been opened to show mitral valve fibrin vegetations due to infection with *Haemophilus parainfluenza.* Autopsy. (From Centers for Disease Control and Prevention Public Images Library. [Online].)

In both acute and subacute–chronic forms of IE, friable, bulky, and potentially destructive vegetative lesions form on the heart valves (Fig. 19-14). The aortic and mitral valves are the most common sites of infection, although the right heart may also be involved, particularly in injection drug abusers. The vegetative lesions consist of a collection of infectious organisms and cellular debris enmeshed in the fibrin strands of clotted blood. The lesions may be singular or multiple, may grow as large as several centimeters, and usually are found loosely attached to the free edges of the valve surface.[8] The infectious loci continuously release bacteria into the bloodstream and are a source of persistent bacteremia. As the lesions grow, they cause valve destruction, leading to valvular regurgitation, ring abscesses with heart block, pericarditis, aneurysm, and valve perforation. The loose organization of these lesions permits the organisms and fragments of the lesions to form emboli and travel in the bloodstream, causing cerebral, systemic, or pulmonary emboli. The fragments may lodge in small blood vessels, causing small hemorrhages, abscesses, and infarction of tissue. The bacteremia also can initiate immune responses thought to be responsible for skin manifestations, polyarthritis, glomerulonephritis, and other immune disorders.[8,34]

Manifestations. Signs and symptoms of IE can include fever and signs of systemic infection, change in the character of an existing heart murmur, and evidence of

embolic distribution of the vegetative lesions.[34] In the acute form, the fever usually is spiking and accompanied by chills. In the subacute form, the fever usually is low grade, of gradual onset, and frequently accompanied by other systemic signs of inflammation, such as anorexia, malaise, and lethargy. Small petechial hemorrhages frequently result when emboli lodge in the small vessels of the skin, nail beds, and mucous membranes. Splinter hemorrhages (i.e., dark red lines) under the nails of the fingers and toes are common.[34] Cough, dyspnea, arthralgia or arthritis, diarrhea, and abdominal or flank pain may occur as the result of systemic emboli.

Diagnosis and Treatment. Infective endocarditis continues to pose major challenges in diagnosis and treatment.[34,35–38] The blood culture remains the most definitive diagnostic procedure and is essential to guide treatment. However, the indiscriminate use of antibiotics has made identifying the causative organism much more difficult. Negative blood cultures can occur in up to 30% of cases of IE, delaying diagnosis and treatment and having a profound effect on outcome.[36] This can occur because of prior antibiotic administration or because the causative organisms are slow growing, require special culture media, or are not readily cultured. Echocardiography is the primary technique for detection of vegetations and cardiac complications resulting from IE and is an important tool in the diagnosis and management of disease.[34]

Treatment of IE focuses on identifying and eliminating the causative microorganism, minimizing the residual cardiac effects, and treating the pathologic effect of emboli. The choice of antimicrobial therapy depends on the organism cultured and whether it occurs in a native or prosthetic valve. The widespread emergence of multidrug-resistant organisms, including *S. aureus,* poses a serious challenge in the treatment of IE. In addition to antibiotic therapy, surgery may be needed for unresolved infection, severe heart failure, and significant emboli.

Prevention of IE through the use of prophylactic antibiotics is controversial. The current recommendations conclude that only a very small number of IE cases might be prevented by antibiotic prophylaxis for dental procedures. Therefore, prophylaxis is recommended only for patients with predisposing congenital or valvular disorders undergoing select dental and surgical procedures.[38,39]

Rheumatic Heart Disease

Rheumatic fever (RF) is an immune-mediated, multisystem inflammatory disease that occurs a few weeks after a group A (β-hemolytic) streptococcal (GAS) pharyngitis (sore throat). It also rarely occurs with streptococcal infections at other sites (e.g., skin).[8] Acute rheumatic heart disease (RHD) is the cardiac manifestation of RF and is associated with inflammation of the myocardium, pericardium, and heart valves. Chronic valvular dysfunction is the most important consequence of RHD. Although RF and RHD are rare in developed countries, they continue to be major health problems in underdeveloped countries, where inadequate health care, poor nutrition, and crowded living conditions still prevail.[40]

Pathogenesis. Many details of the pathogenesis of RF remain unclear despite years of investigation. The time frame for development of symptoms relative to the sore throat and the presence of antibodies to the GAS organism strongly suggests an immunologic response.[8,40–42] It is thought that antibodies directed against the M protein of certain strains of streptococci cross-react with glycoprotein antigens in the heart, joints, and other tissues to produce an autoimmune response through a phenomenon called *molecular mimicry*[40] (see Chapter 16). Although only a small percentage of persons with untreated GAS pharyngitis develop RF, the incidence of recurrence with a subsequent untreated infection is substantially greater. These observations and more recent studies suggest a genetic predisposition to development of the disease.[8]

Clinical Features. Rheumatic fever can manifest as an acute, recurrent, or chronic disorder. The *acute stage* of rheumatic fever includes a history of an initiating streptococcal infection and subsequent development of discrete inflammatory lesions within the connective tissue elements of the heart, blood vessels, joints, and subcutaneous tissues. Within the heart these lesions are called *Aschoff bodies*.[8] The *recurrent phase* usually involves extension of the cardiac effects of the disease. The *chronic phase* of rheumatic fever is characterized by permanent deformity of the heart valves and is a common cause of mitral valve stenosis. Chronic rheumatic heart disease usually does not appear until at least 10 years after the initial attack, sometimes decades later.

Most persons with rheumatic fever have a history of sore throat, headache, fever, abdominal pain, nausea, vomiting, swollen glands (usually at the angle of the jaw), and other signs and symptoms of streptococcal infection. Other clinical features associated with an acute episode of rheumatic fever are related to the acute inflammatory process and the structures involved in the disease process. The course of the disease is characterized by a constellation of findings that includes carditis, migratory polyarthritis of the large joints, erythema marginatum, subcutaneous nodules, and Sydenham chorea.[8,42]

Acute *rheumatic carditis*, which complicates the acute phase of rheumatic fever, is a pancarditis, involving all three layers of the heart (endocardium, myocardium, or pericardium). In some cases, the myocarditis can be so severe that the resulting cardiac dilation causes functional mitral insufficiency and even heart failure. Clinical features of the carditis include pericardial friction rubs, arrhythmias, and a heart murmur in a person without a previous history of rheumatic fever. Usually, both the pericarditis and myocarditis are self-limited manifestations of the acute stage of the rheumatic fever. Involvement of the endocardium and valvular structures produces the permanent and disabling effects of disease. Although any of the four valves can be involved, the mitral and aortic valves are affected most often. During the acute inflammatory stage of the disease, the valvular structures become red and swollen, and small vegetative lesions develop on the valve leaflets. The acute inflammatory changes gradually proceed to the development of fibrous scar tissue, which tends to contract and cause

deformity of the valve leaflets and shortening of the chordae tendineae. In some cases, the edges or commissures of the valve leaflets fuse together as healing occurs.

Although not a cause of permanent disability, *polyarthritis* is the most common, and frequently the first, manifestation of rheumatic fever. It may be the only major diagnostic criterion in adolescents and adults. The arthritis, which may range from arthralgia to disabling arthritis, most often involves the larger joints, particularly the knees and ankles, and occurs less frequently in the wrists, elbows, shoulders, and hips. It is almost always migratory, affecting one joint and then moving to another. Untreated, the arthritis lasts approximately 4 weeks. A striking feature of rheumatic arthritis is the dramatic response (usually within 48 hours) to salicylates. Arthritis usually heals completely and leaves no functional residua.

Erythema marginatum lesions are maplike, macular areas most commonly seen on the trunk or inner aspects of the upper arm and thigh, but never on the face. They occur early in the course of a rheumatic attack and tend to occur with subcutaneous nodules. They are transitory and disappear during the course of the disease. *Subcutaneous nodules* are hard, painless, and freely movable and usually occur over the extensor muscles of the wrist, elbow, ankle, and knee joints, ranging in size from 0.5 to 2 cm. Subcutaneous nodules rarely occur alone in rheumatic fever and occur most often in association with carditis.

Chorea (i.e., Sydenham chorea) is the major central nervous system manifestation of rheumatic fever. It is seen most frequently in young girls and rarely occurs after 20 years of age. There typically is an insidious onset of irritability and other behavior problems. The child often is fidgety, cries easily, begins to walk clumsily, and drops things. The choreiform movements are spontaneous, rapid, purposeless, jerking movements that interfere with voluntary activities. Facial grimaces are common, and even speech may be affected. The chorea is self-limited, usually running its course within a matter of weeks or months, but recurrences are not uncommon.

Diagnosis. Diagnosis of acute rheumatic fever is made by serologic evidence of GAS infection and use of the Jones criteria, which were developed to assist in standardizing the diagnosis of RF. Serologic tests for streptococcal antibodies (antistreptolysin O and antideoxyribonuclease B) can provide retrospective confirmation of recent streptococcal infection in persons thought to have rheumatic fever. Laboratory markers of acute inflammation include an elevated white blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The Jones criteria divide the clinical features of RF into major and minor categories, based on prevalence and specificity.[41,43] The presence of two major signs (i.e., carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules) or one major and two minor signs (i.e., arthralgia, fever, and elevated ESR, CRP, or leukocyte count), accompanied by evidence of a preceding GAS infection, indicates a high probability of RF.

The use of echocardiography has enhanced the understanding of both acute and chronic RHD. It is useful in assessing the severity of valvular stenosis and regurgitation, chamber size and ventricular function, and the presence and size of pleural effusions. Doppler ultrasonography may be useful in identifying cardiac lesions in persons who do not show typical signs of cardiac involvement during an attack of RF.[43]

Treatment and Prevention. It is important that GAS infections be promptly diagnosed and treated to prevent RF. The gold standard for detecting a GAS infection is throat culture. However, it takes 24 to 48 hours to produce a result, delaying treatment. The development of rapid tests for direct detection of GAS antigens has provided at least a partial solution for this problem. Both the throat culture and the rapid antigen tests are highly specific for GAS infection but are limited in terms of their sensitivity (e.g., the person may have a negative test result but have a streptococcal infection). A negative antigen test result should be confirmed with a throat culture when a streptococcal infection is suspected.[43] The presence of GAS in the upper respiratory tract can indicate either a carrier or infectious state, the latter of which can be defined by a rising antibody response. Serologic examinations for GAS antibodies (antistreptolysin O and antideoxyribonuclease B) are measured for retrospective confirmation of recent streptococcal infections in persons thought to have acute RF.

Treatment of acute RF is designed to control the acute inflammatory response and prevent cardiac complications and recurrence of the disease. During the acute phase, antibiotics, anti-inflammatory drugs, and selective restriction of activities are prescribed. No clinical isolate of GAS is resistant to penicillin; therefore, penicillin, or another antibiotic in penicillin-sensitive patients, is the treatment of choice for GAS infection.[43] Salicylates and corticosteroids can be used to suppress the inflammatory response, but should not be given until the diagnosis of RF is confirmed. Surgery is indicated for chronic rheumatic valve disease and is determined by the severity of the symptom or the evidence that cardiac function is significantly impaired. Procedures used include closed mitral commissurotomy, valve repair, and valve replacement.

Persons who have had an attack of RF are at high risk for recurrence after subsequent GAS throat infections. Penicillin is the treatment of choice for secondary prophylaxis, but sulfadiazine or erythromycin may be used in penicillin-allergic individuals. The duration of prophylaxis depends on whether residual valvular disease is present or absent. It is recommended that persons with persistent valvular disease receive prophylaxis for at least 5 years after the acute episode of RF or until age 21 years if there is no evidence of carditis.[42]

Valvular Heart Disease

The past several decades have brought remarkable advances in the treatment and outlook for people with valvular heart disease. This is undoubtedly due to improved methods for noninvasive monitoring of ventricular function, improvement in prosthetic valves, advances in valve reconstruction procedures, and the development

Valvular Heart Disease

- The heart valves determine the direction of blood flow through the heart chambers.
- Valvular heart defects exert their effects by obstructing the flow of blood (stenotic valve disorders) or allowing the backward flow of blood (regurgitant valve disorders).
- Stenotic valvular defects produce distention of the heart chamber that empties blood through the diseased valve and impaired filling of the chamber that receives blood that moves through the valve.
- Regurgitant valves allow blood to move back through the valve when it should be closed. This produces distention and places increased work demands on the chamber ejecting blood through the diseased valve.

of useful guidelines to improve the timing of surgical interventions.[44] Nevertheless, valvular heart disease continues to produce considerable mortality and morbidity.

Hemodynamic Derangements

The function of the heart valves is to promote unidirectional flow of blood through the chambers of the heart. Dysfunction of the valves can result from a number of disorders including congenital defects, trauma, ischemic damage, degenerative changes, and inflammation. Although any of the heart valves can become diseased, the most commonly involved are the mitral and aortic valves. Disorders of the pulmonary and tricuspid valves are less common, probably because of the low pressure in the right side of the heart.

The heart valves consist of thin leaflets of tough, flexible, endothelium-covered fibrous tissue firmly attached at the base to the fibrous valve rings (see Chapter 17). The leaflets of the heart valves may be injured or become the site of an inflammatory process that can deform their line of closure. Healing of the valve leaflets often is associated with increased collagen content and scarring, causing the leaflets to shorten and become stiffer. The edges of the healing valve leaflets can fuse together so that the valve does not open or close properly.

Two types of mechanical disruptions occur with valvular heart disease: narrowing of the valve opening so it does not open properly and distortion of the valve so it does not close properly (Fig. 19-15). *Stenosis* refers to a narrowing of the valve orifice and failure of the valve leaflets to open normally (Fig. 19-16). Significant narrowing of the valve orifice increases the resistance to blood flow through the valve, converting the normally smooth laminar flow to a less efficient turbulent flow. This increases the work and volume of the chamber emptying through the narrowed valve—the left atrium in the

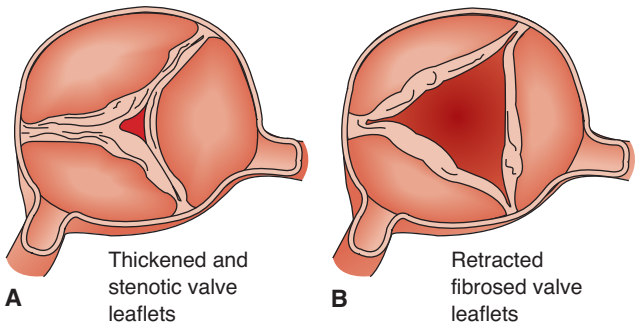


FIGURE 19-15. Disease of the aortic valve as viewed from the aorta. **(A)** Stenosis of the valve opening. **(B)** An incompetent or regurgitant valve that is unable to close completely.

case of mitral stenosis and the left ventricle in aortic stenosis. An *incompetent* or *regurgitant* valve permits backward flow to occur when the valve should be closed—flowing back into the left ventricle during diastole when the aortic valve is affected and back into the left atrium during systole when the mitral valve is diseased. Stenosis and regurgitation can occur in pure forms or may exist in the same valve. Alterations in hemodynamic function that accompany aortic and mitral valve stenosis and regurgitation are illustrated in Figure 19-17.

The effects of valvular heart disease depend on the valve involved, the degree of involvement, the rapidity of onset, and the rate and adequacy of compensatory mechanisms. For example, sudden destruction of an aortic valve cusp by infection can cause massive regurgitation and rapid heart failure, whereas rheumatic mitral stenosis usually develops over years and its effects are remarkably well tolerated. Abnormal flow through diseased valves typically produces abnormal heart sounds called *murmurs*.

Mitral Valve Disorders

The mitral or left atrioventricular valve controls the directional flow of blood between the left atrium and the

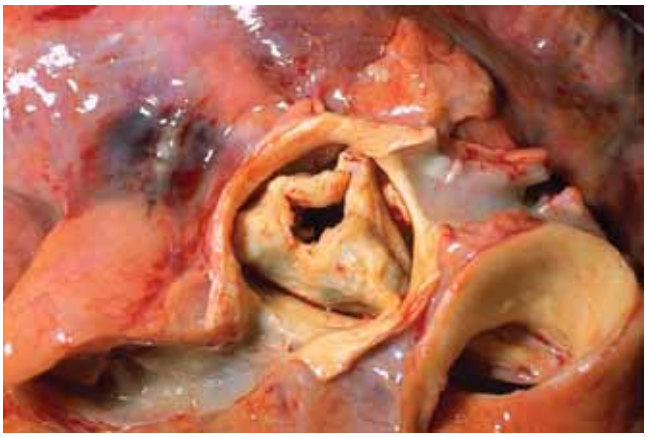


FIGURE 19-16. Gross pathology of rheumatic heart disease: aortic stenosis. Fused aortic valve leaflets and opened coronary arteries from above. (From Centers for Disease Control and Prevention Public Images Library. [Online].)

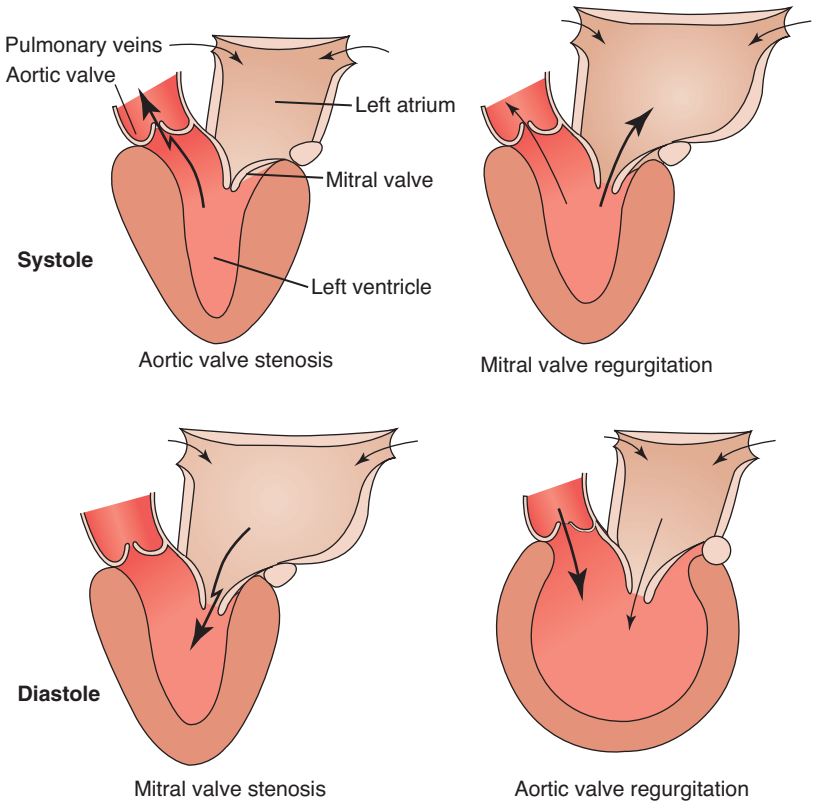


FIGURE 19-17. Alterations in hemodynamic function that accompany aortic valve stenosis, mitral valve regurgitation, mitral valve stenosis, and aortic valve regurgitation. The *thin arrows* indicate direction of normal flow, and *thick arrows* the direction of abnormal flow.

left ventricle. The edges or cusps of the AV valves, which are thinner than those of the semilunar (i.e., pulmonic and aortic) valves, are anchored to the papillary muscles by the chordae tendineae. During much of systole, the mitral valve is subjected to the high pressure generated by the left ventricle as it pumps blood into the systemic circulation. During this period of increased pressure, the chordae tendineae prevent the eversion of the valve leaflets into the left atrium.

Mitral Valve Stenosis. Mitral valve stenosis represents the incomplete opening of the mitral valve during diastole, with left atrial distension and impaired filling of the left ventricle (Fig. 19-17). Mitral valve stenosis most commonly is the result of rheumatic fever.[44,45] Less frequently, the defect is congenital and manifests during infancy or early childhood. Mitral valve stenosis is a continuous, progressive, lifelong disorder consisting of a slow, stable course in the early years and progressive acceleration in later years.

Mitral valve stenosis is characterized by fibrous replacement of valvular tissue, along with stiffness and fusion of the valve apparatus. Typically, the mitral cusps fuse at the edges and involvement of the chordae tendineae causes shortening, which pulls the valvular structures deeply into the ventricles. As the resistance to flow through the valve increases, the left atrium becomes dilated and left atrial pressure increases. The increased left atrial pressure eventually is transmitted to the pulmonary venous system, causing pulmonary congestion. A characteristic auscultatory finding in mitral stenosis is an opening snap following the second heart sound due to the stiff mitral valve. As the stenosis worsens, there is a localized low-pitched diastolic murmur that increases in duration with the severity of the stenosis.

The manifestations of mitral valve stenosis depend on the severity of the obstruction and are related to the elevation in left atrial pressure and pulmonary congestion, decreased cardiac output owing to impaired left ventricular filling, and left atrial enlargement with the development of atrial arrhythmias and mural thrombi. The symptoms are those of pulmonary congestion, including nocturnal paroxysmal dyspnea and orthopnea. Palpitations, chest pain, weakness, and fatigue are common complaints. Paroxysmal atrial tachycardia and atrial fibrillation develop in 30% to 40% of persons with symptomatic mitral stenosis.[45] Together, the fibrillation and distention predispose to mural thrombus formation. The risk of arterial embolization, particularly stroke, is significantly increased in persons with atrial fibrillation.

Mitral Valve Regurgitation. Mitral valve regurgitation is characterized by incomplete closure of the mitral valve, with the left ventricular stroke volume being divided between the forward stroke volume that moves blood into the aorta and the regurgitant stroke volume that moves it back into the left atrium during systole (see Fig. 19-17). Mitral valve regurgitation can result from many processes. Rheumatic heart disease is associated with a rigid and thickened valve that does not open or close completely. In addition to rheumatic heart disease, mitral regurgitation can result from rupture of the chordae

tendineae or papillary muscles, papillary muscle dysfunction, or stretching of the valve structures due to dilation of the left ventricle or valve orifice. Mitral valve prolapse is a common cause of mitral valve regurgitation.

The hemodynamic changes associated with chronic mitral valve regurgitation have a slow rate of progression, allowing for recruitment of compensatory mechanisms. An increase in left ventricular end-diastolic volume permits an increase in total stroke volume, with restoration of forward flow into the aorta. Augmented preload and reduced or normal afterload (provided by unloading the left ventricle into the left atrium) facilitates left ventricular ejection. At the same time, a gradual increase in left atrial size allows for accommodation of the regurgitant volume at a lower filling pressure. A characteristic feature of mitral valve regurgitation is an enlarged left ventricle, a hyperdynamic left ventricular impulse, and a pansystolic (throughout systole) heart murmur. Mitral regurgitation, like mitral stenosis, predisposes to atrial fibrillation.

The increased volume work associated with mitral regurgitation is relatively well tolerated, and many persons with the disorder remain asymptomatic for many years, developing symptoms between 6 and 10 years after diagnosis. The degree of left ventricular enlargement reflects the severity of regurgitation. As the disorder progresses, left ventricular function becomes impaired, the forward (aortic) stroke volume decreases, and the left atrial pressure increases, with the subsequent development of pulmonary congestion. It is usually recommended that valve surgery be performed before the onset of these symptoms.

Mitral Valve Prolapse. Sometimes referred to as the *floppy mitral valve syndrome,* mitral valve prolapse occurs in 1% to 2.5% of the general population.[45] The disorder is seen more frequently in women than in men and may have a familial basis. Familial mitral valve prolapse is transmitted as an autosomal trait, and several chromosomal loci have been identified. Although the exact cause of the disorder usually is unknown, it has been associated with Marfan syndrome, osteogenesis imperfecta, and other connective tissue disorders, and with cardiac, hematologic, neuroendocrine, metabolic, and psychological disorders.

Pathologic findings in persons with mitral valve prolapse include a myxedematous (mucinous) degeneration of mitral valve leaflets that causes them to become enlarged and floppy so that they prolapse or balloon back into the left atrium during systole[44] (Fig. 19-18). Secondary fibrotic changes reflect the stresses and injury that the ballooning movements impose on the valve. Certain forms of mitral valve prolapse may arise from disorders of the myocardium that place undue stress on the mitral valve because of abnormal movement of the ventricular wall or papillary muscle. Mitral valve prolapse may or may not cause mitral regurgitation.

Most people with mitral valve prolapse are asymptomatic and the disorder is discovered during a routine physical examination. A minority of people have chest pain mimicking angina, dyspnea, fatigue, anxiety, palpitations, and light-headedness. Unlike angina, the chest pain often is prolonged, ill defined, and not associated with exercise or exertion. The pain has been attributed to ischemia resulting from traction of the prolapsing valve leaflets. The anxiety, palpitations, and arrhythmias may result from abnormal autonomic nervous system function that commonly accompanies the disorder. Rare cases of sudden death have been reported for persons with mitral valve prolapse, mainly those with a family history of similar occurrences.

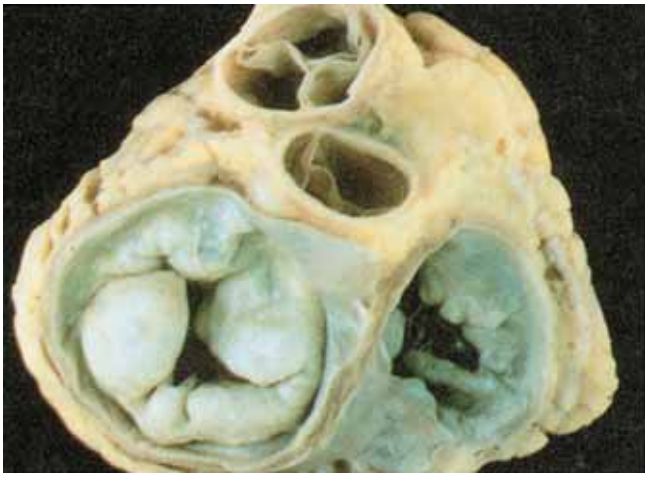


FIGURE 19-18.FF Mitral valve prolapse. A view of the mitral valve from the left atrium shows redundant and deformed leaflets that billow into the left atrial cavity. (From Saffitz J.E. [2008]. The heart. In Rubin E., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 464]. Philadelphia: Lippincott Williams & Wilkins.)

The disorder is characterized by a spectrum of auscultatory findings, ranging from a silent form to one or more midsystolic clicks followed by a late systolic or pansystolic murmur. The clicks are caused by the sudden tensing of the mitral valve apparatus as the leaflets prolapse. Two-dimensional and Doppler echocardiography is used to diagnose mitral valve prolapse.

The treatment of mitral valve prolapse focuses on the relief of symptoms and the prevention of complications.[45] Persons with palpitations and mild tachyarrhythmias or increased adrenergic symptoms, and those with chest discomfort, anxiety, and fatigue often respond to therapy with beta blockers. In many cases, the cessation of stimulants such as caffeine, alcohol, and cigarettes may be sufficient to control symptoms. Infective endocarditis is an uncommon complication in persons with a murmur; antibiotic prophylaxis may be recommended before extensive dental or surgical procedures associated with bacteremia. Transient ischemic attacks occur more frequently in persons with mitral valve prolapse. Therefore, in persons with documented events who are in sinus rhythm with no atrial thrombi, daily aspirin therapy is recommended. Persons with severe valve dysfunction may require valve surgery.

Aortic Valve Disorders

The aortic valve, which is located between the left ventricle and aorta, has three cuplike cusps and sometimes

is referred to as the *aortic semilunar valve* because its leaflets are crescent or moon shaped. The aortic valve has no chordae tendineae. Although their structures are similar, the edges of the aortic valve leaflets are thicker than those of the mitral valve, particularly at the middle of the leaflet (see Chapter 17, Fig. 17-10). The mechanism of action of the aortic valve is also different from that of the mitral valve. During ventricular systole when the ventricles contract and blood is being ejected into the aorta, the cusps of the valve are flattened against the aortic wall and blood rushes past them; when the ventricles relax and the blood (no longer propelled forward by the pressure of ventricular contraction) begins to flow backward toward the heart, it fills the cusps and closes the valve.

An important aspect of the aortic valve is the location of the orifices for the two main coronary arteries, which are located behind the valve and at right angles to the direction of blood flow. It is the lateral pressure in the aorta that propels blood into the coronary arteries. During the ejection phase of the cardiac cycle, the lateral pressure is diminished by conversion of potential energy to kinetic energy as blood moves forward into the aorta. This process is grossly exaggerated in aortic valve stenosis because of the high flow velocities.

Aortic Valve Stenosis. Aortic valve stenosis is characterized by narrowing of the valve orifice with increased resistance to ejection of blood from the left ventricle into the aorta (see Fig. 19-17). The most common causes of aortic valve stenosis are congenital valve malformations and acquired calcification of a normal tricuspid valve. Congenital malformations may result in unicuspid, bicuspid, or misshaped valve leaflets. Acquired aortic stenosis is usually the consequence of calcification associated with the normal "wear and tear" of either previously normal aortic valves or congenitally bicuspid valves (with which approximately 1% of the population are born).[9] The incidence of a acquired aortic valve stenosis is increasing with the rising average age of the population.[8,46]

The progression of calcific aortic stenosis is usually slow and varies widely among individuals. It usually becomes clinically evident in the sixth and seventh decades in persons with bicuspid aortic valves, and not until the eighth and ninth decades in those with previously normal valves. Valve changes range from mild thickening without obstruction to severe calcification with impaired leaflet motion and obstructed left ventricular outflow.[47] Processes in the development of calcific aortic valve disease have been shown to be similar to those in CAD. Both conditions are more common in men, older persons, and persons with hypercholesteremia, and both derive in part from an active inflammatory process.[46] Early lesions of aortic sclerosis show focal subendothelial plaquelike lesions, similar to the initial phases of an atherosclerotic lesion. Aortic sclerosis is distinguished from aortic stenosis by the degree of valve impairment. In aortic sclerosis the valve leaflets are abnormally thickened, but the obstruction to outflow is minimal, whereas in aortic stenosis the functional area of the valve has decreased enough to cause measurable obstruction to outflow. Calcification of the aortic valve progresses from the base of the cusps to the leaflets. This reduces leaflet motion and effective valve area, but without commissural fusion. As calcification progresses, the leaflets become more rigid, there is worsening of obstruction to left ventricular outflow, and fusion of the commissures leads to aortic stenosis.

Because aortic stenosis usually develops gradually, the left ventricle has time to adapt. With increased systolic pressure from obstruction, the left ventricular wall becomes thicker, or hypertrophies, but a normal chamber volume is maintained. This increase in wall thickness can maintain a normal ejection fraction. Little hemodynamic disturbance occurs as the valve opening area is reduced by half its normal size. However, an additional reduction in the valve opening area from one half to one fourth of its normal size produces severe obstruction to flow and a progressive pressure overload on the left ventricle. At this point, the increased work of the heart begins to exceed the coronary blood flow reserve, causing both systolic and diastolic dysfunction and signs of heart failure.[45–47]

Aortic stenosis is usually first diagnosed with auscultation of a loud systolic ejection murmur or a single or paradoxically split second heart sound. Eventually, the classic symptoms of angina, syncope, and heart failure develop, although more subtle signs of a decrease in exercise tolerance or exertional dyspnea should be monitored closely. Angina occurs in approximately two thirds of persons with advanced aortic stenosis and is similar to that observed in CAD. Dyspnea, marked fatigability, peripheral cyanosis, and other signs of low-output heart failure usually are not prominent until late in the course of the disease. Syncope (fainting) is most commonly due to the reduced cerebral circulation that occurs during exertion when the arterial pressure declines consequent to vasodilation in the presence of a fixed cardiac output.

Aortic Valve Regurgitation. Aortic valve regurgitation is the result of an incompetent aortic valve that allows blood to flow back to the left ventricle during diastole (see Fig. 19-17). As a result, the left ventricle must increase its stroke volume to accommodate blood entering from the lungs as well as that leaking back through the regurgitant valve. This defect may result from conditions that cause scarring of the valve leaflets or from enlargement of the valve orifice to the extent that the valve leaflets no longer meet. There are various causes of aortic regurgitation, including rheumatic fever, idiopathic dilation of the aorta, congenital abnormalities, infective endocarditis, and Marfan syndrome. Other causes include hypertension, trauma, and failure of a prosthetic valve.

Acute aortic regurgitation is characterized by the presentation of a sudden, large regurgitant volume to a left ventricle of normal size that has not had time to adapt to the volume overload. It is caused most commonly by disorders such as infective endocarditis, trauma, or aortic dissection. Although the heart responds with use of the Frank-Starling mechanism and an increase in heart rate, these compensatory mechanisms fail to maintain the cardiac output. As a result, there is severe elevation in left ventricular end-diastolic pressure, which is transmitted to the left atrium and pulmonary veins, culminating in

pulmonary edema. A decrease in cardiac output leads to sympathetic stimulation and a resultant increase in heart rate and peripheral vascular resistance that cause the regurgitation to worsen. Death from pulmonary edema, ventricular arrhythmias, or circulatory collapse is common in severe acute aortic regurgitation.

Chronic aortic regurgitation, which usually has a gradual onset, represents a condition of combined left ventricular volume and pressure overload. As the valve deformity increases, regurgitant flow into the left ventricle increases, diastolic blood pressure falls, and the left ventricle progressively enlarges. Hemodynamically, the increase in left ventricular volume results in the ejection of a large stroke volume that usually is adequate to maintain the forward cardiac output until late in the course of the disease. Most persons remain asymptomatic during this compensated phase, which may last decades. The only sign for many years may be a soft systolic aortic murmur.

As the disease progresses, signs and symptoms of left ventricular failure begin to appear. These include exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. In aortic regurgitation, failure of aortic valve closure during diastole causes an abnormal drop in diastolic pressure. Because coronary blood flow is greatest during diastole, the drop in diastolic pressure produces a decrease in coronary perfusion. Although angina is rare, it may occur when the heart rate and diastolic pressure fall to low levels. Persons with severe aortic regurgitation often complain of an uncomfortable awareness of heartbeat, particularly when lying down, and chest discomfort due to pounding of the heart against the chest wall. Tachycardia, occurring with emotional stress or exertion, may produce palpitations, head pounding, and premature ventricular contractions.

The major physical findings relate to the widening of the arterial pulse pressure. The pulse has a rapid rise and fall (Corrigan pulse), with an elevated systolic pressure and low diastolic pressure owing to the large stroke volume and rapid diastolic runoff of blood back into the left ventricle. Korotkoff sounds may persist to zero, even though intra-arterial pressure rarely falls below 30 mm Hg.[44] The large stroke volume and wide pulse pressure may result in prominent carotid pulsations in the neck, throbbing peripheral pulses, and a left ventricular impulse that causes the chest to move with each beat. The hyperkinetic pulse of more severe aortic regurgitation, called a *water-hammer pulse,* is characterized by distention and quick collapse of the artery. The turbulence of flow across the aortic valve during diastole produces a high-pitched or blowing sound.

Diagnosis and Treatment

Valvular defects usually are detected through cardiac auscultation (i.e., heart sounds). Echocardiography provides a means of visualizing valvular motion, patterns of flow, and closure patterns. Pulsed Doppler ultrasonography provides a semiquantitative or qualitative estimation of the severity of transvalvular gradients, right ventricular systolic pressure, and valvular regurgitation. Color flow Doppler provides a visual pattern of flow velocities over the anatomic 2-D echocardiographic image. This allows for demonstration of turbulence from stenotic and regurgitant valves. Transesophageal echocardiography with Doppler ultrasonography is used to obtain echocardiographic data when surface sound transmission is poor, particularly of the AV valves and prosthetic heart valves. Cardiac catheterization may be used to further describe the effects of the defect.

The treatment of valvular defects consists of medical management of heart failure and associated problems and surgical intervention to repair or replace the defective valve. Surgical valve repair or replacement depends on the valve that is involved and the extent of deformity. Valvular replacement with a prosthetic device or a homograft usually is reserved for severe disease because the ideal substitute valve has not as yet been developed. Percutaneous balloon valvuloplasty involves the opening of a stenotic valve by guiding an inflated balloon through the valve orifice. The procedure is done in the cardiac catheterization laboratory and involves the insertion of a balloon catheter into the heart through a peripheral blood vessel.

In summary, infective endocarditis involves the invasion of the endocardium by pathogens that produce vegetative lesions on the endocardial surface. The loose organization of these lesions permits the organisms and fragments of the lesions to be disseminated throughout the systemic circulation. Although several organisms can cause the condition, staphylococci have now become the leading cause of infective endocarditis. Treatment of infective endocarditis focuses on identifying and eliminating the causative microorganism, minimizing the residual cardiac effects, and treating the pathologic effect of emboli.

Rheumatic fever, an immune-mediated, multisystem inflammatory disease associated with a group A (β-hemolytic) streptococcal (GAS) pharyngitis, is an important cause of heart disease. Its most serious and disabling effects result from involvement of the heart valves. Because there is no single laboratory test result, sign, or symptom that is pathognomonic for acute rheumatic fever, the Jones criteria are used to establish the diagnosis during the acute stage of the disease. Primary and secondary prevention strategies focus on appropriate antibiotic therapy.

Dysfunction of the heart valves can result from a number of disorders, including congenital defects, rheumatic heart disease, trauma, ischemic heart disease, degenerative changes, and inflammation. Valvular heart disease produces its effects through disturbances of blood flow. A stenotic valvular defect is one that causes a decrease in blood flow through a valve, resulting in impaired emptying and increased work demands on the heart chamber that empties blood across the diseased valve. A regurgitant valvular defect permits the blood flow to continue when the valve is closed. Valvular heart disorders produce blood flow turbulence and often are detected through cardiac auscultation.

Heart Disease in Infants and Children

Heart disease in children encompasses both congenital and acquired disorders. Approximately 1 of every 125 infants born has a congenital heart defect, making this the most common form of structural birth defect.[1] Advances in diagnostic methods and surgical treatment have greatly increased the long-term survival and outcomes for children born with congenital heart defects. Although thousands of infants born each year will have a congenital heart disease, other children will develop an acquired heart disease, including Kawasaki disease. Two other acquired disorders that affect children, the cardiomyopathies and rheumatic fever, were discussed earlier in the chapter.

Fetal and Perinatal Circulation

The fetal circulation is different anatomically and physiologically from the postnatal circulation. Before birth, oxygenation of blood occurs through the placenta, and after birth, it occurs through the lungs. The fetus is maintained in a low-oxygen state (PO_2 30 to 35 mm Hg; hemoglobin O_2 saturation 60% to 70%). To compensate, fetal cardiac output is higher than at any other time in life (400 to 500 mL/kg/minute) and fetal hemoglobin has a higher affinity for oxygen.[48] Also, the pulmonary vessels in the fetus are markedly constricted because of the fluid-filled lungs and the heightened hypoxic stimulus for vasoconstriction that is present in the fetus. As a result, blood flow through the lungs is less than at any other time in life.

In the fetus, blood enters the circulation through the umbilical vein and returns to the placenta through the two umbilical arteries[49,50] (Fig. 19-19). A vessel called the *ductus venosus* allows the majority of blood from the umbilical vein to bypass the hepatic circulation and pass directly into the inferior vena cava. From the inferior vena cava, blood flows into the right atrium, where approximately 40% of the blood volume moves through the foramen ovale into the left atrium. It then passes into the left ventricle and is ejected into the ascending aorta to perfuse the head and upper extremities. In this way, the best-oxygenated blood from the placenta is used to perfuse the brain. At the same time, venous blood from the head and upper extremities returns to the right side of the heart through the superior vena cava, moves into the right ventricle, and is ejected into the pulmonary artery. Because of the very high pulmonary vascular resistance that is present, almost 90% of blood ejected into the pulmonary artery gets diverted through the ductus arteriosus into the descending aorta. This blood perfuses the lower extremities and is returned to the placenta by the umbilical arteries.

At birth, the infant takes its first breath and switches from placental to pulmonary oxygenation of the blood. The most dramatic alterations in the circulation after birth are the elimination of the low-resistance placental vascular bed and the marked pulmonary vasodilation

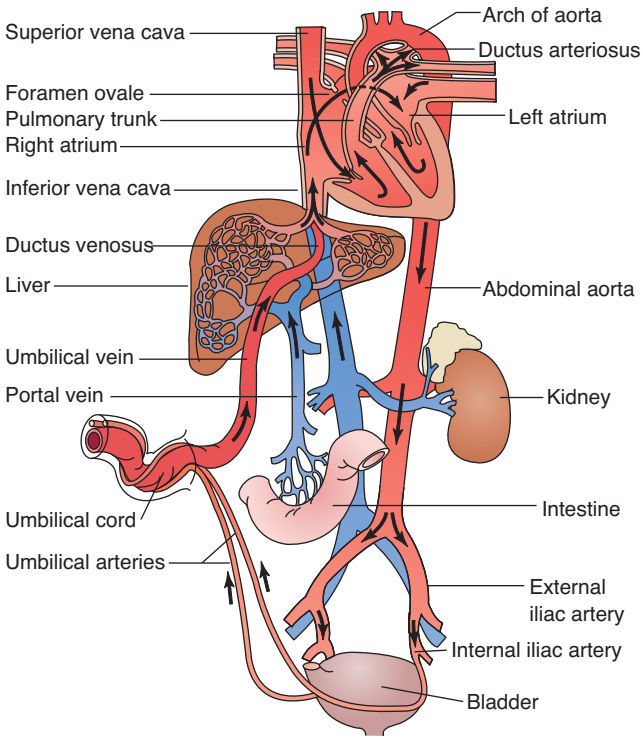


FIGURE 19-19. Fetal circulation.

that is produced by initiation of ventilation. Within minutes of birth, pulmonary blood flow increases from 35 mL/kg/minute to 160 to 200 mL/kg/minute.[48] The pressure in the pulmonary circulation and the right side of the heart falls as fetal lung fluid is replaced by air and as lung expansion decreases the pressure transmitted to the pulmonary blood vessels. With lung inflation, the alveolar oxygen tension increases, causing reversal of the hypoxemia-induced pulmonary vasoconstriction of the fetal circulation. Cord clamping and removal of the low-resistance placental circulation produce an increase in systemic vascular resistance and a resultant increase in left ventricular pressure. The resultant decrease in right atrial pressure and increase in left atrial pressure produce closure of the foramen ovale flap valve. Reversal of the fetal hypoxemic state also produces constriction of ductal smooth muscle, contributing to closure of the ductus arteriosus. The foramen ovale and the ductus arteriosus normally close within the first day of life, effectively separating the pulmonary and systemic circulations.

After the initial precipitous fall in pulmonary vascular resistance, a more gradual decrease occurs, related to regression of the medial smooth muscle layer in the pulmonary arteries that occurs during the first 2 to 9 weeks of life. By the time a healthy, term infant is several weeks old, the pulmonary vascular resistance has fallen to adult levels. Several factors, including alveolar hypoxia, prematurity, lung disease, and congenital heart defects, may affect postnatal pulmonary vascular development. Much of the development of the smooth muscle layer in the pulmonary arterioles occurs during late gestation; as a result, infants born prematurely have less medial smooth muscle.

These infants follow the same pattern of smooth muscle regression, but because less muscle exists, the muscle layer may regress in a shorter time. The pulmonary vascular smooth muscle in premature infants also may be less responsive to hypoxia. For these reasons, a premature infant may demonstrate a larger decrease in pulmonary vascular resistance and a resultant shunting of blood from the aorta through the ductus arteriosus to the pulmonary artery within hours of birth.

Alveolar hypoxia may also delay or prevent the normal decrease in pulmonary vascular resistance that occurs during the first few weeks of life. During this period, the pulmonary arteries remain highly reactive and can constrict in response to hypoxia, acidosis, hyperinflation of the alveoli, and hypothermia. Thus, alveolar hypoxia during the first days of life may delay or prevent the normal decrease in pulmonary vascular resistance.

Congenital Heart Defects

The major development of the fetal heart occurs between the fourth and seventh weeks of gestation, and most congenital heart defects arise during this time. The development of the heart can be altered by environmental, genetic, or chromosomal influences. Most congenital heart defects are thought to be multifactorial in origin, resulting from an interaction between a genetic predisposition toward development of a heart defect and environmental influences.

Knowledge about the genetic basis of congenital heart defects has grown dramatically in recent years. This area of research is particularly important as more individuals with congenital heart disease survive into adulthood and consider having children of their own. Recent knowledge suggests that the genetic contribution to congenital heart disease has been underestimated in the past.[51,52] Some heart defects, such as aortic stenosis, atrial septal defect of the secundum type, pulmonary valve stenosis, tetralogy of Fallot, and certain ventricular septal defects, have a stronger familial predisposition than others. Chromosomal abnormalities are also associated with congenital heart defects, as evidenced by the observation that as much as 30% of children with congenital heart disease have an associated chromosomal abnormality. Heart disease is found in nearly 100% of children with trisomy 18, 50% of those with trisomy 21, and 35% of those with Turner syndrome.[52]

Anatomic and Hemodynamic Effects

Congenital heart diseases are commonly classified according to their anatomic site (atrial septal or ventricular septal defects), the hemodynamic alterations caused by the anatomic defects (left-to-right or right-to-left shunts), and their effect on pulmonary blood flow and tissue oxygenation (cyanotic or noncyanotic defects).

Shunting and Cyanotic Disorders. Shunting of blood refers to the diversion of blood flow from one system to the other—from the arterial to the venous system (i.e., left-to-right shunt) or from the venous to the arterial system (i.e., right-to-left shunt).[50] The shunting of blood in congenital heart defects is determined by the presence of an abnormal opening between the right and left circulations and the degree of resistance to flow through the opening. The shunting of blood can affect both the oxygen content of the blood and the volume of blood being delivered to the vessels in the pulmonary circulation.

The direction of shunting (right-to left or left-to-right) is largely determined by the vascular resistance of the systemic and pulmonary circulations. Because of the high pulmonary vascular resistance in the neonate, atrial and ventricular septal defects usually do not produce significant shunt during the first weeks of life. As the pulmonary vascular smooth muscle regresses in the neonate, the resistance in the pulmonary circulation falls below that of the systemic circulation, causing a left-to-right shunt in uncomplicated atrial or ventricular septal defects. In more complicated ventricular septal defects, increased resistance to outflow may affect the pattern of shunting. For example, defects that increase resistance to aortic outflow (e.g., aortic valve stenosis, coarctation of the aorta, hypoplastic left heart syndrome) increase left-to-right shunting, whereas defects that obstruct pulmonary outflow (e.g., pulmonary valve stenosis, tetralogy of Fallot) increase right-to-left shunting. Crying, defecating, or even the stress of feeding may increase pulmonary vascular resistance and cause an increase in right-to-left shunting in infants with septal defects.

Cyanosis, a bluish color of the skin, most notable in the nail beds and mucous membranes, develops when sufficient deoxygenated blood from the right side of the heart mixes with oxygenated blood in the left side of the heart.[53,54] Abnormal color becomes obvious when the oxygen saturation falls below 80% in the capillaries (equal to 5 g of deoxygenated hemoglobin). Defects that result in a right-to-left shunting or obstruction of pulmonary blood flow are categorized as cyanotic disorders and those involving left-to-right shunting are usually categorized as acyanotic disorders. Of the congenital defects discussed in this chapter, patent ductus arteriosus, atrial and ventricular septal defects, endocardial cushion defects, pulmonary valve stenosis, and coarctation of the aorta are considered defects with little or no cyanosis; tetralogy of Fallot, transposition of the great vessels, and single-ventricle anatomy are considered defects with cyanosis.

A right-to-left shunt results in deoxygenated blood moving from the right side of the heart to the left side and then being ejected into the systemic circulation. With a left-to-right shunt, oxygenated blood intended for ejection into the systemic circulation is recirculated through the right side of the heart and back through the lungs. This increased volume distends the right side of the heart and pulmonary circulation and increases the workload placed on the right ventricle.[55]

Pulmonary Blood Flow. Many of the complications of congenital heart disorders result from a decrease or an increase in pulmonary blood flow. Defects that reduce pulmonary blood flow (e.g., pulmonary stenosis) typically cause symptoms of fatigue, dyspnea, and failure to thrive. In contrast to the arterioles in the systemic circulation,

the arterioles in the pulmonary circulation are normally thin-walled vessels that can accommodate the various levels of stroke volume that are ejected from the right heart. The thinning of the pulmonary vessels occurs during the first weeks after birth, during which the vessel media thin and pulmonary vascular resistance decreases. In a term infant who has a congenital heart defect that produces markedly increased pulmonary blood flow (e.g., ventricular septal defect), the increased flow stimulates pulmonary vasoconstriction and delays or reduces the normal involutional thinning of the small pulmonary arterioles. In most cases pulmonary vascular resistance is only slightly elevated during early infancy, and the major contribution to pulmonary hypertension is the increased blood flow. However, in some infants with a large right-to-left shunt, the pulmonary vascular resistance never decreases.

Congenital heart defects that persistently increase pulmonary blood flow or pulmonary vascular resistance have the potential of causing pulmonary hypertension and producing irreversible pathologic changes in the pulmonary vasculature. When shunting of systemic blood flow into the pulmonary circulation threatens permanent injury to the pulmonary vessels, a surgical procedure should be done to reduce the flow temporarily or permanently. Pulmonary artery banding consists of placing a constrictive band around the main pulmonary artery, thereby increasing resistance to outflow from the right ventricle. The banding technique is a temporary measure to alleviate symptoms and protect the pulmonary vasculature in anticipation of later surgical repair of the defect.

Manifestations and Treatment

It is increasingly common for congenital heart defects to be diagnosed prenatally. In this case, the infant can be evaluated shortly after birth to confirm the diagnosis and develop a treatment plan. Reliable diagnostic images of the fetal heart can be obtained as early as 16 weeks of gestation, and research designed to view the heart at an even earlier stage of development is under way. Among the disorders that can be diagnosed with certainty by fetal echocardiography are AV septal defects, hypoplastic left heart syndrome, aortic valve stenosis, hypertrophic cardiomyopathy, pulmonic valve stenosis, and transposition of the great arteries. Disorders that result in an abnormal four-chamber view, an image typically obtained during routine prenatal ultrasonography, are the most likely to be detected.[56]

In the postnatal period, congenital heart defects may present with numerous signs and symptoms. Some defects, such as patent ductus arteriosus and small ventricular septal defects, close spontaneously. In other less severe defects, there may be no obvious signs and symptoms and the disorder may be discovered during a routine health examination. Cyanosis, pulmonary congestion, cardiac failure, and decreased peripheral perfusion are the major concerns in children with more severe defects. Such defects often cause problems immediately after birth or early in infancy. The child may exhibit cyanosis, respiratory difficulty, and fatigability, and is likely to have difficulty with feeding and failure to thrive. Heart failure manifests itself as tachypnea or dyspnea at rest or on exertion. For the infant, this most commonly occurs during feeding. Recurrent respiratory infections and excessive sweating may also be reported.[57] The infant whose peripheral perfusion is markedly decreased may be in a shocklike state.

A generalized cyanosis that persists longer than 3 hours after birth suggests congenital heart disease. An oxygen challenge (administration of 100% oxygen for 5 to 10 minutes) can help to determine whether congenital heart disease is present in a cyanotic newborn.[57] Because infant cyanosis may appear as duskiness, it is important to assess the color of the mucous membranes, fingernails, toenails, tongue, and lips. Pulmonary congestion in the infant causes an increase in respiratory rate, orthopnea, grunting, wheezing, coughing, and crackles. A chest radiograph can quickly differentiate infants who have reduced pulmonary vascular markings (densities) from those who have normal or increased markings.

The treatment plan usually includes supportive therapy (e.g., digoxin, diuretics, and feeding supplementation) designed to help the infant compensate for the limitations in cardiac reserve and to prevent complications. Surgical intervention often is required for severe defects. It may be done in the early weeks of life or, conditions permitting, delayed until the child is older. A discussion of congestive heart failure in children is presented in Chapter 20.

Children with structural congenital heart disease and those who have had corrective surgery may have a higher-than-expected risk for development of infective endocarditis. Prophylactic antibiotic therapy before dental procedures or other periods of increased risk for bacteremia is suggested for children with certain types of heart defects or surgical procedures.[58]

Types of Defects

Congenital heart defects can affect almost any of the cardiac structures or central blood vessels (Fig. 19-20). Defects include communication between heart chambers, interrupted development of the heart chambers or valve structures, malposition of heart chambers and great vessels, and altered closure of fetal communication channels. The particular defect reflects the embryo's stage of development at the time it occurred. It is common for multiple defects to be present in one child and for some congenital heart disorders, such as tetralogy of Fallot, to involve several defects.

Patent Ductus Arteriosus. Patent ductus arteriosus results from persistence of the fetal ductus beyond the prenatal period.[51] In fetal life, the ductus arteriosus is the vital link by which blood from the right side of the heart bypasses the lungs and enters the systemic circulation (Fig. 19-20G). After birth, this passage no longer is needed, and it usually closes during the first 24 to 72 hours. The physiologic stimulus and mechanisms associated with permanent closure of the ductus are not entirely known, but the fact that infant hypoxia predisposes to a delayed closure

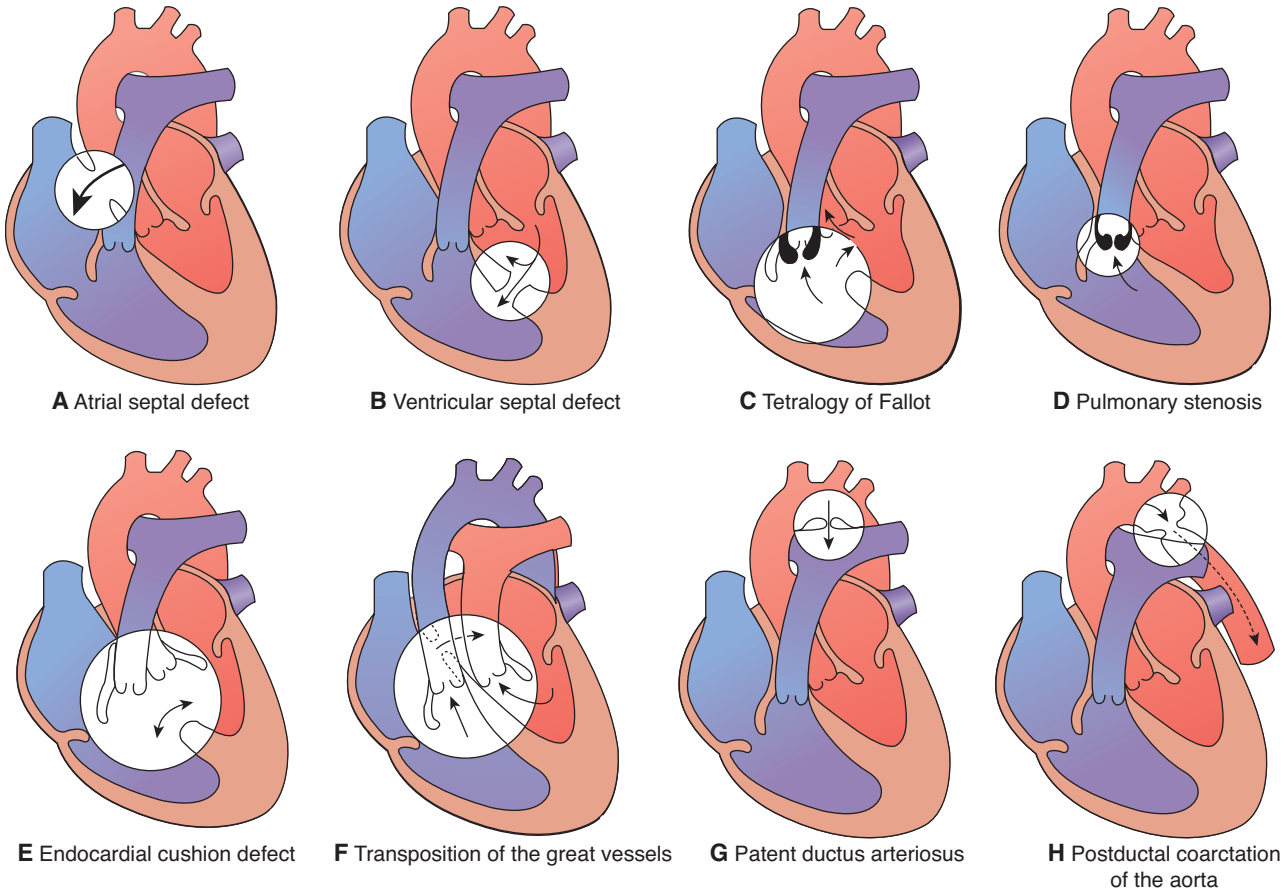


FIGURE 19-20. Congenital heart defects. **(A)** Atrial septal defect. Blood is shunted from left to right. **(B)** Ventricular septal defect. Blood is usually shunted from left to right. **(C)** Tetralogy of Fallot. This involves a ventricular septal defect, dextroposition of the aorta, right ventricular outflow obstruction, and right ventricular hypertrophy. Blood is shunted from right to left. **(D)** Pulmonary stenosis, with decreased pulmonary blood flow and right ventricular hypertrophy. **(E)** Endocardial cushion defect. Blood flows between the chambers of the heart. **(F)** Transposition of the great vessels. The pulmonary artery is attached to the left side of the heart and the aorta to the right side. **(G)** Patent ductus arteriosus. The high-pressure blood of the aorta is shunted back to the pulmonary artery. **(H)** Postductal coarctation of the aorta.

suggests that the increase in arterial oxygen levels that occurs immediately after birth plays a role. Additional factors that contribute to closure are a fall in endogenous levels of prostaglandins and adenosine and the release of vasoactive substances. After constriction, the lumen of the ductus becomes permanently sealed with fibrous tissue within 2 to 3 weeks. Ductal closure may be delayed or prevented in very premature infants, probably as a result of a combination of factors, including decreased medial smooth muscle in the ductus wall, a decreased vasoconstriction response to oxygen, and increased circulating levels of prostaglandins, which have a vasodilating effect. Ductal closure also may be delayed in infants with congenital heart defects that produce a decrease in oxygen tension.[54]

Persistent patency of the ductus arteriosus is defined as a duct that remains open beyond 3 months in the full-term infant. The size of the persistent ductus and the difference between the systemic and pulmonary vascular resistance determine its clinical manifestations. Blood typically shunts across the ductus from the higher-pressure left side (systemic circulation) to the lower-pressure right side (pulmonary circulation). After the infant's pulmonary vascular resistance falls, the patent ductus arteriosus provides for a continuous runoff of aortic blood into the pulmonary artery. With a large patent ductus, the runoff is continuous, resulting in increased pulmonary blood flow, pulmonary congestion, and increased resistance against which the right side of the heart must pump. Increased pulmonary venous return and increased work demands may lead to left ventricular failure.[50]

Spontaneous closure of the ductus seldom occurs after infancy. In the full-term infant or older child, closure can be achieved with either surgical ligation or device occlusion. In children with a small patent ductus, closure is done to prevent infective endocarditis or other complications. In children with a moderate to large patent ductus, closure is accomplished to treat heart failure or prevent the development of pulmonary vascular disease, or both.[50] Drugs that inhibit prostaglandin synthesis

(e.g., indomethacin) may be used to induce closure of a patent ductus in preterm newborns.[54] Indomethacin works best if it is used in infants younger than 13 days of age; it is not effective later than 4 to 6 weeks of age.[54]

Although closure of a patent ductus is uniformly recommended when it is present as an isolated lesion, deliberate maintenance of ductal patency can be a lifesaving therapy for children with complex forms of congenital heart disease who have ductal-dependent pulmonary or systemic blood flow, or those with obligatory mixing of the arterial and venous circulations (i.e., transposition of the great arteries). Intravenous infusion of prostaglandin E_1 (PGE_1) has proved extremely effective in maintaining ductal patency or reopening the ductus in newborns. Today, this therapy is routinely administered to newborns with suspected congenital heart defects until they can be transported to a specialized center where a diagnosis can be confirmed.[54]

Atrial Septal Defects. In atrial septal defects, an opening in the atrial septum persists as a result of improper septal formation[50,54] (see Fig. 19-20A). Partitioning of the atria takes place during the fourth and fifth weeks of development and occurs in two stages, beginning with the formation of a thin, crescent-shaped membrane called the *septum primum* followed by the development of a second membrane called the *septum secundum*. As the septum secundum develops, it gradually overlaps an opening in the upper part of the septum primum, forming an oval opening with a flap-type valve called the *foramen ovale* (Fig. 19-21). The foramen ovale, which closes shortly after birth, allows blood from the umbilical vein to pass directly into the left heart, bypassing the lungs.

Atrial septal defects may be single or multiple and vary from a small, asymptomatic opening to a large, symptomatic opening. The type of defect is determined by its position and may include an abnormal opening in the septum primum (ostium primum defects), the septum secundum (ostium secundum defects), or a patent foramen ovale. An ostium secundum atrial septal defect in the region of the foramen ovale is the most common defect. The defect may be single or multiple (fenestrated atrial septum). Most atrial septal defects are small and young children with these defects are often asymptomatic, with the defects discovered inadvertently during a routine physical examination at a few years of age.[59] In the case of an isolated septal defect large enough to allow shunting, the flow of blood usually is from the left side to the right side of the heart because of the more compliant right ventricle and because the pulmonary vascular resistance is lower than the systemic vascular resistance. This produces right ventricular volume overload and increased pulmonary blood flow.

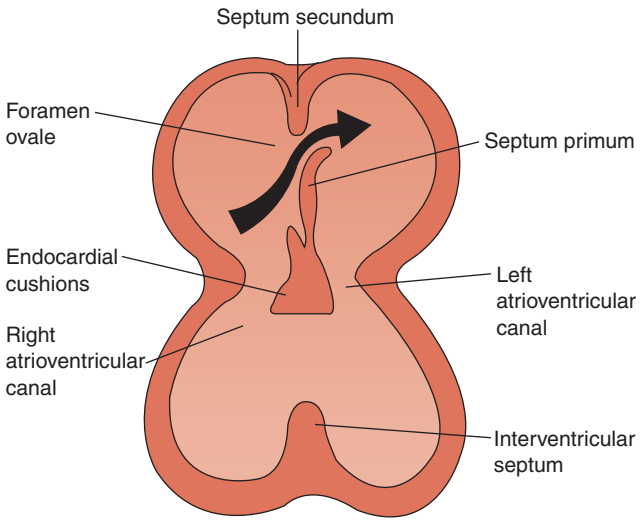


FIGURE 19-21. Development of the endocardial cushions, right and left atrioventricular canals, interventricular septum, and septum primum and septum secundum of the foramen ovale. Note that blood from the right atrium flows through the foramen ovale to the left atrium.

Intracardiac shunting is usually from left to right and may increase with age as the right ventricle becomes more compliant. In most cases there is a moderate shunt resulting in dilation of the right heart chambers and overperfusion of the pulmonary circulation. Children with undiagnosed atrial defects are at risk for pulmonary vascular disease, although this is a rare occurrence before 20 years of age. Rarely, infants with a large shunt may develop congestive heart failure and failure to thrive, prompting early closure of the defect.[59] Adolescents and young adults may experience atrial flutter or atrial fibrillation and palpitations because of atrial dilatation. Larger symptomatic defects are usually treated surgically or by transcatheter device closure. Smaller defects may be observed for spontaneous closure in the young child.

Ventricular Septal Defects. A ventricular septal defect is an opening in the ventricular septum that results from an incomplete separation of the ventricles during early fetal development (see Fig. 19-20B). These defects may be single or multiple and may occur in any position along the ventricular septum. Ventricular septal defects are the most common form of congenital heart defect, accounting for 25% to 30% of congenital heart disorders.[50] A ventricular septal defect may be the only cardiac defect, or it may occur in association with multiple cardiac anomalies.

The ventricular septum originates from two sources: the interventricular groove of the folded tubular heart that gives rise to the muscular part of the septum, and the endocardial cushions that extend to form the membranous portion of the septum. The upper membranous portion of the septum is the last area to close, typically by the seventh week of gestation, and it is here that most defects occur.

Depending on the size of the opening and the pulmonary vascular resistance, the signs and symptoms of a ventricular septal defect may range from an asymptomatic murmur to congestive heart failure.[57] If the defect is small, it allows a small shunt and small increases in pulmonary blood flow. These defects produce few symptoms, and approximately one third close spontaneously. With medium-sized defects, a larger shunt occurs, producing a larger increase in pulmonary blood flow (i.e., twice as much blood may pass through the pulmonary circulation as through the systemic circulation). The increased pulmonary flow most often occurs under relatively low pressure. Most of the children with such

defects are asymptomatic and have a low risk for development of pulmonary vascular disease.

In children with large nonrestrictive defects, right and left ventricular pressure is equalized and the degree of shunting is determined by the ratio of pulmonary to systemic vascular resistance. Pulmonary vascular resistance normally falls rapidly after birth, owing to the onset of ventilation and subsequent release of hypoxic pulmonary vasoconstriction. This process is often delayed in infants with large ventricular septal defects. As a result, the pulmonary vascular resistance remains somewhat higher than normal, and thus the size of the left-to-right shunt may initially be limited. As the pulmonary vascular resistance falls during the first few weeks after birth because of normal thinning of the media of the small pulmonary arterioles, the size of the left-to right shunt increases. Eventually, a large left-to-right shunt develops, and clinical symptoms (e.g., tachypnea; diaphoresis, especially with feeding; and failure to thrive) become apparent. In most cases pulmonary vascular pressure is only slightly elevated during infancy, and the major contributor to pulmonary hypertension is an increase in pulmonary blood flow. However, in some infants with a large septal defect, pulmonary arteriolar thickness never decreases. With continued exposure to high pulmonary blood flow, pulmonary vascular disease develops. In untreated patients, the pulmonary vascular resistance can eventually exceed the systemic resistance. In this case, a reversal of shunt flow occurs and the child demonstrates progressive cyanosis as deoxygenated blood moves from the right to the left side of the heart. These symptoms, coupled with irreversible changes in the pulmonary vasculature, represent an end-stage form of congenital heart disease called *Eisenmenger syndrome*.

The treatment of a ventricular septal defect depends on the size of the defect, accompanying hemodynamic derangements, and symptomatology. Children with small or medium-sized defects may be followed without intervention if they remain free from signs of congestive heart failure or pulmonary hypertension. Ventricular defects do not increase in size, and some spontaneously close over time.[59] Prophylactic antibiotic therapy is given during periods of increased risk for bacteremia. The management of infants with large ventricular defects aims to control heart failure and prevent the development of pulmonary vascular disease. Symptomatic infants may require feeding supplements or tube feeding to promote growth and development. In the symptomatic infant in whom complete repair cannot be achieved because of size or other complicating lesions, a palliative procedure may be performed to reduce symptoms. Placement of a synthetic band around the main pulmonary artery (pulmonary artery banding) can reduce pulmonary blood flow until complete repair can be accomplished. Surgical closure of the defect is completed by placement of a synthetic or autologous patch effectively to close the shunt across the ventricular septum. These procedures are typically done electively in the infant or young child and are associated with low morbidity and mortality rates.

Endocardial Cushion Defects. The endocardial cushions form the AV canals, the upper part of the ventricular septum, and the lower part of the atrial septum. The AV canal connects the atria to the ventricles during early cardiac development. The endocardial cushions surround this canal and contribute tissue to the lower part of the atrial septum, the upper part of the ventricular septum, the septal leaflet of the tricuspid valve, and the anterior leaflet of the mitral valve.[60] Any flaw in the development of these tissues results in an endocardial cushion defect. Endocardial cushion defects are responsible for approximately 2% of all congenital heart defects. As many as 30% of children with Down syndrome have endocardial cushion defects.[54]

Because the endocardial cushions contribute to multiple aspects of heart development, several variations of endocardial cushion defects are possible. The defect may be described as *partial* or *complete*. The anatomy of the AV valve determines the classification. In partial AV canal defects, the two AV valve rings are complete and separate. The most common type of partial AV canal defect is an ostium primum defect, often associated with a cleft in the mitral valve. In a complete canal defect, there is a common AV valve orifice along with defects in both the atrial and ventricular septal tissue (see Fig. 19-20E). Other cardiac defects may be associated with endocardial cushion defects and most commonly include cardiac malposition defects and tetralogy of Fallot.[60]

Physiologically, endocardial cushion defects result in abnormalities similar to those described for atrial or ventricular septal defects. The direction and magnitude of a shunt in a child with an endocardial cushion defect are determined by the combination of defects and the child's pulmonary and systemic vascular resistance. The hemodynamic effects of an isolated ostium primum defect are those of the previously described atrial septal defect. These children are largely asymptomatic during childhood. With a complete AV canal defect, pulmonary blood flow is increased after the pulmonary vascular resistance falls because of left-to-right shunting across both the ventricular and atrial septal defects. Children with complete defects often have effort intolerance, easy fatigability, failure to thrive, recurrent infections, and other signs of congestive heart failure, particularly when the shunt is large. Pulmonary hypertension and increased pulmonary vascular resistance result if the lesion is left untreated.

The timing of treatment for endocardial cushion defects is determined by the severity of the defect and symptoms. With an ostium primum defect, surgical repair usually is planned on an elective basis before the child reaches school age. Corrective surgery is required for all complete AV canal defects. Infants with severe symptoms may require a palliative procedure where the main pulmonary artery is banded to reduce pulmonary blood flow. This typically improves the infant's ability to grow and develop until a complete repair can be performed.[54,57,59]

Pulmonary Stenosis. Obstruction of blood flow from the right ventricle to the pulmonary circulation is termed *pulmonary stenosis*. The obstruction can occur as an isolated valvular lesion, within the right ventricular chamber, in the pulmonary arteries, or as a combination of stenoses in multiple areas. It is a relatively common

defect, estimated to account for approximately 10% of all congenital cardiac disease, and is often associated with other abnormalities.[57,59]

Pulmonary valvular defect, the most common type of disorder, usually produces some impairment of pulmonary blood flow and increases the workload imposed on the right side of the heart (see Fig. 19-20D). Most children with pulmonic valve stenosis have mild stenosis that does not increase in severity. These children are largely asymptomatic and are diagnosed by the presence of a systolic murmur. Moderate or greater stenosis has been shown to progress over time, particularly before 12 years of age, so these children require careful follow-up. Critical pulmonary stenosis in the neonate is evidenced by cyanosis due to right-to-left atrial-level shunting and right ventricular hypertension. These infants require prostaglandin E_1 to maintain circulation to the lungs through the ductus arteriosus.[57,59]

Pulmonary valvotomy is the treatment of choice for all valvular defects with pressure gradients from the right ventricle to the pulmonary circulation greater than 30 mm Hg. Transcatheter balloon valvuloplasty has been quite successful in this lesion. Stenosis in the peripheral pulmonary arteries can also be effectively treated with balloon angioplasty, with or without stent placement.[57,59]

Tetralogy of Fallot. Tetralogy of Fallot is the most common cyanotic congenital heart defect, accounting for approximately 5% to 7% of all congenital heart defects.[50] As the name implies, tetralogy of Fallot consists of four associated defects: (1) a ventricular septal defect involving the membranous septum and the anterior portion of the muscular septum; (2) dextroposition or shifting to the right of the aorta, so that it overrides the right ventricle and is in communication with the septal defect; (3) obstruction or narrowing of the pulmonary outflow channel, including pulmonic valve stenosis, a decrease in the size of the pulmonary trunk, or both; and (4) hypertrophy of the right ventricle because of the increased work required to pump blood through the obstructed pulmonary channels[50] (see Fig. 19-20C). Variations of the defect can include complete atresia of the pulmonary valve or absence of pulmonary valve tissue altogether.

Most children with tetralogy of Fallot display some degree of cyanosis that is caused by a right-to-left shunt across the ventricular septal defect. The degree of cyanosis is determined by the restriction of blood flow into the pulmonary bed. Right ventricular outflow obstruction causes deoxygenated blood from the right ventricle to shunt across the ventricular septal defect and be ejected into the systemic circulation. The degree of obstruction may be dynamic and can increase during periods of stress, causing hypercyanotic attacks ("tet spells"). These spells typically occur in the morning during crying, feeding, or defecating. These activities increase the infant's oxygen requirements. Crying and defecating may further increase pulmonary vascular resistance, thereby increasing right-to-left shunting and decreasing pulmonary blood flow. With the hypercyanotic spell, the infant becomes acutely cyanotic, hyperpneic, irritable, and diaphoretic. Later in the spell, the infant becomes limp and may lose consciousness. Placing the infant in the knee–chest position increases systemic vascular resistance, which increases pulmonary blood flow and decreases right-to-left shunting. During a hypercyanotic spell, toddlers and older children may spontaneously assume the squatting position, which functions like the knee–chest position to relieve the spell.

Total surgical correction is required for all children with tetralogy of Fallot. Early definitive repair in infancy is currently advocated in most centers experienced in intracardiac surgery in infants.[61]

Transposition of the Great Arteries. In complete transposition of the great arteries, the aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle (see Fig. 19-20F). The defect is more common in infants whose mothers have diabetes and is two to three times more common in boys.[50,62]

Cyanosis is the most common presenting symptom resulting from an anomaly that allows the systemic venous return to be circulated through the right heart and ejected into the aorta, and the pulmonary venous return to be recirculated to the lungs through the left ventricle and main pulmonary artery.[57] In infants born with this defect, survival depends on communication between the right and left sides of the heart in the form of a patent ductus arteriosus or septal defect. Ventricular septal defects are present in 50% of infants with transposition of the great arteries at birth and may allow effective mixing of blood. Prostaglandin E_1 should be administered to neonates when this lesion is suspected in an effort to maintain the patency of the ductus arteriosus. Balloon atrial septostomy may be done to increase the blood flow between the two sides of the heart. In this procedure, a balloon-tipped catheter is inserted into the heart through the vena cava and then passed through the foramen ovale into the left atrium. The balloon is then inflated and pulled back through the foramen ovale, enlarging the opening as it goes.

Corrective surgery is essential for long-term survival. An arterial switch procedure, the current operation of choice, has survival rates greater than 90%.[57] This procedure, which corrects the relation of the systemic and pulmonary blood flows, is preferably performed in the first 2 to 3 weeks of life, before the postnatal reduction in pulmonary vascular resistance occurs. The coronary arteries are moved to the left-sided great artery and any ventricular septal defects are closed during the same operation. Complications of the arterial switch procedure may include coronary insufficiency, supravalvar pulmonary stenosis, neoaortic regurgitation, and rhythm abnormalities.[62]

Coarctation of the Aorta. Coarctation of the aorta consists of a localized narrowing of the aorta. It can occur proximal to (preductal) (see Fig. 19-20H), distal to (postductal), or opposite of (juxtaductal) the entry of the ductus arteriosus. Approximately 98% of coarctations are juxtaductal. The defect is frequently associated with other congenital cardiac lesions, most commonly bicuspid aortic valve, and occurs in approximately 10% of subjects with Turner syndrome, suggesting a genetic linkage[50,59] (see Chapter 6).

The classic sign of coarctation of the aorta is a disparity in pulsations and blood pressures in the arms and legs. The femoral, popliteal, and dorsalis pedis pulsations are weak or delayed compared with the bounding pulses of the arms and carotid vessels. Normally, the systolic blood pressure in the legs obtained by the cuff method is 10 to 20 mm Hg higher than in the arms. In coarctation, the pressure in the legs is lower and may be difficult to obtain. Patients with coarctation are often identified during a diagnostic workup for hypertension. Most patients with moderate coarctation remain otherwise asymptomatic owing to collateral vessels that form around the area of narrowing. Left untreated, however, coarctation will result in left ventricular hypertension and hypertrophy and significant systemic hypertension (see Chapter 18). Infants with severe coarctation demonstrate early symptoms of heart failure and may present in critical condition upon ductal closure. Reopening of the duct with prostaglandin E_1, if possible, and emergent surgery are needed in this subgroup.[57,59]

Children with coarctation causing a blood pressure gradient between the arms and legs of 20 mm Hg or greater should be treated ideally by 2 years of age to reduce the likelihood of persistent hypertension.[57,59] A surgical approach typically involves resection of the narrowed segment of the aorta and end-to-end anastomosis of healthy tissue. This can usually be accomplished without cardiopulmonary bypass, with a mortality rate near zero. Balloon angioplasty with or without stent placement has also been used, although the presence of residual gradients and the reliability of the surgical approach have limited this technique.[57,59]

Functional Single-Ventricle Anatomy. Several forms of complex congenital heart disease result in only one functional ventricle. Functional single-ventricle anatomy is the most common form of congenital heart disease diagnosed on routine prenatal ultrasonography. There may be a single right or a single left ventricle, or a ventricle of indeterminate morphology. Hypoplastic left heart syndrome, a term used to describe a group of closely related cardiac anomalies characterized by underdevelopment of the left cardiac chambers, is the most common form of this disorder. Several other forms of double-inlet ventricle have been described; however, all forms of this disease result in similar pathologic effects and follow a common pathway of intervention.[63–65]

All forms of single-ventricle anatomy result in a common mixing chamber of pulmonary and systemic venous return and cause varying degrees of cyanosis (Fig. 19-22). The single ventricle must pump blood to both the pulmonary and systemic circulations, and thus the flow to each circulation is determined by the resistance in each system.[64,65] As pulmonary vascular resistance falls, flow to the pulmonary circulation will be preferential and systemic circulation will be compromised. In some defects, such as hypoplastic left heart syndrome, systemic flow depends on a patent ductus arteriosus. Neonates with this lesion typically present with extreme cyanosis and symptoms of heart failure as the ductus begins to close.[66]

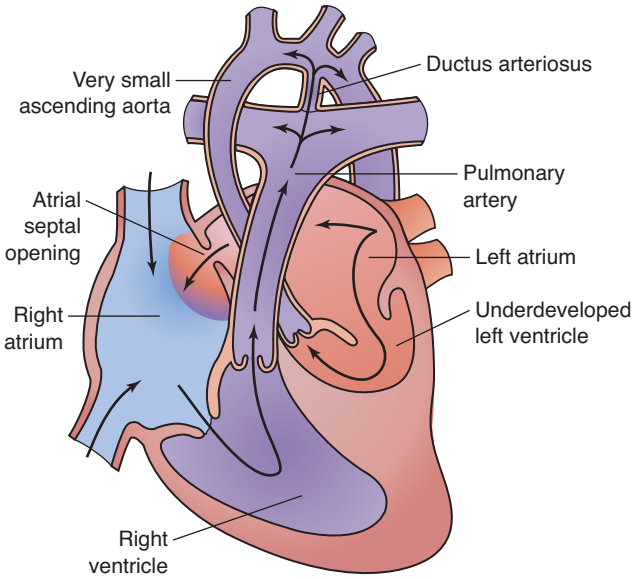


FIGURE 19-22. Functional single-ventricle anatomy with an underdeveloped left ventricle and small ascending aorta. Because of the markedly decreased left ventricular compliance, most of the pulmonary venous blood returning to the left atrium shunts left to right at the atrial level. Pulmonary arterial blood flows into the pulmonary arteries as well as right to left across a patent ductus arteriosus into the aorta.

Although functional single-ventricle anatomy cannot be completely repaired, the surgical palliation of these defects has been one of the most innovative interventions for congenital heart disease. The goal of surgical palliation is to redirect systemic venous return directly to the pulmonary arteries and allow the single ventricle to deliver oxygenated blood to the systemic circulation. This is accomplished in a series of two to three staged surgical palliation interventions during the child's first years of life. Stage one palliation is designed to ensure unobstructed systemic blood flow and adequate flow to the pulmonary circulation. Stage two, a bidirectional cavopulmonary shunt, redirects systemic venous return from the superior vena cava directly to the pulmonary arteries. Stage three connects flow from the inferior vena cava directly into the pulmonary arteries so that the pulmonary and systemic circulations are effectively separated.[63–65] Cardiac transplantation is also used as an intervention for the most complex forms of single-ventricle congenital heart disease.

Survival rates for children with complex forms of single-ventricle heart disease have improved markedly, but long-term outcomes remain uncertain. Ventricular dysfunction, arrhythmias, and thromboses plague this population of patients. Defining the optimal medical and surgical management strategies for these patients remains an active area of research in pediatric cardiology and cardiac surgery.[63–65]

Kawasaki Disease

Kawasaki disease is an acute vasculitis with potential for involvement of the coronary arteries. The disease occurs

predominantly in young children; about 80% of patients are younger than 5 years of age.[67–69] First described in Japan in 1967 by Dr. Tomisaku Kawasaki, the disease is the leading cause of acquired heart disease in North America and Japan.[67,68] Although most common in Japan, the disease affects children of many races, occurs worldwide, and is increasing in frequency.

The disease is characterized by a vasculitis (i.e., inflammation of the blood vessels) that begins in the small vessels (i.e., arterioles, venules, and capillaries) and progresses to involve some of the larger arteries, such as the coronaries. The exact etiology and pathogenesis of the disease remain unknown, but it is thought to be of immunologic origin.[67,68] Immunologic abnormalities, including increased activation of helper T cells and increased levels of immune mediators and antibodies that destroy endothelial cells, have been detected during the acute phase of the disease. It has been hypothesized that some unknown antigen, possibly a common infectious agent, triggers the immune response in a genetically predisposed child.

Manifestations and Clinical Course

The course of the disease is triphasic and includes an acute febrile phase that lasts approximately 7 to 14 days, a subacute phase that follows the acute phase and lasts from days 10 through 24, and a convalescent phase that follows the subacute stage and continues until the signs of the acute-phase inflammatory response have subsided and the signs of the illness have disappeared.[67–69]

The *acute phase* begins with an abrupt onset of fever, followed by bilateral conjunctivitis, usually without exudates; erythema of the oral and pharyngeal mucosa with "strawberry tongue" and dry, fissured lips; redness and swelling of the hands and feet; rash of various forms; and enlarged cervical lymph nodes. The fever typically is high, reaching 40°C (104°F) or more; has an erratic spiking pattern; is unresponsive to antibiotics; and persists for 5 or more days.[68] The conjunctivitis begins shortly after the onset of fever, persists throughout the febrile course of the disease, and may last as long as 3 to 5 weeks.

The *subacute phase* begins with abatement of the fever and lasts until all signs of the disease have disappeared. During the subacute phase, desquamation (i.e., peeling) of the skin of the fingers and toe tips begins and progresses to involve the entire surface of the palms and soles. Patchy peeling of skin areas other than the hands and feet may occur in some children. The convalescent stage persists from the complete resolution of symptoms until all signs of inflammation have disappeared. This usually takes approximately 8 weeks.

In addition to the major manifestations that occur during the acute stage of the illness, there are several associated, less specific characteristics of the disease, including arthritis, urethritis and pyuria, gastrointestinal manifestations (e.g., diarrhea, abdominal pain), and hepatitis. Arthritis is more common in girls and may occur early in the illness along with the fever and other acute manifestations of the disease or during the second or third week, generally affecting the hands, knees, ankles, or toes.[68] Central nervous system involvement occurs in almost all children and is characterized by pronounced irritability and lability of mood.

Cardiac involvement is the most important manifestation of Kawasaki disease. Coronary artery abnormalities develop in approximately 20% of children, manifested by coronary artery dilation and aneurysm formation as seen on 2-D echocardiography.[68] The manifestations of coronary artery involvement include signs and symptoms of myocardial ischemia or, rarely, overt myocardial infarction or rupture of a coronary aneurysm. Pericarditis, myocarditis, endocarditis, heart failure, and arrhythmias also may develop.

Diagnosis and Treatment

No specific diagnostic test for Kawasaki disease is available; therefore, the diagnosis is made on clinical grounds following published guidelines.[70] The guidelines specify fever persisting at least 5 days or more without another source in association with at least four principal features, including oral changes that may include erythema or cracking of the lips, strawberry tongue, and erythema of the oral mucosa; bilateral, nonexudative conjunctivitis; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform) with accentuation in the groin region; erythema and swelling of the hands or feet with desquamation of fingers and toes 1 to 3 weeks after onset of illness; and cervical lymphadenopathy, often unilateral, with at least one node that is 1.5 cm in size.[71] Chest radiographs, ECG tests, and 2-D echocardiography are used to detect coronary artery involvement and follow its progress. Coronary angiography may be used to determine the extent of coronary artery involvement.

Intravenous gamma globulin and aspirin are considered the best therapies for prevention of coronary artery abnormalities in children with Kawasaki disease. During the acute phase of the illness, aspirin usually is given in larger doses (80 to 100 mg/kg/day divided in four doses) for its anti-inflammatory and antipyretic effects. After the fever is controlled, the aspirin dose is lowered (3 to 5 mg/kg/day, single dose), and the drug is given for its anti–platelet-aggregating effects for 6 to 8 weeks.[69,70]

Recommendations for cardiac follow-up evaluation (i.e., stress testing and sometimes coronary angiography) are based on the level of coronary artery changes. Anticoagulant therapy may be recommended for children with multiple or large coronary aneurysms. Some restrictions in activities such as competitive sports may be advised for children with significant coronary artery abnormalities.[69]

In summary, congenital heart defects arise during fetal heart development, which occurs during weeks 3 through 8 after conception, and reflect the stage of development at the time the causative event occurred. Several factors contribute to the development of congenital heart defects, including genetic and chromosomal influences, viruses, and environmental agents such as drugs and radiation.

Congenital heart defects may produce no effects, or they may markedly affect cardiac function. The defects may produce shunting of blood from the right to the left side of the heart or from the left to the right side of the heart. Left-to-right shunts typically increase the volume of the right side of the heart and pulmonary circulation, and right-to-left shunts transfer deoxygenated blood from the right side of the heart to the left side, diluting the oxygen content of blood that is being ejected into the systemic circulation and causing cyanosis. The direction and degree of shunt depend on the size and position of the defect that connects the two sides of the heart and the difference in resistance between the two sides of the circulation. Congenital heart defects often are classified as defects that produce cyanosis and those that produce little or no cyanosis. Depending on the severity of the defect, congenital heart defects may be treated medically or surgically.

Kawasaki disease is an acute febrile disease of young children that affects the skin, brain, eyes, joints, liver, lymph nodes, and heart. The disease can produce aneurysmal disease of the coronary arteries and is the most common cause of acquired heart disease in young children.

REVIEW EXERCISES

1. A 40-year-old man presents in the emergency department complaining of substernal chest pain that is also felt in his left shoulder. He is short of breath and nauseated. His blood pressure is 148/90 mm Hg and his heart rate is 110 beats/minute. His ECG shows an ST-segment elevation with T-wave inversion. He is given aspirin, morphine, and oxygen. Blood tests reveal elevated CK-MB and troponin I.

A. What is the probable cause of the man's symptoms?
B. Explain the origin of the left arm pain, nausea, and increased heart rate.
C. What is the significance of the ST-segment changes and elevation in CK-MB and troponin I?
D. Relate the actions of aspirin, morphine, and oxygen to the treatment of this man's condition.

2. A 50-year-old woman presents with complaints of nocturnal paroxysmal dyspnea and orthopnea, palpitations, and fatigue. An echocardiogram demonstrates a thickened, immobile mitral valve with anterior and posterior leaflets moving together; slow early diastolic filling of the ventricle; and left atrial enlargement.

A. What is the probable cause of this woman's symptoms?
B. Explain the pathologic significance of the slow early diastolic filling, distended left atrium, and palpitations.
C. Given the echocardiographic data, what type of cardiac murmur would you expect to find in this woman?
D. Which circulation (systemic or pulmonary) would you expect to be affected as this woman's mitral valve disorder progresses?

3. A 4-month-old male infant is brought into the pediatric clinic by his mother. She reports that she noted over the past several weeks that her baby's lips and mouth and his fingernails and toenails have become a bluish-gray color. She also states that he seems to tire easily and that even nursing seems to wear him out. Lately, he has had several spells where he has suddenly turned blue, has had difficulty breathing, and has been very irritable. During one of these spells he turned limp and seemed to have passed out for a short time. An echocardiogram reveals a thickening of the right ventricular wall with overriding of the aorta, a large subaortic ventricular septal defect, and narrowing of the pulmonary outflow with stenosis of the pulmonary valve.

A. What is this infant's probable diagnosis?
B. Describe the shunting of blood that occurs with this disorder and its relationship to the development of cyanosis.
C. The mother is instructed to place the infant in the knee–chest position when he has one of the spells in which he becomes blue and irritable. How does this position help to relieve the cyanosis and impaired oxygenation of tissues?
D. The surgical creation of a shunt between the aorta and pulmonary artery may be performed as a palliative procedure for infants with marked hypoplasia of the pulmonary artery, with corrective surgery performed later in childhood. Explain how this procedure increases blood flow to the lungs.

REFERENCES

1. American Heart Association. (2009). *Heart disease and stroke statistics: 2009 update at a glance*. [Online] Available: http://www.americanheart.org. Accessed May 28, 2009.
2. Gaziano J.M. (2008). Global burden of cardiovascular disease. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1–22). Philadelphia: Saunders Elsevier.
3. LeWinter M.M. (2008). Pericardial diseases. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1829–1853). Philadelphia: Saunders Elsevier.
4. Lange R.A., Hillis L. (2004). Acute pericarditis. *New England Journal of Medicine* 351, 2195–2202.
5. Little W.C., Freeman G.L. (2006). Pericardial disease. *Circulation* 113, 1622–1632.
6. Guyton A., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 249–253). Philadelphia: Elsevier Saunders.

7. Canty J.M. (2008). Coronary blood flow and myocardial ischemia. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1167–1194). Philadelphia: Saunders Elsevier.
8. Schoen F.J., Mitchell R.N. (2010). The heart. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 529–587). Philadelphia: Saunders Elsevier.
9. Forrester J.S. (2000). Role of plaque rupture in acute coronary syndromes. *American Journal of Cardiology* 86(suppl), 15J–23J.
10. Smith S.W., Whitwam W. (2006). Acute coronary syndromes. *Emergency Medicine Clinics of North America* 24, 53–89.
11. Antman E.M., Braunwald E. (2008). ST-elevation myocardial infarction: Pathology, pathophysiology, and clinical features. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1207–1232). Philadelphia: Saunders Elsevier.
12. Bhatheja R., Mukherjee D. (2007). Acute coronary syndromes: Unstable angina/non-ST elevation myocardial infarction. *Critical Care Clinics* 23, 709–735.
13. Mirvis D.M., Goldberger A.L. (2008). Electrocardiography. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 172–179). Philadelphia: Saunders Elsevier.
14. Cannon C.P., Braunwald E. (2008). Unstable angina and non-ST elevation myocardial infarction. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1319–1351). Philadelphia: Saunders Elsevier.
15. Cannon C.P., Lee T.H. (2008). Approach to the patient with chest pain. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1195–1205). Philadelphia: Saunders Elsevier.
16. Antman E.M. (2008). ST-elevation myocardial infarction: Management. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1233–1299). Philadelphia: Saunders Elsevier.
17. Popma J.I., Baim D.S., Resnic F.S. (2008). Percutaneous coronary and valvular intervention. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1419–1456). Philadelphia: Saunders Elsevier.
18. Morrow D.A., Gersh B.J. (2008). Chronic coronary artery disease. In Libby P., Bonow R., Mann D.L., et al. (Eds.). *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1353–1417). Philadelphia: Saunders Elsevier.
19. Gibbons R.J., Abrams J., Chatterjee K., et al. (2003). ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. *Circulation* 107, 149–158.
20. Maron B.J., Towbin J.A., Thiene G., et al. (2006). Contemporary definitions and classification of the cardiomyopathies. *Circulation* 113, 1807–1816.
21. Nishimura R.A., Holmes D.R. (2004). Hypertrophic obstructive cardiomyopathy. *New England Journal of Medicine* 350, 1320–1327.
22. Moran B.J. (2008) Hypertrophic cardiomyopathy. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1763–1774). Philadelphia: Saunders Elsevier.
23. Ho C.Y., Seidman C.E. (2006). A contemporary approach to hypertrophic cardiomyopathy. *Circulation* 113, 858–862.
24. Anderson E.L. (2006). Arrhythmic right ventricular dysplasia. *American Family Physician* 73, 1391–1398.
25. Saffitz J.E. (2008). The heart. In Rubin E., Strayer D.E. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 465–474). Philadelphia: Lippincott Williams & Wilkins.
26. Liu P.P., Schultheiss H-P. (2008). Myocarditis. In Libby P., Bonow R., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1775–1792). Philadelphia: Saunders Elsevier.
27. Feldman A.M., McNammara D. (2000). Myocarditis. *New England Journal of Medicine* 343, 1387–1398.
28. Magnani J.W., Dec G.W. (2006). Myocarditis: Current trends in diagnosis and treatment. *Circulation* 113, 876–890.
29. Newby L.K., Douglas P.S. (2008). Cardiovascular disease in women. In Libby P., Bonow R., Mann D.L., et al. (Eds.). *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1974–1975). Philadelphia: Saunders Elsevier.
30. Ro A., Frishman W.H. (2006). Peripartum cardiomyopathy. *Cardiology in Review* 14(1), 35–42.
31. Pearson G.D., Veille J.C., Rahimtoola S., et al. (2000). Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) Workshop recommendations and review. *Journal of the American Medical Association* 283, 1183–1188.
32. Gianni M., Dentali F., Grandi A.M., et al. (2006). Apical ballooning syndrome or takotsubo cardiomyopathy: A systematic review. *European Heart Journal* 27, 1523–1529.
33. Merli E., Sutcliffe S., Gori M., et al. (2006). Tako-tsubo cardiomyopathy: New insights into the possible underlying pathophysiology. *European Journal of Echocardiography* 7, 53–61.
34. Mylonakis E., Calderwood S.B. (2001). Infective endocarditis in adults. *New England Journal of Medicine* 345, 1318–1330.
35. Holcomb S. (2005). Infective endocarditis guidelines assist in early identification. *Nurse Practitioner* 30(11), 7–17.
36. Baddour L.M., Wilson W.R., Bayer A.S., et al. (2005). Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications. *Circulation* 111, 394–434.
37. Devlin R.K., Andrews M.M., von Reyn C.F. (2004). Recent trends in infective endocarditis: Influence of case definitions. *Current Opinion in Cardiology* 19, 134–139.
38. Prendergast B.D. (2006). The changing face of infective endocarditis. *Heart* 92, 879–885.
39. Wilson W., Taubert K.A., Gewitz M., et al. (2007). Prevention of infective endocarditis: Guidelines from the American Heart Association. *Circulation* 115, 1656–1658.
40. Guilherme L., Cury P., Demarchi L.M.F., et al. (2004). Rheumatic heart disease. *American Journal of Pathology* 165, 1583–1591.
41. World Health Organization. (2004). *Rheumatic fever and rheumatic heart disease: Report of WHO expert consultation.* WHO Technical Report Series 923. Geneva: World Health Organization.
42. Radju B.S., Turi Z.G. (2008). Rheumatic fever. In Libby P., Bonow R.O., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 2079–2086). Philadelphia: Elsevier Saunders.
43. Ferrieri P., for the Jones Criteria Working Group. (2002). Proceedings of the Jones criteria workshop. *Circulation* 106, 2521–2527.
44. Otto C.M., Bonow R.O. (2008). Valvular heart disease. In Libby P., Bonow R.O., Mann D.L., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (8th ed., pp. 1625–1712). Philadelphia: Elsevier Saunders.
45. Bonow R.O., Carabello B.A., Chatterjee K., et al. (2006). ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *Circulation* 114, e84–e231.
46. Carabello B.A. (2004). Aortic stenosis. *New England Journal of Medicine* 346, 677–682.
47. Freeman R.V., Otto C.M. (2005). Spectrum of calcific aortic valve disease: Pathogenesis, disease progression, and treatment strategies. *Circulation* 111, 3316–3326.

48. Freed M.D. (2006). Fetal and transitional circulation. In Keane J.F., Lock J.E., Fyler D.C. (Eds.), *Nadas' pediatric cardiology* (2nd ed., pp. 75–79). Philadelphia: Elsevier Saunders.
49. Moore K.L., Persaud T.V.N. (2003). *The developing human: Clinically oriented embryology* (7th ed., pp. 332–380). Philadelphia: Saunders.
50. Bernstein D. (2007). The cardiovascular system. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1851–1857, 1906–1912). Philadelphia: Saunders Elsevier.
51. Sander T.L., Klinkner D.B., Tomita-Mitchell A., et al. (2006). Molecular and cellular basis of congenital heart disease. *Pediatric Clinics of North America* 53, 989–1009.
52. Pierpont M.E., Basson C.T., Benson D.W., et al. (2007). Genetic basis for congenital heart defects: Current knowledge. *Circulation* 115, 1–24.
53. Nouri S. (1997). Congenital heart defects: Cyanotic and acyanotic. *Pediatric Annals* 26, 92–98.
54. Wright J.W. (2007). The cardiovascular system. In Kenner C., Lott J.W. (Eds.), *Comprehensive neonatal care: An intradisciplinary approach* (4th ed., pp. 32–64). Philadelphia: Saunders Elsevier.
55. Nadas A.S., Fyler D.C. (2006). Hypoxemia. In Keane J.F., Lock J.E., Fyler D.C. (Eds.), *Nadas' pediatric cardiology* (2nd ed., pp. 97–101). Philadelphia: Elsevier Saunders.
56. Allan L.D. (2002). Prenatal detection of congenital heart disease. In Anderson R.H., Baker E.J., Macartney F.J., et al. (Eds.), *Paediatric cardiology* (2nd ed., pp. 687–699). London: Churchill Livingstone.
57. Tynan M., Anderson R.H. (2002). Clinical presentation of heart disease in infants and children, ventricular septal defect, complete transposition, pulmonary stenosis. In Anderson R.H., Baker E.J., Macartney F.J., et al. (Eds.), *Paediatric cardiology* (2nd ed., pp. 275–283, 983–1014, 1281–1320, 1461–1479). London: Churchill Livingstone.
58. Wilson W., Taubert K.A., Gewitz M., et al. (2007). Prevention of infective endocarditis. *Circulation* 106, 1–20.
59. Keane J.F., Geva T., Fyler D.C. (2006). Atrial septal defect, ventricular septal defect, coarctation of the aorta, single ventricle, pulmonary stenosis. In Keane J.F., Lock J.E., Fyler D.C. (Eds.), *Nadas' pediatric cardiology* (2nd ed., pp. 527–558). Philadelphia: Elsevier Saunders.
60. Marx G.R., Fyler D.C. (2006). Endocardial cushion defects. In Keane J.F., Lock J.E., Fyler D.C. (Eds.), *Nadas' pediatric cardiology* (2nd ed., pp. 663–674). Philadelphia: Elsevier Saunders.
61. LoBreitbart R.E., Fyler D.C. (2006). Tetralogy of Fallot. In Keane J.F., Lock J.E., Fyler D.C. (Eds.), *Nadas' pediatric cardiology* (2nd ed., pp. 559–580). Philadelphia: Elsevier Saunders.
62. Fulton D.R., Fyler D.C. (2006). D-Transposition of the great arteries. In Keane J.F., Lock J.E., Fyler D.C. (Eds.), *Nadas' pediatric cardiology* (2nd ed., pp. 645–662). Philadelphia: Elsevier Saunders.
63. O'Brien P., Boisvert J.T. (2001). Current management of infants and children with single ventricle anatomy. *Journal of Pediatric Nursing* 16, 338–350.
64. Khairy P., Poirier N., Mercier L.A. (2007). Univentricular heart. *Circulation* 115, 800–812.
65. Tweddell J.S., Litwin S.B., Thomas J.P., et al. (1999). Recent advances in the surgical management of the single ventricle pediatric patient. *Pediatric Clinics of North America* 46, 465–480.
66. Alsoufi B., Bennetts J., Verma S., et al. (2007). New developments in the treatment of hypoplastic left heart syndrome. *Pediatrics* 119, 109–117.
67. Pinna G.S., Dafetzis D.A., Tselkas O.I., et al. (2008). Kawasaki disease. *Current Opinions in Infectious Diseases* 21, 263–270.
68. Rowley A.H., Shulman S.T. (2007). Kawasaki disease. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 1037–1042). Philadelphia: Saunders Elsevier.
69. Freeman A.F., Shulman S.T. (2006). Kawasaki disease: Summary of the American Heart Association guidelines. *American Family Physician* 74, 1141–1150.
70. American Heart Association, Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. (2004). Diagnostic guidelines for Kawasaki disease. *Circulation* 110, 2747–2711.

Heart Failure
Pathophysiology of Heart Failure
Control of Cardiac Performance and Output
Types of Heart Failure
Systolic Versus Diastolic Dysfunction
Left Versus Right Ventricular Dysfunction
High-Output Versus Low-Output Failure
Compensatory Mechanisms
Length-Tension/Frank-Starling Mechanism
Sympathetic Nervous System Activity
Renin-Angiotensin-Aldosterone Mechanism
Natriuretic Peptides
Endothelins
Myocardial Hypertrophy and Remodeling
Manifestations of Heart Failure
Fluid Retention and Edema
Respiratory Manifestations
Fatigue, Weakness, and Mental Confusion
Cachexia and Malnutrition
Cyanosis
Arrhythmias and Sudden Cardiac Death
Acute Heart Failure Syndromes
Acute Pulmonary Edema
Diagnosis and Treatment
Diagnostic Methods
Treatment
Circulatory Failure (Shock)
Pathophysiology of Shock
Cellular Responses
Compensatory Mechanisms
Types of Shock
Cardiogenic Shock
Hypovolemic Shock
Obstructive Shock
Distributive Shock
Complications of Shock
Acute Lung Injury/Acute Respiratory Distress Syndrome
Acute Renal Failure
Gastrointestinal Complications
Disseminated Intravascular Coagulation
Multiple Organ Dysfunction Syndrome
Heart Failure in Children and the Elderly
Heart Failure in Infants and Children
Manifestations
Diagnosis and Treatment
Heart Failure in the Elderly
Manifestations
Diagnosis and Treatment

Chapter 20

Heart Failure and Circulatory Shock

Adequate perfusion of body tissues depends on the pumping ability of the heart, a vascular system that transports blood to the tissues of the body and back to the heart, sufficient blood to fill the circulatory system, and tissues that are able to extract and use oxygen and nutrients from the blood. Heart failure and circulatory shock are separate conditions that reflect failure of the circulatory system. Both conditions exhibit common compensatory mechanisms even though they differ in terms of pathogenesis and causes.

Heart Failure

Heart failure has been defined as a complex syndrome resulting from any functional or structural disorder of the heart that results in or increases the risk of developing manifestations of low cardiac output and/or pulmonary or systemic congestion.[1,2] The syndrome of heart failure can be produced by any heart condition that reduces the pumping ability of the heart. Among the most common causes of heart failure are coronary artery disease, hypertension, dilated cardiomyopathy, and valvular heart disease.[1] Heart failure can occur in any age group but primarily affects the elderly. Although morbidity and mortality rates from other cardiovascular diseases have decreased over the past several decades, the incidence of heart failure is increasing at an alarming rate. This change undoubtedly reflects improved treatment methods and increased survival from other forms of heart disease.

Pathophysiology of Heart Failure

The term *heart failure* denotes the failure of the heart to pump enough blood to meet the metabolic needs of the body. The efficiency of the heart as a pump is determined by the amount of blood that it ejects each minute. The heart has the amazing capacity to adjust its output to meet the varying needs of the body. During sleep, the output declines, and during exercise, it increases markedly. The ability of the heart to increase its output during increased

activity is called the *cardiac reserve*. For example, competitive swimmers and long-distance runners have large cardiac reserves. During exercise, the cardiac output of these athletes rapidly increases to as much as five to six times their resting level.[3] In sharp contrast with healthy athletes, persons with heart failure often use their cardiac reserve at rest. For them, just climbing a flight of stairs may cause shortness of breath because they have exceeded their cardiac reserve.

Control of Cardiac Performance and Output

Cardiac output, which is the major determinant of cardiac performance, reflects how often the heart beats each minute (heart rate) and how much blood it ejects with each beat (stroke volume) and can be expressed as the product of the heart rate and stroke volume (i.e., cardiac output = heart rate × stroke volume). The heart rate is regulated by a balance between the activity of the sympathetic nervous system, which produces an increase in heart rate, and the parasympathetic nervous system, which slows it down, whereas the stroke volume is a function of preload, afterload, and myocardial contractility.[3–5]

Preload and Afterload. The work that the heart performs consists mainly of ejecting blood that has returned to the ventricles during diastole into the pulmonary or systemic circulation. It is determined largely by the loading conditions, or what are called the *preload* and *afterload*.

Preload reflects the volume or loading conditions of the ventricle at the end of diastole, just before the onset of systole. It is the volume of blood stretching the heart muscle at the end of diastole and is normally determined mainly by the venous return to the heart. Known as the *end-diastolic volume,* this volume causes an increase in the length of the myocardial muscle fibers. Within limits, as end-diastolic volume or preload increases, the stroke volume increases in accord with the Frank-Starling mechanism (to be discussed).

Afterload represents the force that the contracting heart muscle must generate to eject blood from the filled heart. The main components of afterload are the systemic (peripheral) vascular resistance and ventricular wall tension. When the systemic vascular resistance is elevated, as with arterial hypertension, an increased left intraventricular pressure must be generated to first open the aortic valve and then move blood out of the ventricle and into the systemic circulation. This increased pressure equates to an increase in ventricular wall stress or tension.

Myocardial Contractility. Myocardial contractility, also known as *inotropy,* refers to the contractile performance of the heart, or the ability of the contractile elements (actin and myosin filaments) of the heart muscle to interact and shorten against a load[3–5] (see Chapter 1, Fig. 1-18). Contractility increases cardiac output independent of preload and afterload. The interaction between the actin and myosin filaments during cardiac muscle contraction (i.e., cross-bridge attachment and detachment) requires the use of energy supplied by the breakdown of adenosine triphosphate (ATP) and the presence of calcium ions (Ca^{++}).

As with skeletal muscle, calcium is released from the sarcoplasmic reticulum of cardiac muscle during an action potential (Fig. 20-1). This calcium, in turn, diffuses into the myofibrils and catalyzes the chemical reactions that promote the sliding of the actin and myosin filaments along one another to produce muscle shortening. In addition to the calcium released from the sarcoplasmic reticulum at the time of an action potential, a large quantity of extracellular calcium diffuses into the sarcoplasm through voltage-dependent L-type calcium channels located in the T tubules and myocardial cell membrane. Without the extra calcium that enters through the L-type calcium channels, the strength of the cardiac contraction would be considerably weaker. Opening of the L-type calcium channels is facilitated by the second messenger cyclic adenosine monophosphate (cAMP), the formation of which is coupled to β-adrenergic receptors. The catecholamines (norepinephrine and epinephrine) exert their inotropic effects by binding to these receptors. The L-type calcium channel also contains several other types of drug receptors. Blockade of L-type calcium channels by drugs that bind to these receptors (i.e., calcium channel-blocking drugs) results in a selective reduction in cardiac contractility.

Another mechanism that can modulate inotropy is the sodium ion (Na^+)/Ca^{++} exchange pump and the ATPase-dependent Ca^{++} pump in the myocardial cell membrane (see Fig. 20-1). These pumps transport calcium out of the cell, thereby preventing the cell from becoming overloaded with calcium. If calcium extrusion is inhibited, the rise in intracellular calcium produces an increase inotropy. Digitalis and related cardiac glycosides are inotropic agents that exert their effects by inhibiting the Na^+/potassium ion (K^+)-ATPase pump in the myocardial cell membrane, thereby leading to an increase in intracellular calcium through the Na^+/Ca^{++} exchange pump.

Types of Heart Failure

Heart failure may be described according to the contractile (systolic dysfunction) or filling (diastolic dysfunction) properties of the ventricles, the predominance of left or right ventricular dysfunction, or ventricular output (high output versus low output).

Systolic Versus Diastolic Dysfunction

A functional classification of heart failure separates the pathophysiology of heart failure into systolic and diastolic dysfunction.[6] In systolic ventricular dysfunction, myocardial contractility is impaired, leading to a decrease in the ejection fraction (percentage of the end-diastolic volume that the heart ejects with each contraction). Diastolic dysfunction is characterized by altered ventricular filling in the presence of normal or near-normal systolic function and ejection fraction. Many persons with heart failure have combined elements of both systolic and diastolic ventricular dysfunction, and the division between the two may be somewhat artificial, particularly as it relates to manifestations and treatment.[7] It is important to

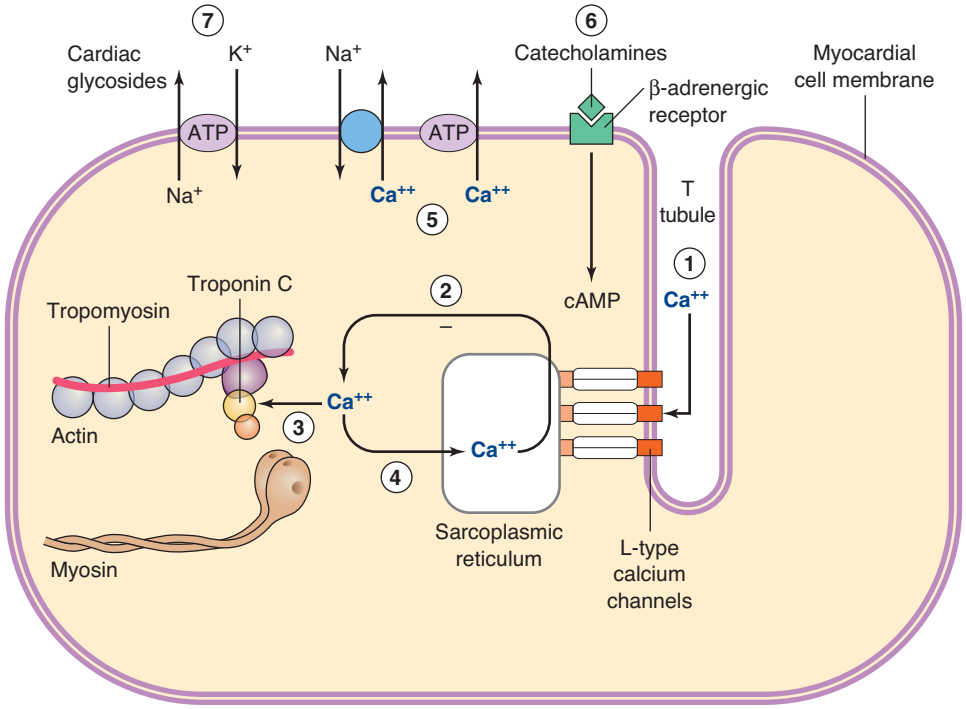


FIGURE 20-1. Schematic representation of the role of calcium ions (Ca^{++}) in cardiac excitation–contraction coupling. The influx (site 1) of extracellular Ca^{++} through the L-type Ca^{++} channels in the T tubules during excitation triggers (site 2) release of Ca^{++} by the sarcoplasmic reticulum. This Ca^{++} binds to troponin C (site 3). The Ca^{++}–troponin complex interacts with tropomyosin to unblock active sites on the actin and myosin filaments, allowing cross-bridge attachment and contraction of the myofibrils (systole). Relaxation (diastole) occurs as a result of calcium reuptake by the sarcoplasmic reticulum (site 4) and extrusion of intracellular Ca^{++} by the Na^+/Ca^{++} exchange transporter or, to a lesser extent, by the Ca^{++} adenosine triphosphatase (ATPase) pump (site 5). Mechanisms that raise systolic Ca^{++} increase the level of developed force (inotropy). Binding of catecholamines to β-adrenergic receptors (site 6) increases Ca^{++} entry by phosphorylation of the Ca^{++} channels through a cyclic adenosine monophosphate (cAMP)–dependent second messenger mechanism. The cardiac glycosides (site 7) increase intracellular Ca^{++} by inhibiting the Na^+/K^+-ATPase pump. The elevated intracellular Na^+ reverses the Na^+/Ca^{++} exchange transporter (site 5), so less Ca^{++} is removed from the cell. (Modified from Klabunde R.E. [2005]. *Cardiovascular physiology concepts* [p. 46]. Philadelphia: Lippincott Williams & Wilkins.)

note that ventricular dysfunction is not synonymous with heart failure. It can, however, lead to heart failure.

Systolic Dysfunction. Systolic dysfunction is primarily defined as a decrease in myocardial contractility, characterized by an ejection fraction of less than 40%.[8] A normal heart ejects approximately 65% of the blood that is present in the ventricle at the end of diastole. In systolic heart failure, the ejection fraction declines progressively with increasing degrees of myocardial dysfunction.

The principal clinical manifestations of systolic dysfunction result from an inadequate cardiac output or ventricular dilation. With a decrease in ejection fraction and cardiac output, there is a resultant increase in end-systolic and end-diastolic volumes, ventricular dilation, and wall tension, and a rise in ventricular end-diastolic pressure.[9] This increased volume, added to the normal venous return, leads to an increase in ventricular preload. The rise in preload is thought to be a compensatory mechanism to help maintain stroke volume through the Frank-Starling mechanism despite a drop in ejection fraction (discussed in the section on compensatory mechanisms). Although it serves as a compensatory mechanism, increased preload can also lead to one of the most deleterious consequences of systolic ventricular dysfunction—accumulation of blood in the atria and the pulmonary venous system (which empties into the atria), causing pulmonary congestion.

Systolic dysfunction commonly results from conditions that impair the contractile performance of the heart (e.g., ischemic heart disease and cardiomyopathy), produce a volume overload (e.g., valvular insufficiency and anemia), or generate a pressure overload (e.g., hypertension and valvular stenosis) on the heart. The extent of systolic ventricular dysfunction can be estimated by measuring the cardiac output and ejection fraction and by assessment for manifestations of left-sided heart failure, particularly pulmonary congestion.

Heart Failure

- The function of the heart is to move deoxygenated blood from the venous system through the right heart into the pulmonary circulation, and oxygenated blood from the pulmonary circulation through the left heart and into the arterial circulation.
- Systolic dysfunction represents a decrease in cardiac myocardial contractility and an impaired ability to eject blood from the left ventricle; whereas, diastolic dysfunction represents an abnormality in ventricular relaxation and filling.
- Right-sided heart failure represents failure of the right ventricle to move unoxygenated blood from the venous system into the pulmonary circulation, with an eventual backup in the systemic venous circulation; whereas, left-sided heart failure represents failure of the left ventricle to move oxygenated blood from the pulmonary circulation into the arterial circulation with eventual backup of blood in the lungs. Both types result in decreased forward flow, resulting in poor circulation of oxygenated blood in the body.

Diastolic Dysfunction. Although heart failure is commonly associated with impaired systolic function, in approximately 40% to 50% of cases systolic function has been preserved and heart failure results from an inability of the left ventricle to fill sufficiently during diastole.[10,11]

Among the conditions that cause diastolic dysfunction are those that impede expansion of the ventricle (e.g., pericardial effusion, constrictive pericarditis), increase ventricular wall thickness and reduce chamber size (e.g., myocardial hypertrophy, hypertrophic cardiomyopathy), or delay diastolic relaxation of the ventricle (e.g., aging, ischemic heart disease).[11] The prevalence of diastolic failure increases with age and is higher in women than men, and in persons with obesity, hypertension, and diabetes.[10,11] Aging is often accompanied by a delay in relaxation of the heart during diastole such that diastolic filling begins while the ventricle is still stiff and resistant to stretching. A similar delay occurs in myocardial ischemia, resulting from a lack of energy to break the rigor bonds that forms between the actin and myosin filaments and to move calcium out of the cytosol and back into the sarcoplasmic reticulum.[11]

With diastolic dysfunction ventricular relaxation and distensibility are impaired, leading to an increase in intraventricular pressure at any given volume. The elevated pressures are transmitted backward from the left ventricle into the left atrium and pulmonary venous system, causing pulmonary congestion and a decrease in lung compliance, which increases the work of breathing and evokes symptoms of dyspnea. Cardiac output is decreased, not because of a reduced ventricular ejection fraction as seen with systolic dysfunction, but because of a decrease in ventricular filling. Diastolic function is further influenced by the heart rate, which determines how much time is available for ventricular filling.[12] An increase in heart rate shortens the diastolic filling time. Thus, diastolic dysfunction can be aggravated by tachycardia and improved by a reduction in heart rate, which allows the heart to fill over a longer period of time.

Left Versus Right Ventricular Dysfunction

Heart failure can be classified according to the side of the heart (left ventricular or right ventricular) that is primarily affected[8] (Fig. 20-2). An important feature of the circulatory system is the fact that the left and right ventricles act as two pumps that are connected in series. To function effectively, the left and right ventricles must maintain equal outputs. Although the initial event that leads to heart failure may be primarily left or right ventricular in origin, long-term heart failure usually involves both ventricles.

Left Ventricular Dysfunction. The clinical features of left-sided heart failure primarily result from a diminished cardiac output with a resultant decrease in peripheral blood flow and a progressive accumulation of blood within the pulmonary circulation. With impairment of left ventricular function, there is a decrease in ejection of blood into the systemic circulation, an increase in left ventricular and left atrial end-diastolic pressures, and congestion of the pulmonary circulation (Fig. 20-3). When the filtration pressure in the pulmonary capillaries (normally approximately 10 mm Hg) exceeds the capillary osmotic pressure (normally approximately 25 mm Hg), there is a shift of intravascular fluid into the interstitium of the lung and development of pulmonary edema (Fig. 20-3). An episode of pulmonary edema often occurs at night, after the person has been reclining for some time and the gravitational forces have been removed from the circulatory system. It is then that the edema fluid that had been sequestered in the lower extremities during the day is returned to the vascular compartment and redistributed to the pulmonary circulation.

The most common causes of left ventricular dysfunction are hypertension and acute myocardial infarction. Left ventricular heart failure and pulmonary congestion can develop very rapidly in persons with acute myocardial infarction. Even when the infarcted area is small, there may be a surrounding area of ischemic tissue. This may result in large areas of ventricular wall hypokinesis or akinesis and rapid onset of pulmonary congestion and edema. Another cause of left heart failure is valvular defects such as stenosis or regurgitation of the aortic or mitral valve. These valvular defects increase the work of the left heart and eventually lead to heart failure if untreated.

Right Ventricular Dysfunction. The major clinical features of right heart failure differ from those of left heart failure in that pulmonary congestion is minimal, while

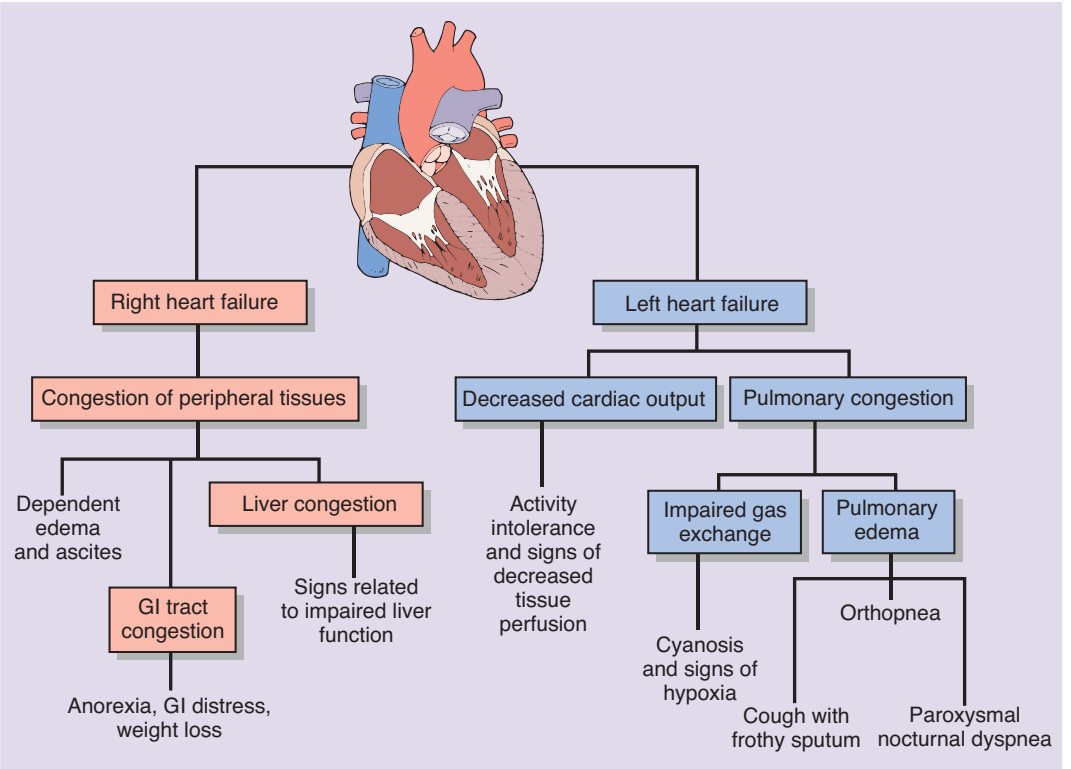


FIGURE 20-2. Manifestations of right- and left-sided heart failure. GI, gastrointestinal.

engorgement of the systemic and hepatic venous systems is pronounced. Right-sided heart failure is usually the consequence of left-sided heart failure, in which an increase in pulmonary blood volume eventually produces an increased burden on the right side of the heart. Isolated right-sided heart failure is less common and occurs in persons with intrinsic lung disease or pulmonary vasculature resistance that results from pulmonary hypertension. It can also occur in persons with pulmonic or tricuspid valvular disease, right ventricular infarction, and cardiomyopathy. Congenital heart defects with right-to-left cardiac shunt can cause isolated right heart failure as well (see Chapter 19). When the right heart failure occurs in response to chronic pulmonary disease, it is referred to as *cor pulmonale*[13] (see Chapter 23).

Right heart failure impairs the ability to move blood from the systemic venous circulation into the pulmonary circulation. Consequently, when the right ventricle fails, there is a reduction in the amount of blood that is moved forward from the systemic venous circulation into the pulmonary circulation and then into the left side of the heart. This causes an increase in right ventricular end-diastolic, right atrial, and systemic venous pressures. A major effect of right-sided heart failure is the development of peripheral edema (see Fig. 20-2). Because of the effects of gravity, the edema is most pronounced in the dependent parts of the body—in the lower extremities when the person is in the upright position and in the area over the sacrum when the person is supine. The accumulation of edema fluid is evidenced by a gain in weight (i.e., 1 pint [568 mL] of accumulated fluid results in a 1-lb [0.45-kg] weight gain). Daily measurement of weight can be used as a means of assessing fluid accumulation in a patient with chronic heart failure. As a rule, a weight gain of more than 2 lb (0.91 kg) in 24 hours or 5 lb (2.25 kg) in 1 week is considered a sign of worsening failure.

Right-sided heart failure also produces congestion of the viscera. As venous distention progresses, blood backs up in the hepatic veins that drain into the inferior vena cava and the liver becomes engorged. This may cause hepatomegaly and right upper quadrant pain. In severe and prolonged right-sided failure, liver function is impaired and hepatic cells may die. Congestion of the portal circulation also may lead to engorgement of the spleen and the development of ascites. Congestion of the gastrointestinal tract may interfere with digestion and absorption of nutrients, causing anorexia and abdominal discomfort. In severe right-sided failure, the external jugular veins become distended and can be visualized when the person is sitting up or standing.

High-Output Versus Low-Output Failure

High- and low-output heart failure are described in terms of cardiac output. *High-output failure* is an uncommon type of heart failure that is caused by an excessive need for cardiac output. With high-output failure, the function of the heart may be supranormal but inadequate owing to excessive metabolic needs. Causes of high-output failure include severe anemia, thyrotoxicosis, conditions that cause arteriovenous shunting, and Paget

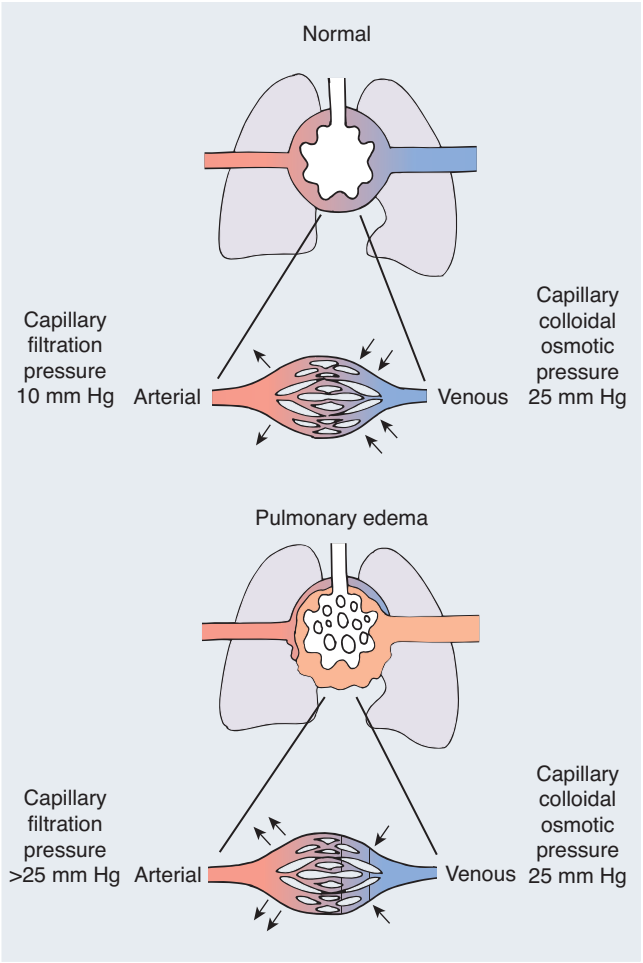


FIGURE 20-3. Mechanism of respiratory symptoms in left-sided heart failure. In the normal exchange of fluid in the pulmonary capillaries (*top*), the capillary filtration pressure that pushes fluid out of the capillary into the lung is less than the capillary colloidal osmotic pressure that pulls fluid back into the capillary. Development of pulmonary edema (*bottom*) occurs when the capillary filtration pressure exceeds the capillary colloidal osmotic pressure that pulls fluid back into the capillary.

disease. *Low-output failure* is caused by disorders that impair the pumping ability of the heart, such as ischemic heart disease and cardiomyopathy. Low-output failure is characterized by clinical evidence of systemic vasoconstriction with cold, pale, and sometimes cyanotic extremities.[8]

Compensatory Mechanisms

In heart failure, the cardiac reserve is largely maintained through compensatory mechanisms such as the Frank-Starling mechanism, activation of neurohumoral influences such as the sympathetic nervous system reflexes, the renin-angiotensin-aldosterone mechanism, natriuretic peptides, locally produced vasoactive substances, and myocardial hypertrophy and remodeling[5–7,14] (Fig. 20-4). The first two of these adaptations occur rapidly over minutes to hours of myocardial dysfunction and may be adequate to maintain the overall pumping performance of the heart at relatively normal levels. Myocardial hypertrophy and remodeling occur slowly over weeks to months and play an important role in the long-term adaptation to hemodynamic overload. In the failing heart, early decreases in cardiac function may go unnoticed because these compensatory mechanisms maintain the cardiac output. However, these mechanisms contribute not only to the adaptation of the failing heart but also to the pathophysiology of heart failure.[12]

Length-Tension/Frank-Starling Mechanism

The Frank-Starling mechanism describes the process whereby the heart increases its stroke volume through an increase in end-diastolic volume or preload (Fig. 20-5). With increased diastolic filling, there is increased stretching of the myocardial fibers, more optimal approximation of the actin and myosin filaments, and a resultant increase in the force of the next contraction (see Chapter 17). As illustrated in Figure 20-5, there is no one single Frank-Starling curve.[4] An increase in contractility will increase cardiac output at any end-diastolic volume, causing the curve to move up and to the left, whereas a decrease in contractility will cause the curve to move down and to the right.

In heart failure, a decrease in cardiac output and renal blood flow leads to increased sodium and water retention by the kidney with a resultant increase in vascular volume and venous return to the heart, and an increase in ventricular end-diastolic volume. Within limits, as preload and ventricular end-diastolic volume increase, there is a resultant increase in cardiac output. Although this may preserve the resting cardiac output, the resulting chronic elevation of left ventricular end-diastolic pressure is transmitted to the atria and the pulmonary circulation, causing pulmonary congestion.

An increase in cardiac muscle stretch, as occurs with the Frank-Starling mechanism, also produces an increase in ventricular wall tension with a resultant increase in myocardial oxygen consumption. Because increased wall tension increases myocardial oxygen requirements, it can produce ischemia and contribute to further impairment of cardiac function. The use of diuretics in persons with heart failure helps to reduce vascular volume and ventricular filling, thereby unloading the heart and reducing ventricular wall tension.

Sympathetic Nervous System Activity

Stimulation of the sympathetic nervous system plays an important role in the compensatory response to decreased cardiac output and in the pathogenesis of acute heart failure.[12,14] Both cardiac sympathetic tone and catecholamine (epinephrine and norepinephrine) levels are elevated during the late stages of most forms of heart failure. By direct stimulation of heart rate and cardiac contractility, regulation of vascular tone, and enhancement of renal sodium and water retention, the sympathetic nervous system initially helps to maintain

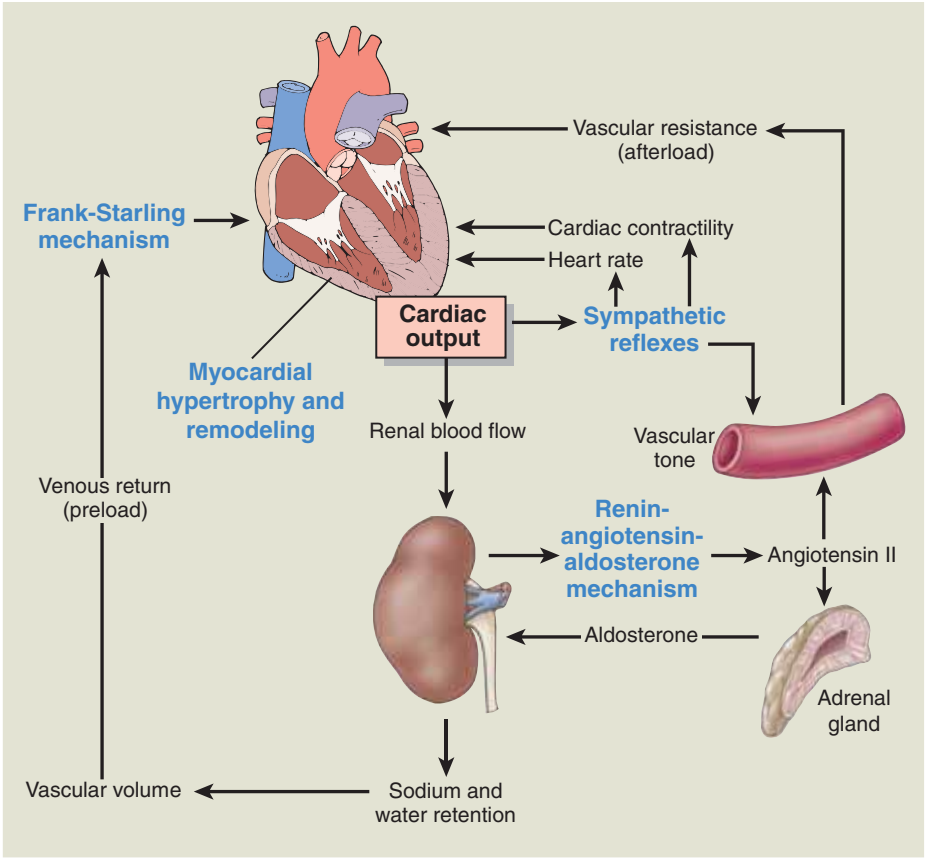


FIGURE 20-4. Compensatory mechanisms in heart failure. The Frank-Starling mechanism, sympathetic reflexes, renin-angiotensin-aldosterone mechanism, and myocardial hypertrophy function in maintaining cardiac output for the failing heart.

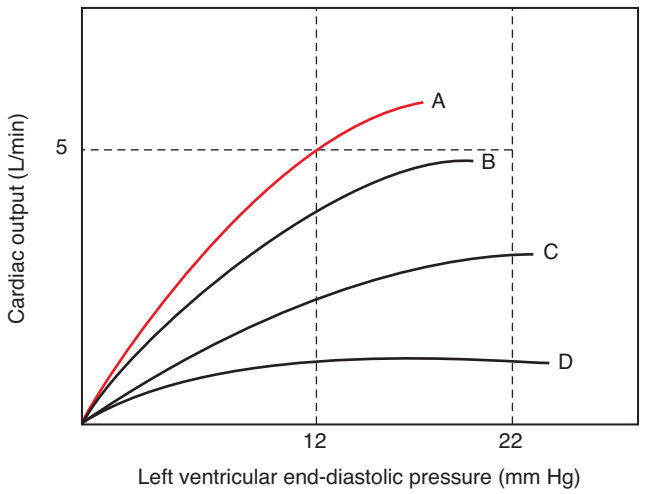


FIGURE 20-5. Left ventricular length-tension (Frank-Starling) function curves. *Curve A:* Normal function curve, with a normal cardiac output and optimal left ventricular end-diastolic (LVED) filling pressure. *Curve B:* Compensated heart failure with normal cardiac output at higher LVED pressures. *Curve C:* Decompensated heart failure with a decrease in cardiac output and elevated LVED pressures, with eventual elevation of pulmonary capillary pressure and development of pulmonary congestion. *Curve D:* Cardiogenic shock, with an extreme decrease in cardiac output and marked increase in LVED pressures.

perfusion of the various body organs. In persons who progress to more severe heart failure, blood is diverted to the more critical cerebral and coronary circulations.

Although the sympathetic nervous system response is meant to maintain blood pressure and cardiac output, it quickly becomes maladaptive and contributes to the deterioration of heart function. An increase in sympathetic activity can lead to tachycardia, vasoconstriction, and cardiac arrhythmias. Acutely, tachycardia significantly increases the workload of the heart, thus increasing myocardial oxygen demand and leading to cardiac ischemia, myocyte damage, and decreased contractility (inotropy). An increase in systemic vascular resistance causes an increase in cardiac afterload and ventricular wall stress. By promoting arrhythmias, the catecholamines released with sympathetic nervous system stimulation also may contribute to the high rate of sudden death seen with heart failure. Other effects include decreased renal perfusion and additional augmentation of the renin-angiotensin-aldosterone system, as well as decreased blood flow to skin, muscle, and abdominal organs.[15]

Renin-Angiotensin-Aldosterone Mechanism

One of the most important effects of lowered cardiac output in heart failure is a reduction in renal blood flow and glomerular filtration rate, which leads to sodium and water retention. With decreased renal blood flow, there is

a progressive increase in renin secretion by the kidneys with parallel increases in circulating levels of angiotensin II.[15] The increased concentration of angiotensin II contributes directly to a generalized and excessive vasoconstriction, as well as facilitating norepinephrine release and inhibiting reuptake of norepinephrine by the sympathetic nervous system.[4] Angiotensin II also provides a powerful stimulus for aldosterone production by the adrenal cortex (see Chapter 18). Aldosterone increases tubular reabsorption of sodium, with an accompanying increase in water retention. Because aldosterone is metabolized in the liver, its levels are further increased when heart failure causes liver congestion. Angiotensin II also increases the level of antidiuretic hormone (ADH), which serves as a vasoconstrictor and inhibitor of water excretion (see Chapter 8).

In addition to their individual effects on sodium and water balance, angiotensin II and aldosterone are also involved in regulating the inflammatory and reparative processes that follow tissue injury.[16] They stimulate inflammatory cytokine production (e.g., tumor necrosis factor [TNF] and interleukin-6), attract inflammatory cells (e.g., neutrophils and macrophages), activate macrophages at sites of injury and repair, and stimulate the growth of fibroblasts and synthesis of collagen fibers. Fibroblast and collagen deposition results in ventricular hypertrophy and myocardial wall fibrosis, which decreases compliance (i.e., increases stiffness), ultimately causing inappropriate remodeling of the heart and progression of both systolic and diastolic ventricular dysfunction.[17]

Natriuretic Peptides

The heart muscle produces and secretes a family of related peptide hormones, called the *natriuretic peptides* (NPs), that have potent diuretic, natriuretic, vascular smooth muscle, and other neurohumoral actions that affect cardiovascular function. Two of the four known NPs most commonly associated with heart failure are atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).[18]

As the name indicates, ANP is released from atrial cells in response to atrial stretch, pressure, or fluid overload. BNP, so named because it was originally found in extracts of the porcine brain, is primarily secreted by the ventricles as a response to increased ventricular pressure or fluid overload. Although the NPs are not secreted from the same chambers in the heart, they have very similar functions. In response to increased chamber stretch and pressure, they promote rapid and transient natriuresis and diuresis through an increase in the glomerular filtration rate and an inhibition of tubular sodium and water reabsorption. The NPs also facilitate complex interactions with the neurohormonal system, inhibiting the sympathetic nervous system, the renin-angiotensin-aldosterone system, and vasopressin.[19] In addition, the NPs directly affect the central nervous system and the brain, inhibiting the secretion of the antidiuretic hormone (ADH) and the function of the salt appetite and thirst center.[19]

Circulating levels of both ANP and BNP are elevated in persons with heart failure. The concentrations are well correlated with the extent of ventricular dysfunction, increasing up to 30-fold in persons with advanced heart disease.[18] Assays of BNP are used clinically in the diagnosis of heart failure and to predict the severity of the condition. Human BNP, synthesized by recombinant deoxyribonucleic acid (DNA) technology, is now available for treatment of persons with acutely decompensated heart failure.

Endothelins

The endothelins, released from the endothelial cells throughout the circulation, are potent vasoconstrictors. Like angiotensin II, endothelin can also be synthesized and released by a variety of cell types, such as cardiac myocytes. Four endothelin peptides (endothelin-1 [ET-1], ET-2, ET-3, and ET-4) have been identified.[20] In addition to vasoconstrictor actions, the endothelins induce vascular smooth muscle cell proliferation and cardiac myocyte hypertrophy; increase the release of ANP, aldosterone, and catecholamines; and exert antinatriuretic effects on the kidneys. They also have been shown to have a negative inotropic action in patients with heart failure.[21] Production of ET-1 is regulated by many factors that are significant for cardiovascular function and have implications for heart failure; for example, it is enhanced by angiotensin II, ADH, and norepinephrine and by factors such as shear stress and endothelial stretching.[21] Plasma ET-1 levels also correlate directly with pulmonary vascular resistance, and it is thought that the peptide may play a role in mediating pulmonary hypertension in persons with heart failure. An endothelin receptor antagonist is now available for use in persons with pulmonary arterial hypertension due to severe heart failure.

Myocardial Hypertrophy and Remodeling

The development of myocardial hypertrophy constitutes one of the principal mechanisms by which the heart compensates for an increase in workload.[12,14] Although ventricular hypertrophy improves the work performance of the heart, it is also an important risk factor for subsequent cardiac morbidity and mortality. Inappropriate hypertrophy and remodeling can result in changes in structure (i.e., muscle mass, chamber dilation) and function (i.e., impaired systolic or diastolic function) that often lead to further pump dysfunction and hemodynamic overload.

Myocardial hypertrophy and remodeling involve a series of complex events at both the molecular and cellular levels. The myocardium is composed of myocytes, or muscle cells, and nonmyocytes. The myocytes are the functional units of cardiac muscle. Their growth is limited by an increment in cell size, as opposed to an increase in cell number. The nonmyocytes include cardiac macrophages, fibroblasts, vascular smooth muscle, and endothelial cells. These cells, which are present in the interstitial space, remain capable of an increase in cell number and provide support for the myocytes. The nonmyocytes also determine many of the inappropriate changes that occur during myocardial hypertrophy. For example, uncontrolled fibroblast growth is associated

with increased synthesis of collagen fibers, myocardial fibrosis, and ventricular wall stiffness.

Recent research has focused on the type of hypertrophy that develops in persons with heart failure. At the cellular level, cardiac muscle cells respond to stimuli from stress placed on the ventricular wall by pressure and volume overload by initiating several different processes that lead to hypertrophy. These include stimuli that produce a *symmetric hypertrophy* with a proportionate increase in muscle length and width, as occurs in athletes; *concentric hypertrophy* with an increase in wall thickness, as occurs in hypertension; and *eccentric hypertrophy* with a disproportionate increase in muscle length, as occurs in dilated cardiomyopathy[22] (Fig. 20-6). When the primary stimulus for hypertrophy is *pressure overload,* the increase in wall stress leads to parallel replication of myofibrils, thickening of the individual myocytes, and concentric hypertrophy. Concentric hypertrophy may preserve systolic function for a time, but eventually the work performed by the ventricle exceeds the vascular reserve, predisposing to ischemia. When the primary stimulus is *ventricular volume overload,* the increase in wall stress leads to replication of myofibrils in series, elongation of the cardiac muscle cells, and eccentric hypertrophy. Eccentric hypertrophy leads to a decrease in ventricular wall thickness with an increase in diastolic volume and wall tension.

The stimuli for hypertrophy and remodeling are thought to reflect not only the mechanical stress placed on the myocytes, but also growth signals provided by the release of substances such as angiotensin II, ANP, and ET-1. It is hoped that further research into the signals that cause specific features of inappropriate myocardial hypertrophy and remodeling will lead to the identification of targets whose actions can be interrupted or modified.

Manifestations of Heart Failure

The manifestations of heart failure depend on the extent and type of cardiac dysfunction that is present and the rapidity with which it develops. A person with previously stable compensated heart failure may develop signs of heart failure for the first time when the condition has advanced to a critical point, such as with a progressive increase in pulmonary hypertension in a person with mitral valve regurgitation. Overt heart failure also may be precipitated by conditions such as infection, emotional stress, uncontrolled hypertension, or fluid overload.[9] Many persons with serious underlying heart disease, regardless of whether they have previously experienced heart failure, may be relatively asymptomatic as long they carefully adhere to their treatment regimen. A dietary excess of sodium is a frequent cause of sudden cardiac decompensation.

The manifestations of heart failure reflect the physiologic effects of the impaired pumping ability of the heart, decreased renal blood flow, and activation of sympathetic compensatory mechanisms. The severity and progression of symptoms depend on the extent and type of dysfunction that is present (systolic versus diastolic, left versus right sided). The signs and symptoms include fluid retention and edema, shortness of breath and other respiratory manifestations, fatigue and limited exercise tolerance, cachexia and malnutrition, and cyanosis.

Fluid Retention and Edema

Many of the manifestations of heart failure result from the increased capillary pressures (increased hydrostatic pressures) that develop in the peripheral circulation in persons with right-sided heart failure and in the pulmonary circulation in persons with left-sided heart failure. The increased capillary pressure reflects an overfilling of the vascular system because of increased sodium and water retention and venous congestion, resulting from impaired cardiac output.[9] *Nocturia* is a nightly increase in urine output that occurs relatively early in the course of heart failure. It occurs because of the increased cardiac output, renal blood flow, and glomerular filtration rate that follow the increased blood return to the heart when the person is in a supine position. *Oliguria,* which is a decrease in urine output, is a late sign related to a severely reduced cardiac output and resultant renal failure.

Transudation of fluid into the pleural cavity (pleural effusion or hydrothorax) or the peritoneal cavity (ascites) may occur in persons with advanced heart failure. Because the pleural veins drain into both the systemic and pulmonary venous beds, hydrothorax is observed more commonly in persons with hypertension involving both venous systems.[9] Pleural effusion occurs as the excess fluid in the lung interstitial spaces crosses the visceral pleura, which in turn overwhelms the capacity of the pulmonary lymphatic

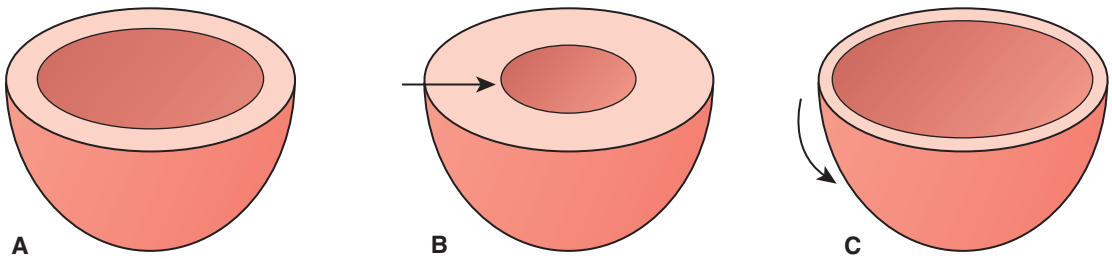


FIGURE 20-6. Different types of myocardial hypertrophy. **(A)** Normal symmetric hypertrophy with proportionate increases in myocardial wall thickness and length. **(B)** Concentric hypertrophy with a disproportionate increase in wall thickness. **(C)** Eccentric hypertrophy with a disproportionate decrease in wall thickness and ventricular dilation.

system. Ascites can occur in persons with increased pressure in the hepatic veins and veins draining the peritoneum. It usually reflects right ventricular failure and long-standing elevation of systemic venous pressure.[9]

Respiratory Manifestations

Shortness of breath due to congestion of the pulmonary circulation is one of the major manifestations of left-sided heart failure. Perceived shortness of breath (i.e., breathlessness) is called *dyspnea*. Dyspnea related to an increase in activity is called *exertional dyspnea*. *Orthopnea* is shortness of breath that occurs when a person is supine. Gravitational forces cause fluid to become sequestered in the lower legs and feet when the person is standing or sitting. When the person assumes the recumbent position, fluid from the legs and dependent parts of the body is mobilized and redistributed to an already distended pulmonary circulation. *Paroxysmal nocturnal dyspnea* is a sudden attack of dyspnea that occurs during sleep. It disrupts sleep, and the person awakens with a feeling of extreme suffocation that resolves when he or she sits up.

A subtle and often overlooked symptom of heart failure is a chronic dry, nonproductive cough that becomes worse when the person is lying down. Bronchospasm due to congestion of the bronchial mucosa may cause wheezing and difficulty in breathing. This condition is sometimes referred to as *cardiac asthma*.[9]

Cheyne-Stokes respiration is a pattern of periodic breathing characterized by a gradual increase in the depth and sometimes the rate of breathing to a maximum, followed by a decrease, resulting in apnea. Although no longer associated solely with heart failure, it is recognized as an independent risk factor for worsening of heart failure. It has been suggested that Cheyne-Stokes respirations may not be just a marker for increasing severity of heart failure, but may also aggravate it.[23] During sleep, Cheyne-Stokes breathing causes recurrent awakening and thereby reduces slow-wave and rapid eye movement (REM) sleep. The recurrent cycling of hypoventilation/apnea and hyperventilation may also increase sympathetic activity and predispose to arrhythmias.

Fatigue, Weakness, and Mental Confusion

Fatigue and weakness often accompany diminished output from the left ventricle. Cardiac fatigue is different from general fatigue in that it usually is not present in the morning but appears and progresses as activity increases during the day. In acute or severe left-sided failure, cardiac output may fall to levels that are insufficient for providing the brain with adequate oxygen, causing mental confusion and disturbed behavior. Confusion, impairment of memory, anxiety, restlessness, and insomnia are common in elderly persons with advanced heart failure, particularly in those with cerebral atherosclerosis. These symptoms may confuse the diagnosis of heart failure in the elderly because of other possible causes associated with aging.

Cachexia and Malnutrition

Cardiac cachexia is a condition of malnutrition and tissue wasting that occurs in persons with end-stage heart failure. A number of factors probably contribute to its development, including fatigue and depression that interfere with food intake, congestion of the liver and gastrointestinal structures that impairs digestion and absorption and produces feelings of fullness, and circulating toxins and mediators released from poorly perfused tissues that impair appetite and contribute to tissue wasting.

Cyanosis

Cyanosis, or a bluish discoloration of the skin and mucous membranes is caused by excess desaturated hemoglobin in the blood; it often is a late sign of heart failure. Cyanosis may be central, caused by arterial desaturation resulting from impaired pulmonary gas exchange, or peripheral, caused by venous desaturation resulting from extensive extraction of oxygen at the capillary level. Central cyanosis is caused by conditions that impair oxygenation of the arterial blood, such as pulmonary edema, left heart failure, or right-to-left cardiac shunting. Peripheral cyanosis is caused by conditions such as low-output failure that result in delivery of poorly oxygenated blood to the peripheral tissues, or by conditions such as peripheral vasoconstriction that cause excessive removal of oxygen from the blood. Central cyanosis is best monitored in the lips and mucous membranes because these areas are not subject to conditions, such as a cold environment, that cause peripheral cyanosis. Persons with right-sided or left-sided heart failure may develop cyanosis especially around the lips and in the peripheral parts of the extremities.

Arrhythmias and Sudden Cardiac Death

Both atrial and ventricular arrhythmias can occur in persons with heart failure. Atrial fibrillation is the most common arrhythmia (see Chapter 17). Manifestations associated with atrial fibrillation are related to loss of atrial contraction, tachycardia, irregular heart rate, and symptoms related to a drop in blood pressure.[24] There is also strong evidence that persons with heart failure are at increased risk for sudden cardiac arrest, that is, unwitnessed death or death that occurs within 1 hour of symptom onset. In persons with ventricular dysfunction, sudden death is caused most commonly by ventricular tachycardia or ventricular fibrillation.

Acute Heart Failure Syndromes

The acute heart failure syndromes (AHFS) are defined as "gradual or rapid change in heart failure signs and symptoms resulting in a need for urgent therapy."[25] These signs and symptoms are primarily the result of severe pulmonary edema due to elevated left ventricular filling pressures, with or without a low cardiac output.[25–28] The syndromes are among the most common disorders seen in emergency

departments; chronic heart failure, often complicated by episodes of acute worsening, is the most common cause of the syndrome. Until recently, the underlying cause of heart failure hospitalization was viewed as merely a problem with volume overload or low cardiac output precipitated by dietary indiscretions or medication nonadherence. Hospitalization therefore was considered to be an expected part of the chronic heart failure trajectory.

The AHFS are thought to encompass three different types of conditions: (1) worsening of chronic systolic or diastolic dysfunction that appears to respond to treatment; (2) new-onset acute heart failure that occurs secondary to a precipitating event such as a large myocardial infarction or a sudden increase in blood pressure superimposed on a noncompliant left ventricle; and (3) worsening of end-stage/advanced heart failure that is refractory to treatment, with predominantly left ventricular systolic dysfunction associated with a low-output state.[26] The difference between new-onset AHFS and AHFS caused by chronic heart failure is in the degree of physiologic response, which is more pronounced in the new-onset AHFS and more subtle in chronic heart failure because of the compensatory pathophysiology. For example, with new-onset AHFS, the person will have a strong sympathetic response with enhanced pulmonary vascular permeability causing rapid and dramatic symptoms of pulmonary edema. Because many compensatory mechanisms operate in persons with chronic heart failure, they tolerate higher pulmonary vascular pressures. Chronic changes in neurohormonal regulation lead to a strong activation of the angiotensin-aldosterone system with a resultant volume overload, and venous congestion in both the systemic and pulmonary circulations.[27]

Acute Pulmonary Edema

Acute pulmonary edema is the most dramatic symptom of AHFS. It is a life-threatening condition in which capillary fluid moves into the alveoli.[9] The accumulated fluid in the alveoli and airways causes lung stiffness, makes lung expansion more difficult, and impairs the gas exchange function of the lung. With the decreased ability of the lungs to oxygenate the blood, the hemoglobin leaves the pulmonary circulation without being fully oxygenated, resulting in shortness of breath and cyanosis.

The person with severe pulmonary edema is usually seen sitting and gasping for air. The pulse is rapid, the skin is moist and cool, and the lips and nail beds are cyanotic. As the pulmonary edema worsens and oxygen supply to the brain drops, confusion and stupor appear. Dyspnea and air hunger are accompanied by a productive cough with frothy (resembling beaten egg whites) and often blood-tinged sputum—the effect of air mixing with the serum albumin and red blood cells that have moved into the alveoli. The movement of air through the alveolar fluid produces fine crepitant sounds called *crackles*, which can be heard with chest auscultation. As fluid moves into the larger airways, the crackles become louder and coarser.

Diagnosis and Treatment

Diagnostic Methods

Diagnostic methods in heart failure are directed toward establishing the cause of the disorder and determining the extent of the dysfunction.[1,2] Because heart failure represents the failure of the heart as a pump and can occur in the course of a number of heart diseases or other systemic disorders, the diagnosis of heart failure often is based on signs and symptoms related to the failing heart itself, such as shortness of breath and fatigue. The functional classification of the New York Heart Association (NYHA) is one guide to classifying the extent of dysfunction (Table 20-1).

The methods used in the diagnosis of heart failure include history and physical examination, laboratory studies, electrocardiography, chest radiography, and echocardiography. The history should include information related to dyspnea, cough, nocturia, generalized fatigue, and other signs and symptoms of heart failure. A complete physical examination includes assessment of

TABLE 20-1 New York Heart Association Functional Classification of Patients with Heart Disease

Classification	Characteristics
Class I	Patients with cardiac disease but without the resulting limitations in physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with heart disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. The symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

From Criteria Committee of the New York Heart Association. (1964). *Diseases of the heart and blood vessels: Nomenclature and criteria for diagnosis* (6th ed., pp. 112–113). Boston: Little, Brown.

heart rate, heart sounds, blood pressure, jugular veins for venous congestion, lungs for signs of pulmonary congestion, and lower extremities for edema. Pulse oximetry can be used to measure the percentage of hemoglobin oxygen saturation.

Laboratory tests are used in the diagnosis of anemia and electrolyte imbalances and to detect signs of chronic liver congestion. Measurements of BNP are recommended to confirm the diagnosis of heart failure; to evaluate the severity of left ventricular compromise, estimate the prognosis, and predict future cardiac events such as sudden death; and to evaluate the effectiveness of treatment.

Echocardiography plays a key role in assessing right and left ventricular wall motion (normal, akinesis, or hypokinesis), wall thickness, ventricular chamber size, valve function, heart defects, ejection fraction, and pericardial disease. Radionuclide ventriculography and cardiac angiography are recommended if there is reason to suspect coronary artery disease as the underlying cause for heart failure. Chest radiographs provide information about the size and shape of the heart and pulmonary vasculature, and also can indicate the relative severity of the failure by revealing if pulmonary edema is predominantly vascular or interstitial or has advanced to the alveolar and bronchial stages. Cardiac magnetic resonance imaging and cardiac computed tomography are used to document ejection fraction, ventricular preload, and regional wall motion.

Invasive hemodynamic monitoring may be used for assessment in acute, life-threatening episodes of heart failure.[29] These monitoring methods include central venous pressure (CVP), pulmonary artery pressure monitoring, thermodilution measurements of cardiac output, and intra-arterial measurements of blood pressure. CVP reflects the amount of blood returning to the right side of the heart. Measurements of CVP are best obtained by a catheter inserted into the right atrium through a peripheral vein or by the right atrial port (opening) in a pulmonary artery catheter.

Ventricular volume pressures are obtained indirectly, such as by means of a flow-directed, balloon-tipped pulmonary artery catheter. This catheter is introduced through a peripheral or central vein and then advanced into the right atrium. The balloon is then inflated with air, enabling the catheter to float through the right ventricle into the pulmonary artery until it becomes wedged in a small pulmonary vessel. With the balloon inflated, the catheter monitors pulmonary capillary pressures (also called *pulmonary wedge pressure* [PWP]), which are in direct communication with pressures from the left ventricle. The pulmonary capillary pressures provide a means of assessing the pumping ability of the left ventricle. One type of pulmonary artery catheter is equipped with a thermistor probe to obtain *thermodilution measurements* of cardiac output. Catheters with oximeters built into their tips that permit continuous monitoring of oxygen saturation (SvO_2) also are available. Intra-arterial blood pressure monitoring provides a means for continuous monitoring of blood pressure. It is used in persons with acute heart failure when aggressive intravenous medication therapy or a mechanical assist device is required.

Treatment

The goals of treatment for heart failure are determined by the rapidity of onset and severity of the heart failure. Persons with acute heart failure require urgent therapy directed at stabilizing and correcting the cause of the cardiac dysfunction. For persons with chronic heart failure, the goals of treatment are directed toward relieving the symptoms, improving the quality of life, and reducing or eliminating risk factors (hypertension, diabetes, or obesity) with the long-term goal of slowing, halting, or reversing the cardiac dysfunction.[1,2]

Treatment measures for both acute and chronic heart failure include pharmacologic and nonpharmacologic approaches. Mechanical support devices, including the aortic balloon pump (for acute failure) and ventricular assist devices (VADs), can be used to sustain life in persons with severe heart failure. Heart transplant remains an option for some people with end-stage heart disease.

Nonpharmacologic Methods. Exercise intolerance is typical of persons with chronic heart failure. Consequently, individualized exercise training is important to maximize muscle conditioning. Persons who are not accustomed to exercise and those with more severe heart failure are started at a lower intensity and shorter duration than those who are largely asymptomatic. Sodium and fluid restriction and weight management are important for all persons with heart failure, with the level of sodium and fluid restriction individualized to the severity of sodium intake, and diuretic therapy facilitates the excretion of edema fluid. Counseling, health teaching, and ongoing evaluation programs assist persons with heart failure manage and cope with their treatment regimen.

Pharmacologic Treatment. Once heart failure is moderate to severe, polypharmacy becomes a management standard and often includes diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and β-adrenergic blocking agents.[1,2,30] The choice of pharmacologic agents is determined by problems caused by the disorder (i.e., systolic or diastolic dysfunction) and those brought about by activation of compensatory mechanisms (e.g., excess fluid retention, inappropriate activation of sympathetic mechanisms).

Diuretics are among the most frequently prescribed medications for moderate to severe heart failure. They promote the excretion of fluid and help to sustain cardiac output and tissue perfusion by reducing preload and allowing the heart to operate at a more optimal part of the Frank-Starling curve. In emergencies, such as acute pulmonary edema, loop diuretics such as furosemide can be administered intravenously. When given intravenously, these medications act quickly to reduce venous return through vasodilation so that right ventricular output and pulmonary vascular resistance are decreased. This response to intravenous administration is extrarenal and precedes the onset of diuresis.

The *ACE inhibitors,* which prevent the conversion of angiotensin I to angiotensin II, have been used effectively in the treatment of chronic heart failure. The renin-angiotensin-aldosterone system is activated early in the course of heart failure and plays an important role in its progression. It results in an increase in angiotensin II, which causes vasoconstriction, unregulated ventricular remodeling, and increased aldosterone production with a subsequent increase in sodium and water retention by the kidneys. ACE inhibitors have been shown to limit these harmful complications. The *angiotensin II receptor blockers* appear to have similar but more limited beneficial effects. They have the advantage of not causing a cough, which is a troublesome side effect of the ACE inhibitors for many persons. Aldosterone has a number of deleterious effects in individuals with heart failure. *Aldosterone receptor antagonists* may be used in combination with other agents for persons with moderately severe to severe heart failure.

β-*Adrenergic receptor blocking drugs* are used to decrease left ventricular dysfunction associated with activation of the sympathetic nervous system. Large clinical trials have shown that long-term therapy with β-adrenergic receptor blocking agents reduces morbidity and mortality in persons with chronic heart failure. The mechanism of this benefit remains unclear, but it is likely that chronic elevation of catecholamines and sympathetic nervous system activity causes progressive myocardial damage, leading to a worsening of left ventricular function and a poorer prognosis in persons with heart failure.

Digitalis has been a recognized treatment for heart failure for over 200 years. The various forms of digitalis are called *cardiac glycosides*. They improve cardiac function by increasing the force and strength of ventricular contractions. Digitalis and related cardiac glycosides are inotropic agents that exert their effects by inhibiting the Na^+/K^+-ATPase membrane pump, which increases intracellular sodium; this in turn leads to an increase in intracellular calcium through the Na^+/Ca^+ exchange pump (see Fig. 20-1). The cardiac glycosides also decrease sinoatrial node activity and decrease conduction through the atrioventricular node, thereby slowing the heart rate and increasing diastolic filling time. For this reason, they may also be used to control tachycardia.

Vasodilator agents such as isosorbide dinitrate and hydralazine may be added to other standard medications for patients with chronic heart failure. Agents such as nitroglycerin, nitroprusside, and nesiritide (B-type natriuretic peptide) are used in AHFSs to improve left heart performance by decreasing the preload (through vasodilation) or reducing the afterload (through arteriolar dilation), or both.

Oxygen Therapy. Oxygen therapy increases the oxygen content of the blood and is often used in patients with acute episodes of heart failure. Noninvasive ventilation using continuous positive airway pressure (CPAP) may be used to relieve dyspnea, respiratory distress, and/or pulmonary edema.[26,28] CPAP by face mask reduces the need for endotracheal intubation and has minimal adverse effects or complications. Because CPAP increases intrathoracic pressure, it also has the potential for decreasing venous return and left ventricular preload, thereby improving the cardiac ejection fraction and stabilizing the hemodynamic status in persons with severe heart failure.[26,28] Noninvasive ventilation can also be provided by bilevel ventilation (BiPAP), which delivers positive pressure during both inspiration and expiration.

Cardiac Resynchronization and Implantable Cardioverter–Defibrillators. Some persons with heart failure have abnormal intraventricular conduction that results in dyssynchronous and ineffective contractions. Cardiac resynchronization has been shown to improve ventricular function and blood pressure, increase the quality of life, and reduce the risk of death.[31]

Individuals with heart failure are at significant risk of sudden cardiac death from ventricular fibrillation or ventricular tachycardia. Implantation of a cardioverter–defibrillator is indicated in selected patients with heart failure to prevent sudden cardiac death.[1,2] A cardioverter–defibrillator is a programmable implanted device that monitors the cardiac rhythm. It has the capacity to pace the heart and deliver electrical shocks to terminate lethal arrhythmias.

Mechanical Support and Heart Transplantation. Refractory heart failure reflects deterioration in cardiac function that is unresponsive to medical or surgical interventions. With improved methods of treatment, more people are reaching a point where a cure is unachievable and death is imminent without mechanical support or heart transplantation.

Since the early 1960s, significant progress has been made in improving the efficacy of *ventricular assist devices* (VADs), which are mechanical pumps used to support ventricular function. VADs are used to decrease the workload of the myocardium while maintaining cardiac output and systemic arterial pressure. This decreases the workload on the ventricle and allows it to rest and recover. Most VADs require an invasive open chest procedure for implantation. They may be used in patients who fail or have difficulty being weaned from cardiopulmonary bypass after cardiac surgery, those who develop cardiogenic shock after myocardial infarction, those with end-stage cardiomyopathy, and those who are awaiting cardiac transplantation. Earlier and more aggressive use of VADs as a bridge to transplantation and destination therapy (permanent support) has been shown to increase survival.[28,32] VADs that allow the patient to be mobile and managed at home are sometimes used for long-term or permanent support for treatment of end-stage heart failure, rather than simply as a bridge to transplantation. VADs can be used to support the function of the left ventricle, right ventricle, or both.[32]

Heart transplantation is the preferred treatment for many persons with end-stage cardiac failure and otherwise good life expectancy.[1,2] Despite the overall success of heart transplantation, donor availability remains a key problem, and thousands are denied transplantation each year. Left ventricular remodeling is a surgical procedure designed to restore the size and shape of the ventricle and

is thought to be a viable surgical alternative to cardiac transplantation for persons with severe left ventricular dysfunction.[33]

In summary, heart failure occurs when the heart fails to pump sufficient blood to meet the metabolic needs of body tissues. The physiology of heart failure reflects the interplay between a decrease in cardiac output that accompanies impaired function of the failing heart and the compensatory mechanisms that preserve the cardiac reserve. Compensatory mechanisms include the Frank-Starling mechanism, sympathetic nervous system activation, the renin-angiotensin-aldosterone mechanism, natriuretic peptides, endothelins, and myocardial hypertrophy and remodeling. In the failing heart, early decreases in cardiac function may go unnoticed because these compensatory mechanisms maintain the cardiac output. Unfortunately, the mechanisms were not intended for long-term use, and in severe and prolonged heart failure the compensatory mechanisms no longer are effective, and instead contribute to the progression of heart failure.

Heart failure may be described in terms of systolic versus diastolic dysfunction and right ventricular versus left ventricular dysfunction. With systolic dysfunction, there is impaired ejection of blood from the heart during systole; with diastolic dysfunction, there is impaired filling of the heart during diastole. Left ventricular dysfunction is characterized by congestion in the pulmonary circulation and impaired blood flow in the peripheral circulation, and right ventricular dysfunction by congestion in the peripheral circulation.

The manifestations of heart failure include fluid retention and edema, shortness of breath, nocturia, fatigue and impaired exercise tolerance, impaired gastrointestinal function and malnutrition, and cyanosis. In right-sided failure, there is dependent edema of the lower parts of the body, engorgement of the liver, and ascites. In left-sided failure, pulmonary congestion with shortness of breath and chronic, nonproductive cough are common. The acute heart failure syndromes represent a gradual or rapid change in heart failure signs and symptoms, indicating the need for urgent therapy. These symptoms are primarily the result of pulmonary congestion due to elevated left ventricular filling pressures with or without a low cardiac output.

The diagnostic methods in heart failure are directed toward establishing the cause and extent of the disorder. Treatment is directed toward correcting the cause whenever possible, improving cardiac function, maintaining the fluid volume within a compensatory range, and developing an activity pattern consistent with individual limitations in cardiac reserve. Among the medications used in the treatment of heart failure are diuretics, digitalis, ACE inhibitors and angiotensin receptor blocking agents, β-adrenergic receptor blockers, and vasodilators. Mechanical support devices, including VADs, sustain life in persons with severe heart failure. Heart transplantation remains the treatment of choice for many persons with end-stage heart failure.

Circulatory Failure (Shock)

Circulatory shock can be described as an acute failure of the circulatory system to supply the peripheral tissues and organs of the body with an adequate blood supply, resulting in cellular hypoxia.[3,34] Most often hypotension and hypoperfusion are present, but shock may occur in the presence of normal vital signs. Shock is not a specific disease but a syndrome that can occur in the course of many life-threatening traumatic conditions or disease states.

Pathophysiology of Shock

Circulatory failure results in hypoperfusion of organs and tissues, which in turn results in insufficient supply of oxygen and nutrients for cellular function. The cellular injury created by an inadequate delivery of oxygen and substrates also induces the production and release of inflammatory mediators that further compromise perfusion through functional and structural changes within the microvascular circulation. This leads to a vicious cycle in which impaired perfusion is responsible for cellular injury, which causes maldistribution of blood flow, further compromising cell perfusion.

Cellular Responses

Shock ultimately exerts its effect at the cellular level, with failure of the circulation to supply body cells with the oxygen and nutrients needed for production of ATP. The cell uses ATP for a number of purposes, including operation of the Na^+/K^+-ATPase membrane pump that moves

Circulatory Shock

- Circulatory shock represents the inability of the circulation to adequately perfuse the tissues of the body.
- It can result from failure of the heart as a pump (cardiogenic shock), a loss of fluid from the vascular compartment (hypovolemic shock), obstruction of flow through the vascular compartment (obstructive shock), or an increase in the size of the vascular compartment that interferes with the distribution of blood (distributive shock).
- The manifestations of shock reflect both the impaired perfusion of body tissues and the body's attempt to maintain tissue perfusion through conservation of water by the kidney, translocation of fluid from the extracellular to the intravascular compartment, and activation of sympathetic nervous system mechanisms that increase heart rate and divert blood from less to more essential body tissues.

sodium out of the cell and returns potassium to the inside of the cell. The cell uses two pathways to convert nutrients to ATP (see Chapter 1). The first is the anaerobic (non–oxygen-dependent) glycolytic pathway, located in the cytoplasm, which converts glucose to ATP and pyruvate. The second is the aerobic (oxygen-dependent) pathway, which is located in the mitochondria. When oxygen is available, pyruvate from the anaerobic pathway moves into the mitochondria and enters the aerobic pathway, where it is transformed into ATP and the metabolic byproducts carbon dioxide and water. When oxygen is lacking, pyruvate is converted to lactic acid.

In severe shock, cellular metabolic processes are essentially anaerobic owing to the decreased availability of oxygen. Excess amounts of lactic acid accumulate in the cellular and the extracellular compartments, and limited amounts of ATP are produced. Without sufficient energy production, normal cell function cannot be maintained. The Na^+/K^+-ATPase membrane pump function is impaired, resulting in intracellular accumulation of sodium and loss of potassium. The increase in intracellular sodium results in cellular edema and increased cell membrane permeability. Mitochondrial activity becomes severely depressed and lysosomal membranes may rupture, resulting in the release of enzymes that cause further intracellular destruction. This is followed by cell death and the release of intracellular contents into the extracellular space. The extent of the cell injury and organ dysfunction is primarily determined by the degree and duration of the shock state.

Compensatory Mechanisms

The clinical manifestations of shock are at least partly due to the body's compensatory responses to hypoperfusion. The most immediate of the compensatory mechanisms are those of the sympathetic nervous system and the renin-angiotens in mechanism, which are designed to maintain cardiac output and blood pressure.

The sympathetic nervous system provides important reflexive mechanisms that are essential to the support of the circulatory system during shock, particularly hypovolemic shock. These reflexes increase heart rate and stimulate constriction of blood vessels throughout the body. There are two types of adrenergic receptors for the sympathetic nervous system: alpha (α) and beta (β). The β receptors are further subdivided into β_1 and β_2 receptors. Stimulation of the α receptors causes vasoconstriction; stimulation of β_1 receptors, an increase in heart rate and force of myocardial contraction; and of β_2 receptors, vasodilation of the skeletal muscle beds and relaxation of the bronchioles. In shock, there is an increase in sympathetic outflow that results in increased epinephrine and norepinephrine release and activation of both α and β receptors. Thus, increases in heart rate and vasoconstriction occur in most types of shock. The arterioles constrict in most parts of the systemic circulation, thereby increasing the peripheral vascular resistance, and the veins and venous reservoirs constrict, thereby helping to maintain adequate venous return to the heart.

There also is an increase in renin release, leading to an increase in angiotensin II, which augments vasoconstriction and leads to an aldosterone-mediated increase in sodium and water retention by the kidneys. In addition, there is a local release of vasoconstrictors, including norepinephrine, angiotensin II, vasopressin, and endothelin, which contribute to arterial and venous vasoconstriction.

The compensatory mechanisms that the body recruits are not effective over the long term and become detrimental when the shock state is prolonged. The intense vasoconstriction causes a decrease in tissue perfusion and insufficient supply of oxygen. Cellular metabolism is impaired, vasoactive inflammatory mediators such as histamine are released, production of oxygen free radicals is increased, and excessive lactic acid and hydrogen ions result in intracellular acidity.[5] Each of these factors promotes cellular dysfunction or death. If circulatory function is reestablished, whether the shock is irreversible or the patient will survive is determined largely at the cellular level.

Types of Shock

Circulatory shock can be caused by an alteration in cardiac function (cardiogenic shock), a decrease in blood volume (hypovolemic shock), obstruction of blood flow through the circulatory system (obstructive shock), or excessive vasodilation with maldistribution of blood flow (distributive shock). The main types of shock are summarized in Chart 20-1 and depicted in Figure 20-7.

Cardiogenic Shock

Cardiogenic shock occurs when the heart fails to pump blood sufficiently to meet the body's demands (see Fig. 20-7). Clinically, it is defined as decreased cardiac output,

CHART 20-1 Classification of Circulatory Shock

Cardiogenic
- Myocardial damage (myocardial infarction, contusion)
- Sustained arrhythmias
- Acute valve damage, ventricular septal defect
- Cardiac surgery

Hypovolemic
- Loss of whole blood
- Loss of plasma
- Loss of extracellular fluid

Obstructive
- Inability of the heart to fill properly (cardiac tamponade)
- Obstruction to outflow from the heart (pulmonary embolus, cardiac myxoma, pneumothorax, or dissecting aneurysm)

Distributive
- Loss of sympathetic vasomotor tone (neurogenic shock)
- Presence of vasodilating substances in the blood (anaphylactic shock)
- Presence of inflammatory mediators (septic shock)

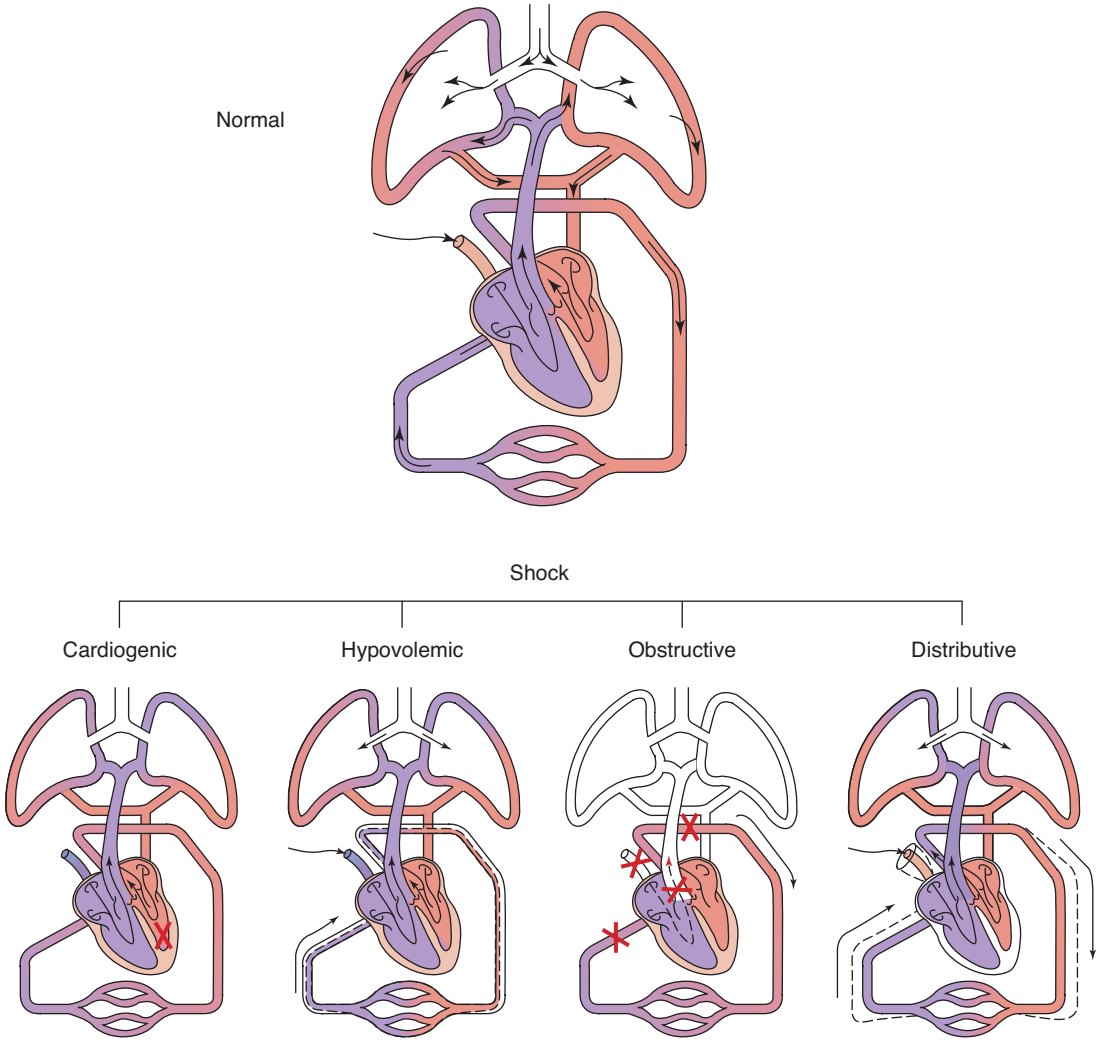


FIGURE 20-7. Types of shock.

hypotension, hypoperfusion, and indications of tissue hypoxia despite an adequate intravascular volume.[35,36] Cardiogenic shock may occur suddenly from a number of causes, including myocardial infarction, myocardial contusion, acute mitral valve regurgitation due to papillary muscle rupture, sustained arrhythmias, severe dilated cardiomyopathy, and cardiac surgery. Cardiogenic shock can also occur with other types of shock because of inadequate coronary blood flow. The most common cause of cardiogenic shock is myocardial infarction. Most patients who die of cardiogenic shock have had extensive damage to the contracting muscle of the left ventricle because of a recent infarct or a combination of recent and old infarctions.

Regardless of cause, in persons with cardiogenic shock there is failure to eject blood from the heart, hypotension, and inadequate cardiac output. Compensatory neurohumoral responses take place, which include activation of the sympathetic and renin-angiotensin systems leading to vasoconstriction, tachycardia, and fluid retention. Increased systemic vascular resistance often contributes to the deterioration of cardiac function by increasing afterload or the resistance to ventricular systole. Preload, the filling pressure, also is increased as blood returning to the heart is added to blood that previously was not pumped forward, resulting in an increase in end-systolic ventricular volume. Increased resistance to ventricular systole (i.e., afterload) combined with decreased myocardial contractility causes an increase in end-systolic ventricular volume and preload, further complicating cardiac status.

Manifestations. The signs and symptoms of cardiogenic shock are consistent with those of extreme heart failure. The lips, nail beds, and skin may become cyanotic because of stagnation of blood flow and increased extraction of oxygen from the hemoglobin as it passes through the capillary bed. Mean arterial and systolic blood pressures decrease due to poor stroke volume, and there is a narrow pulse pressure and near-normal diastolic blood pressure because of arterial vasoconstriction. Urine output decreases because of lower renal

perfusion pressures and the increased release of aldosterone. Elevated preload is reflected in a rise in CVP and pulmonary capillary wedge pressure. Neurologic changes, such as alterations in cognition or consciousness, may occur because of low cardiac output and poor cerebral perfusion.

Treatment. Treatment of cardiogenic shock requires striking a precarious balance between improving cardiac output, reducing the workload and oxygen needs of the myocardium, and increasing coronary perfusion.[36,37] Fluid volume must be regulated within a level that optimizes the filling pressure and stroke volume. Pulmonary edema and arrhythmias should be corrected or prevented to increase stroke volume and decrease the oxygen demands of the heart. Coronary artery perfusion is increased by promoting coronary artery vasodilation, increasing blood pressure, decreasing ventricular wall tension, and decreasing intracardiac pressures.

The goal of pharmacologic treatment is to increase cardiac contractility without increasing heart rate. Dopamine and dobutamine are the most commonly used inotropic agents.[37] Initially, dopamine is the drug of choice because it acts as an inotrope as well as a vasoconstrictor. Dobutamine, an inotrope with arterial dilator properties, can be used in persons with less severe hypotension. Catecholamines, such as norepinephrine, increase cardiac contractility but must be used with extreme caution because they also result in arterial constriction and increased heart rates, which worsens the imbalance between myocardial oxygen supply and demand.

The intra-aortic balloon pump, also referred to as *counterpulsation,* enhances coronary and systemic perfusion, yet decreases afterload and myocardial oxygen demands.[28,36,37] The device, which pumps in synchrony with the heart, consists of a 10-inch-long balloon that is inserted through a catheter into the descending aorta (Fig. 20-8). The balloon is timed to inflate during ventricular diastole and deflate just before ventricular systole. Diastolic inflation creates a pressure wave in the ascending aorta that increases coronary artery blood flow and a less intense wave in the lower aorta that enhances organ perfusion. The abrupt balloon deflation at the onset of systole results in a displacement of blood volume that lowers the resistance to ejection of blood from the left ventricle. Thus, the heart's pumping efficiency is increased, myocardial oxygen supply is increased, and myocardial oxygen consumption is decreased.

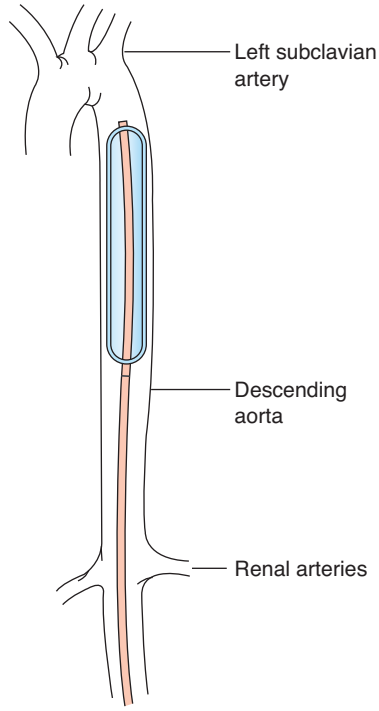


FIGURE 20-8. Aortic balloon pump placed in the descending aorta. (From Hudak C.M., Gallo B.M. [1994]. *Critical care nursing* [6th ed.]. Philadelphia: J.B. Lippincott.)

Hypovolemic Shock

Hypovolemic shock is characterized by diminished blood volume such that there is inadequate filling of the vascular compartment[3,38,39] (see Fig. 20-7). It occurs when there is an acute loss of 15% to 20% of the circulating blood volume. The decrease may be caused by an external loss of whole blood (e.g., hemorrhage), plasma (e.g., severe burns), or extracellular fluid (e.g., severe dehydration or loss of gastrointestinal fluids with vomiting or diarrhea). Hypovolemic shock also can result from an internal hemorrhage or from third-space losses, when extracellular fluid is shifted from the vascular compartment to the interstitial space or compartment.

Hypovolemic shock, which has been the most widely studied type of shock, is often used as a prototype in discussions of the manifestations of shock. Approximately 10% of the total blood volume can be removed without changing cardiac output or arterial pressure. The average blood donor loses approximately 500 mL or 10% of his or her blood without experiencing adverse effects.[3] As increasing amounts of blood (10% to 25%) are removed, the stroke volume falls but arterial pressure is maintained because of sympathetic-mediated increases in heart rate and vasoconstriction. Blood pressure is the product of cardiac output and systemic vascular resistance (blood pressure = cardiac output × systemic vascular resistance). Vasoconstriction results in an increased diastolic pressure and narrow pulse pressure. An increase in systemic vascular resistance maintains mean arterial pressure for a short time despite decreased cardiac output. Without compensatory mechanisms to maintain cardiac output and blood pressure, the loss of vascular volume would result in a rapid progression from the initial to the progressive and irreversible stages of shock.

The most immediate of the compensatory mechanisms are the sympathetic-mediated responses designed to maintain cardiac output and blood pressure (Fig. 20-9). Shortly after the onset of hemorrhage or the loss of blood volume, tachycardia, increased cardiac contractility, vasoconstriction, and other signs of sympathetic and adrenal medullary activity appear. The sympathetic vasoconstrictor response also mobilizes blood that has been stored in the venous side of the circulation as a means of increasing

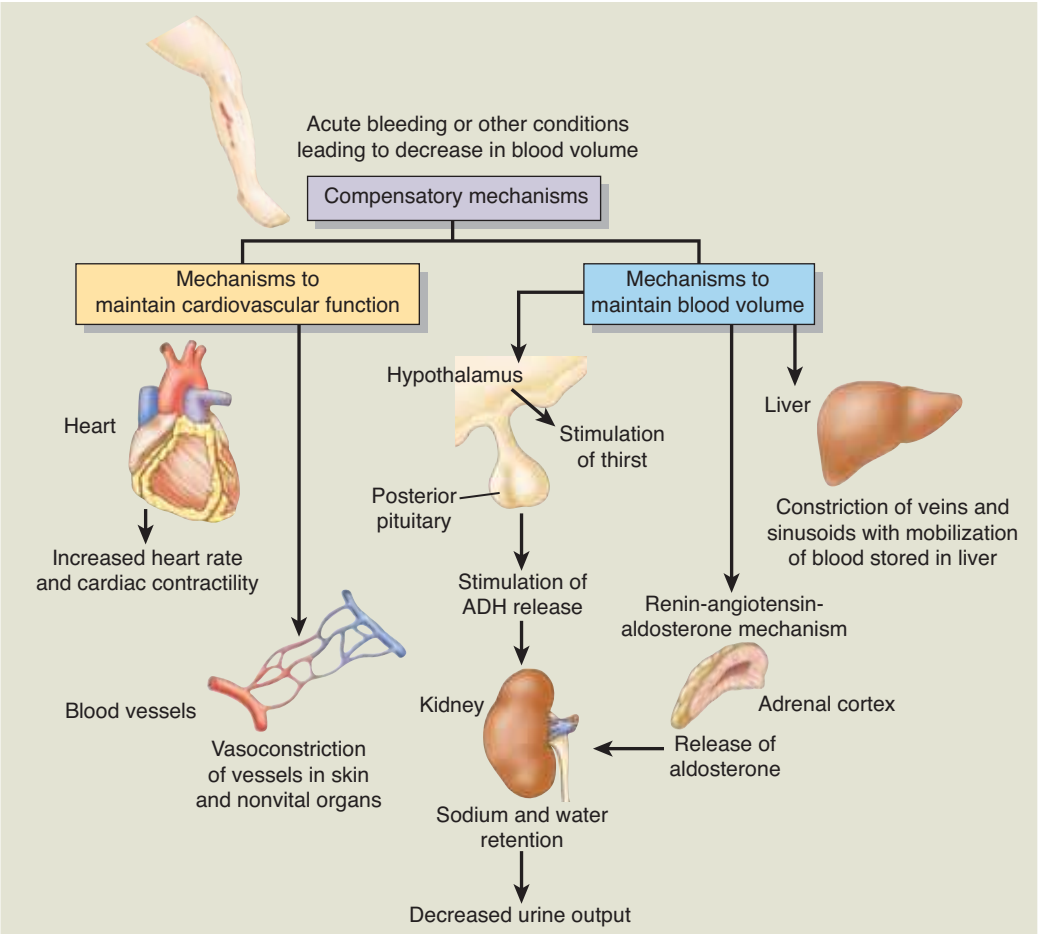


FIGURE 20-9. Compensatory mechanisms used to maintain circulatory function and blood volume in hypovolemic shock. ADH, antidiuretic hormone.

venous return to the heart. There is considerable capacity for blood storage in the large veins of the abdomen, and approximately 350 mL of blood that can be mobilized in shock is stored in the liver.[3] Sympathetic stimulation does not initially cause constriction of the cerebral and coronary vessels, and blood flow to the heart and brain is maintained at essentially normal levels as long as the mean arterial pressure remains above 70 mm Hg.[3]

Compensatory mechanisms designed to restore blood volume include absorption of fluid from the interstitial spaces, conservation of sodium and water by the kidneys, and thirst. Extracellular fluid is distributed between the interstitial spaces and the vascular compartment. When there is a loss of vascular volume, capillary pressures decrease and water is drawn into the vascular compartment from the interstitial spaces. The maintenance of vascular volume is further enhanced by renal mechanisms that conserve fluid. A decrease in renal blood flow and glomerular filtration rate results in activation of the renin-angiotensin-aldosterone mechanism, which produces an increase in sodium reabsorption by the kidneys. The decrease in blood volume also stimulates centers in the hypothalamus that regulate ADH release and thirst. ADH, also known as *vasopressin,* constricts the peripheral arteries and veins and greatly increases water retention by the kidneys. Although the mechanism of ADH is more sensitive to changes in serum osmolality, a decrease of 10% to 15% in blood volume serves as a strong stimulus for ADH and thirst.[3]

During the early stages of hypovolemic shock, vasoconstriction decreases the size of the vascular compartment and increases systemic vascular resistance. This response usually is all that is needed when the injury is slight and blood loss is minimal. As hypovolemic shock progresses, vasoconstriction of the blood vessels that supply the skin, skeletal muscles, kidneys, and abdominal organs becomes more severe, with a further decrease in blood flow and conversion to anaerobic metabolism resulting in cellular injury.

Manifestations. The signs and symptoms of hypovolemic shock depend on its severity and are closely related to low peripheral blood flow and excessive sympathetic stimulation. They include thirst, increased heart rate, cool and clammy skin, decreased arterial blood pressure, decreased urine output, and changes in mentation. Laboratory tests of hemoglobin and hematocrit provide information regarding the severity of blood loss or hemoconcentration due to dehydration. Serum lactate and arterial pH provide information about the severity of acidosis due to anaerobic metabolism.[39]

An increase in heart rate is an early sign of hypovolemic shock, as the body tries to maintain cardiac output despite the decrease in stroke volume. As shock progresses, the pulse becomes weak and thready, indicating vasoconstriction and reduced filling of the vascular compartment. Thirst is an early symptom in hypovolemic shock.

Arterial blood pressure is decreased in moderate to severe shock. However, controversy exists over the value of blood pressure measurements in the early diagnosis and management of shock. This is because compensatory mechanisms tend to preserve blood pressure until shock is relatively far advanced. Furthermore, a normal arterial pressure does not ensure adequate perfusion and oxygenation of vital organs at the cellular level. This does not imply that blood pressure should not be closely monitored in patients at risk for development of shock, but it does indicate the need for other assessment measures.

As shock progresses, the respirations become rapid and deep, to compensate for the increased production of acid and decreased availability of oxygen. Decreased intravascular volume results in decreased venous return to the heart and a decreased CVP. When shock becomes severe, the peripheral veins may collapse. Sympathetic stimulation leads to intense vasoconstriction of the skin vessels, which results in cool and mottled skin. In hemorrhagic shock, the loss of red blood cells results in pallor of the skin and mucous membranes.

Urine output decreases very quickly in hypovolemic shock. Compensatory mechanisms decrease renal blood flow as a means of diverting blood flow to the heart and brain. Oliguria of 20 mL/hour or less indicates inadequate renal perfusion. Continuous measurement of urine output is essential for assessing the circulatory and volume status of the person in shock.

Restlessness, agitation, and apprehension are common in early shock because of increased sympathetic outflow and increased levels of epinephrine. As the shock progresses and blood flow to the brain decreases, restlessness is replaced by altered arousal and mentation. Loss of consciousness and coma may occur if the person does not receive or respond to treatment.

Treatment. The treatment of hypovolemic shock is directed toward correcting or controlling the underlying cause and improving tissue perfusion. Ongoing loss of blood must be corrected, such as in surgery. Oxygen is administered to increase oxygen delivery to the tissues. Medications usually are administered intravenously. Frequent measurements of heart rate and cardiac rhythm, blood pressure, and urine output are used to assess the severity of circulatory compromise and to monitor treatment.

In hypovolemic shock, the goal of treatment is to restore vascular volume.[38,39] This can be accomplished through intravenous administration of fluids and blood. The crystalloids (e.g., isotonic saline and Ringer lactate) are readily available and effective, at least temporarily. Plasma volume expanders (e.g., pentastarch and colloidal albumin) have a high molecular weight, do not necessitate blood typing, and remain in the vascular space for longer periods than crystalloids such as dextrose and saline. Blood or blood products (packed or frozen red cells) are administered based on hematocrit and hemodynamic findings. Fluids and blood are best administered based on volume indicators such as CVP and urine output.

Vasoactive medications are agents capable of constricting or dilating blood vessels. Considerable controversy exists about the advantages or disadvantages related to the use of these drugs. As a general rule, vasoconstrictor agents are not used as a primary form of therapy in hypovolemic shock, and may be detrimental. These agents are given only when volume deficits have been corrected yet hypotension persists.

Obstructive Shock

The term *obstructive shock* describes circulatory shock that results from mechanical obstruction of the flow of blood through the central circulation (great veins, heart, or lungs; see Fig. 20-7). Obstructive shock may be caused by a number of conditions, including dissecting aortic aneurysm, cardiac tamponade, pneumothorax, atrial myxoma, and evisceration of abdominal contents into the thoracic cavity because of a ruptured hemidiaphragm. The most frequent cause of obstructive shock is pulmonary embolism.

The primary physiologic result of obstructive shock is elevated right heart pressure due to impaired right ventricular function. Pressures are increased despite impaired venous return to the heart. Signs of right heart failure occur, including elevation of CVP and jugular venous distention. Treatment modalities focus on correcting the cause of the disorder, frequently with surgical interventions such as pulmonary embolectomy, pericardiocentesis (i.e., removal of fluid from the pericardial sac) for cardiac tamponade, or the insertion of a chest tube for correction of a tension pneumothorax or hemothorax. In severe or massive pulmonary embolus, fibrinolytic drugs may be used to break down the clots causing the obstruction.

Distributive Shock

Distributive or vasodilatory shock is characterized by loss of blood vessel tone, enlargement of the vascular compartment, and displacement of the vascular volume away from the heart and central circulation.[40] In distributive shock, the capacity of the vascular compartment expands to the extent that a normal volume of blood does not fill the circulatory system (see Fig. 20-7). Therefore, this type of shock is also referred to as *normovolemic shock*. Two main causes result in the loss of vascular tone: a decrease in the sympathetic control of vasomotor tone or the release of excessive vasodilator substances. It can also occur as a complication of vessel damage resulting from prolonged and severe hypotension due to hemorrhage, known as *irreversible* or *late-phase hemorrhagic shock*.[40] There are three shock states that share the basic circulatory pattern of distributive shock: neurogenic shock, anaphylactic shock, and septic shock.

Neurogenic Shock. Neurogenic shock is caused by decreased sympathetic control of blood vessel tone due to a defect in the vasomotor center in the brain stem or the sympathetic outflow to the blood vessels.[3] The term *spinal shock* describes the neurogenic shock that occurs in persons with spinal cord injury (see Chapter 36). Output from the vasomotor center can be interrupted by brain injury, the depressant action of drugs, general anesthesia, hypoxia, or lack of glucose (e.g., insulin reaction). Fainting due to emotional causes is a transient form of impaired sympathetic outflow. Many general anesthetic agents can cause a neurogenic shocklike reaction, especially during induction, because of interference with sympathetic nervous system function. Spinal anesthesia or spinal cord injury above the midthoracic region can interrupt the transmission of outflow from the vasomotor center. In contrast to other shock states due to the loss of blood volume or impaired cardiac function, the heart rate in neurogenic shock often is slower than normal, and the skin is dry and warm. This type of distributive shock is rare and usually transitory.

Anaphylactic Shock. Anaphylaxis is a clinical syndrome that represents the most severe systemic allergic reaction.[41–43] Anaphylactic shock results from an immunologically mediated reaction in which vasodilator substances such as histamine are released into the blood (see Chapter 16). These substances cause vasodilation of arterioles and venules along with a marked increase in capillary permeability. The vascular response in anaphylaxis is often accompanied by life-threatening laryngeal edema and bronchospasm, circulatory collapse, contraction of gastrointestinal and uterine smooth muscle, and urticaria (hives) or angioedema.

Among the most frequent causes of anaphylactic shock are reactions to medications, such as penicillin; foods, such as nuts and shellfish; and insect venoms. The most common cause is stings from insects of the order Hymenoptera (i.e., bees, wasps, and fire ants). Latex allergy causes life-threatening anaphylaxis in a growing segment of the population (see Chapter 16). Health care workers and others who are exposed to latex are developing latex sensitivities that range from mild urticaria, contact dermatitis, and mild respiratory distress to anaphylactic shock.[44] Children with spina bifida also are at extreme risk for this serious and increasingly common allergy.

The onset and severity of anaphylaxis depend on the sensitivity of the person and the rate and quantity of antigen exposure. Signs and symptoms associated with impending anaphylactic shock include abdominal cramps; apprehension; warm or burning sensation of the skin, itching, and urticaria (i.e., hives); and coughing, choking, wheezing, chest tightness, and difficulty in breathing. After blood begins to pool peripherally, there is a precipitous drop in blood pressure and the pulse becomes so weak that it is difficult to detect. Life-threatening airway obstruction may ensue as a result of laryngeal angioedema or bronchial spasm. Anaphylactic shock often develops suddenly; death can occur within minutes unless appropriate medical intervention is promptly instituted.

Treatment includes immediate discontinuation of the inciting agent or institution of measures to decrease its absorption (e.g., application of ice to the site of an insect bite); close monitoring of cardiovascular and respiratory function; and maintenance of respiratory gas exchange, cardiac output, and tissue perfusion. Epinephrine is given in an anaphylactic reaction because it constricts blood vessels and relaxes the smooth muscle in the bronchioles, thus restoring cardiac and respiratory function.[42] Other treatment measures include the administration of oxygen, antihistamine drugs, and corticosteroids. The person should be placed in a supine position, because the sitting position can produce a severe decrease in venous return.[42]

The prevention of anaphylactic shock is preferable to treatment. Once a person has been sensitized to an antigen, the risk of repeated anaphylactic reactions with subsequent exposure is high. All health care providers should question patients regarding previous drug reactions and inform patients as to the name of the medication they are to receive before it is administered or prescribed. Persons with known hypersensitivities should wear Medic Alert jewelry and carry an identification card to alert medical personnel if they become unconscious or unable to relate this information. Persons who are at risk for anaphylaxis should be provided with emergency medications (e.g., epinephrine autoinjector) and instructed in procedures to follow in case they are inadvertently exposed to the offending antigen.[42]

Sepsis and Septic Shock. Septic shock, which is the most common type of vasodilatory shock, is associated with the systemic response to severe infection (Fig. 20-9).[45–48] The nomenclature related to sepsis and septic shock has been evolving. *Sepsis* has been defined as a suspected or proven infection plus the clinical manifestations of what has been termed the *systemic inflammatory response* (e.g., fever, tachycardia, and elevated white blood cell count [leukocytosis]).[45,46] *Severe sepsis* is sepsis plus evidence of sepsis-induced organ dysfunction or tissue hypoxia (e.g., hypotension, hypoxemia, oliguria, metabolic acidosis, thrombocytopenia).[46,47] *Septic shock* is defined as severe sepsis with hypotension, despite fluid resuscitation.[46,47]

Severe sepsis accompanied by acute organ dysfunction is a frequently occurring condition in critically ill patients. The growing incidence has been attributed to enhanced awareness of the diagnosis, increased number of resistant organisms, growing number of immunocompromised and elderly persons, and greater use of invasive procedures. With early intervention and advances in treatment methods, the mortality rate has decreased; however, the number of deaths has increased because of the increased prevalence.

The pathogenesis of sepsis involves a complex process of cellular activation resulting in the release of proinflammatory mediators such as cytokines; recruitment of neutrophils and monocytes; involvement of neuroendocrine reflexes; and activation of complement, coagulation, and fibrinolytic systems.[49] Initiation of the response begins with activation of the innate immune system and release of a number of proinflammatory and anti-inflammatory

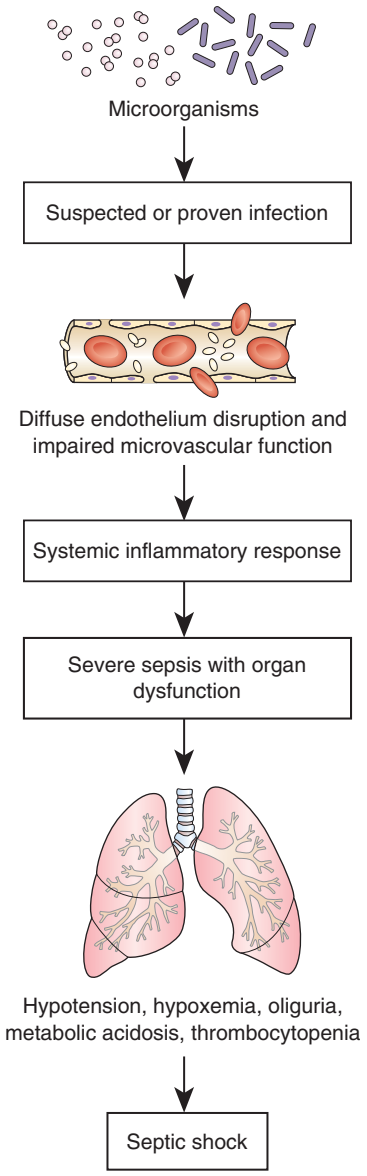


FIGURE 20-10. Pathogenic mechanisms leading from infection to septic shock.

mediators (Chapter 15). Two of these mediators, TNF-α and interleukin-1, are involved in leukocyte adhesion, local inflammation, neutrophil activation, generation of fever, tachycardia, lactic acidosis, ventilation–perfusion abnormalities, and other signs of sepsis. Although activated neutrophils kill microorganisms, they also injure the endothelium by releasing mediators that increase vascular permeability. In addition, activated endothelial cells release nitric oxide, a potent vasodilator that acts as a key mediator of septic shock.

Another important aspect of sepsis is an alteration of the procoagulation–anticoagulation balance with an increase in procoagulation factors and a decrease in anticoagulation factors. Lipopolysaccharide on the surface of microorganisms stimulates endothelial cells lining blood vessels to increase their production of tissue factor, thus activating coagulation[46] (see Chapter 12). Fibrinogen is then converted to fibrin, leading to the formation of microvascular thrombi that further amplify tissue injury. In addition, sepsis lowers levels of protein C, protein S, antithrombin III, and tissue factor pathway inhibitor, substances that modulate and inhibit coagulation.[46]

Manifestations. Sepsis and septic shock are typically manifested by hypotension and warm, flushed skin. Whereas other forms of shock (i.e., cardiogenic, hypovolemic, and obstructive) are characterized by a compensatory increase in systemic vascular resistance, septic shock often presents with a decrease in systemic vascular resistance. There is hypovolemia due to arterial and venous dilatation, plus leakage of plasma into the interstitial spaces. Abrupt changes in cognition or behavior are due to reduced cerebral blood flow and may be early indications of septic shock. Regardless of the underlying cause, fever and increased leukocytes are present. An elevated serum lactate or metabolic acidosis indicates anaerobic metabolism due to tissue hypoxia or cellular dysfunction and altered cellular metabolism.[50] Tissue hypoxia produces continued production and activation of inflammatory mediators, resulting in further increases in vascular permeability, impaired vascular regulation, and altered hemostasis.

Treatment. The treatment of sepsis and septic shock focuses on control of the causative agent and support of the circulation.[45–49] The administration of antibiotics that are specific for the infectious agent is essential. However, antibiotics do not treat the inflammatory response to the infection; thus, the cardiovascular status of the patient must be supported to increase oxygen delivery to the cells and prevent further cellular injury. Swift and aggressive fluid administration is needed to compensate for third spacing. Equally aggressive use of vasopressor agents, such as norepinephrine or dopamine, is needed to counteract the vasodilation caused by inflammatory mediators. Persons with severe sepsis and hyperglycemia should receive intravenous insulin therapy to maintain their blood glucose levels at a target level of less than 150 mg/dL, based on frequent measurement of blood glucose levels.[47] Ongoing assessment of CVP, central or mixed venous oxygen saturation, mean arterial pressure, urinary output, and laboratory measurements of serum lactate, base deficit, and pH are used to evaluate the progression of sepsis and adequacy of treatment.

Among the more recent advances in the treatment of sepsis is the administration of recombinant human activated protein C (rhAPC).[45–48] rhAPC is a naturally occurring anticoagulant factor that acts by inactivating coagulation factors Va and VIII (see Chapter 12).[45–47] In addition to its anticoagulant actions, rhAPC has direct anti-inflammatory properties, including inhibiting the production of cytokines by monocytes and blocking cell adhesion. It also has antiapoptotic actions that may contribute to its effectiveness. rhAPC is not recommended for use in children or adults with risk for bleeding.[47]

Complications of Shock

As the late Carl Wiggers, a noted circulatory physiologist, once stated, "shock not only stops the machine, but it wrecks the machinery."[51] Many body systems are wrecked by severe shock. Five major complications of severe shock are pulmonary injury, acute renal failure, gastrointestinal ulceration, disseminated intravascular coagulation, and multiple organ dysfunction syndrome. These complications of shock are serious and often fatal.

Acute Lung Injury/Acute Respiratory Distress Syndrome

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a potentially lethal form of pulmonary injury that may be either the cause or result of shock (see Chapter 23). ARDS is a more severe aspect of ALI and is differentiated primarily for early intervention, prevention, and research purposes.

ALI/ARDS is marked by the rapid onset of profound dyspnea that usually occurs 12 to 48 hours after the initiating event. The respiratory rate and effort of breathing increase. Arterial blood gas analysis establishes the presence of profound hypoxemia that is refractory to supplemental oxygen. The hypoxemia results from impaired matching of ventilation and perfusion and from the greatly reduced diffusion of blood gases across the thickened alveolar membranes.

The exact cause of ALI/ARDS is unknown. Neutrophils are thought to play a key role in its pathogenesis. A cytokine-mediated activation and accumulation of neutrophils in the pulmonary vasculature and subsequent endothelial injury are thought to cause leaking of fluid and plasma proteins into the interstitium and alveolar spaces.[52] The fluid leakage causes atelectasis, impairs gas exchange, and makes the lung stiff and more difficult to inflate. Abnormalities in the production, composition, and function of surfactant may contribute to alveolar collapse and gas exchange abnormalities. Inappropriate vasodilation and vasoconstriction worsen the ventilation and perfusion mismatch.

Interventions for ALI/ARDS focus on increasing the oxygen concentration in the inspired air and supporting ventilation mechanically to optimize gas exchange while avoiding oxygen toxicity and preventing further lung injury. Despite the delivery of high levels of oxygen using high-pressure mechanical ventilatory support and positive end-expiratory pressure, many persons with ALI/ARDS remain hypoxic, often with a fatal outcome.[53]

Acute Renal Failure

The renal tubules are particularly vulnerable to ischemia, and acute renal failure is an important factor in mortality due to severe shock. Most cases of acute renal failure are due to impaired renal perfusion or direct injury to the kidneys. The degree of renal damage is related to the severity and duration of shock. The normal kidney is able to tolerate severe ischemia for 15 to 20 minutes. The renal dysfunction most frequently seen after severe shock is acute tubular necrosis. Acute tubular necrosis usually is reversible, although return to normal renal function may require weeks or months (see Chapter 25). Continuous monitoring of urinary output during shock provides a means of assessing renal blood flow. Frequent monitoring of serum creatinine and blood urea nitrogen levels also provides valuable information regarding renal status.

Gastrointestinal Complications

The gastrointestinal tract is particularly vulnerable to ischemia because of the changes in distribution of blood flow to its mucosal surface. In shock, there is widespread constriction of blood vessels that supply the gastrointestinal tract, causing a redistribution of blood flow and a severe decrease in mucosal perfusion. Histamine 2–receptor antagonists, proton pump inhibitors, or sucralfate may be given prophylactically to prevent gastrointestinal ulcerations and bleeding caused by shock and severe sepsis.[47]

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is characterized by widespread activation of the coagulation system with resultant formation of fibrin clots and thrombotic occlusion of small and midsized vessels (see Chapter 12). The systemic formation of fibrin results from increased generation of thrombin, the simultaneous suppression of physiologic anticoagulation mechanisms, and the delayed removal of fibrin as a consequence of impaired fibrinolysis. Clinically overt DIC is reported to occur in as many as 30% to 50% of persons with sepsis and septic shock.[54] As with other systemic inflammatory responses, the derangement of coagulation and fibrinolysis is thought to be mediated by inflammatory mediators and cytokines.

The contribution of DIC to morbidity and mortality in sepsis depends on the underlying clinical condition and the intensity of the coagulation disorder. Depletion of the platelets and coagulation factors increases the risk of bleeding. Deposition of fibrin in the vasculature of organs contributes to ischemic damage and organ failure. In a number of clinical trials, the occurrence of DIC appeared to be associated with an unfavorable outcome and was an independent predictor of mortality. However, it remains uncertain whether DIC was a predictor of unfavorable outcome or merely a marker of the seriousness of the underlying condition causing the DIC.

The management of sepsis-induced DIC focuses on treatment of the underlying disorder and measures to interrupt the coagulation process. Anticoagulation therapy and administration of platelets and plasma may be used. Clinical trials have shown modest to marked reductions in mortality based on the dose of antithrombin III used.[54]

Multiple Organ Dysfunction Syndrome

Multiple organ dysfunction syndrome (MODS) represents the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained

without intervention. As the name implies, MODS commonly affects multiple organ systems, including the kidneys, lungs, liver, brain, and heart. MODS is a particularly life-threatening complication of shock, especially septic shock. It has been reported as the most frequent cause of death in the noncoronary intensive care unit. Mortality rates vary from 30% to 100%, depending on the number of organs involved.[55] Mortality rates increase with an increased number of organs failing. A high mortality rate is associated with failure of the brain, liver, kidneys, and lungs. The pathogenesis of MODS is not clearly understood, and current management therefore is primarily supportive. Major risk factors for the development of MODS are severe trauma, sepsis, prolonged periods of hypotension, hepatic dysfunction, infarcted bowel, advanced age, and alcohol abuse. Interventions for multiple organ failure are focused on support of the affected organs.

In summary, circulatory shock is an acute emergency in which body tissues are deprived of oxygen and cellular nutrients or are unable to use these materials in their metabolic processes. Circulatory shock may develop because the heart is unable to adequately pump blood through the circulatory system (cardiogenic shock), there is insufficient blood in the circulatory system (i.e., hypovolemic shock), blood flow or venous return is obstructed (i.e., obstructive shock), or there is a maldistribution of blood due to abnormalities in the vascular resistance (i.e., distributive shock). Three types of shock share the basic circulatory pattern of distributive shock: neurogenic shock, anaphylactic shock, and septic shock. Sepsis and septic shock, which is the most common of the three types, are associated with a severe, overwhelming inflammatory response and has a high mortality rate.

The manifestations of hypovolemic shock, which serves as a prototype for circulatory shock, are related to low peripheral blood flow and excessive sympathetic stimulation. The low peripheral blood flow produces thirst, changes in skin temperature, decreased blood pressure, increased heart rate, decreased venous pressure, decreased urine output, and changes in the sensorium. The intense vasoconstriction that serves to maintain blood flow to the heart and brain causes a decrease in tissue perfusion, impaired cellular metabolism, liberation of lactic acid, and, eventually, cell death. Whether the shock is irreversible or the patient will survive is determined largely by changes that occur at the cellular level.

The complications of shock result from the deprivation of blood flow to vital organs or systems, such as the lungs, kidneys, gastrointestinal tract, and blood coagulation system. Shock can cause or be accompanied by ALI/ARDS, which is characterized by changes in the permeability of the alveolar–capillary membrane with development of interstitial edema and severe hypoxemia that does not respond to oxygen therapy. The renal tubules are particularly vulnerable to ischemia, and acute renal failure is an important complication of shock. Gastrointestinal ischemia may lead to gastrointestinal bleeding and increased vascular permeability to intestinal bacteria, which can cause further sepsis and shock. DIC is characterized by formation of small clots in the circulation. It is thought to be caused by inappropriate activation of the coagulation cascade because of toxins or other products released as a result of the shock state. The multiple organ failure of MODS, perhaps the most ominous complication of shock, rapidly depletes the body's ability to compensate and recover from a shock state.

Heart Failure in Children and the Elderly

Heart Failure in Infants and Children

As in adults, heart failure in infants and children results from the inability of the heart to maintain the cardiac output required to sustain metabolic demands.[56–58] The etiology of heart failure, however, is very different between children and adults. Structural (congenital) heart defects are the most common cause of heart failure in children. Surgical correction of congenital heart defects may cause heart failure as a result of intraoperative manipulation of the heart and resection of heart tissue, with subsequent alterations in pressure, flow, and resistance relations. Usually, the heart failure that results is acute and resolves after the effects of the surgical procedure have subsided. Another cause of heart failure in children is cardiomyopathy related to a genetic or inherited disorder, infectious disease, drugs, toxins, and Kawasaki disease.[57] Chart 20-2 lists some of the more common causes of heart failure in children. Inflammatory heart disorders (e.g., myocarditis, rheumatic fever, bacterial endocarditis, Kawasaki disease), cardiomyopathy, and congenital heart disorders are discussed in Chapter 19.

Manifestations

Many of the signs and symptoms of heart failure in infants and children are similar to those in adults. In children, overt symptoms of heart failure occur late in the disease process. Breathlessness, tachypnea, and tachycardia are the most common symptoms.[56] Other symptoms include fatigue, effort intolerance, cough, anorexia, and abdominal pain. A subtle sign of cardiorespiratory distress in infants and children is a change in disposition or responsiveness, including irritability or lethargy. Sympathetic stimulation produces peripheral vasoconstriction and diaphoresis. Decreased renal blood flow often results in a decrease in urine output despite adequate fluid intake.

When right ventricular function is impaired, systemic venous congestion develops. Hepatomegaly due to liver congestion often is one of the first signs of systemic venous congestion in infants and children. However,

CHART 20-2 Causes of Heart Failure in Children

Newborn Period

- Congenital heart defects
  - Severe left ventricular outflow disorders
    - Hypoplastic left heart
    - Critical aortic stenosis or coarctation of the aorta
  - Large arteriovenous shunts
    - Ventricular septal defects
    - Patent ductus arteriosus
  - Transposition of the great vessels
- Heart muscle dysfunction (secondary)
  - Asphyxia
  - Sepsis
  - Hypoglycemia
- Hematologic disorders (e.g., anemia)

Infants 1 to 6 Months

- Congenital heart disease
  - Large arteriovenous shunts (ventricular septal defect)
- Heart muscle dysfunction
  - Myocarditis
  - Cardiomyopathy
- Pulmonary abnormalities
  - Bronchopulmonary dysplasia
  - Persistent pulmonary hypertension

Toddlers, Children, and Adolescents

- Acquired heart disease
  - Cardiomyopathy
  - Viral myocarditis
  - Rheumatic fever
  - Endocarditis
  - Systemic disease
    - Sepsis
    - Kawasaki disease
    - Kidney disease
    - Sickle cell disease
- Congenital heart defects
  - Nonsurgically treated disorders
  - Surgically treated disorders

dependent edema or ascites rarely is seen unless the CVP is extremely high. Because of their short, fat necks, jugular venous distention is difficult to detect in infants; it is not a reliable sign until the child is of school age or older. A third heart sound, or gallop rhythm, is a common finding in infants and children with heart failure. It results from rapid filling of a noncompliant ventricle. However, it is difficult to distinguish at high heart rates.

Most commonly, children develop interstitial pulmonary edema rather than alveolar pulmonary edema. This reduces lung compliance and increases the work of breathing, causing tachypnea and increased respiratory effort. Older children display use of accessory muscles (i.e., scapular and sternocleidomastoid). Head bobbing and nasal flaring may be observed in infants. Signs of respiratory distress often are the first and most noticeable indication of heart failure in infants and young children. Pulmonary congestion may be mistaken for bronchiolitis or lower respiratory tract infection. The infant or young child with respiratory distress often grunts with expiration. This grunting effort (essentially, exhaling against a closed glottis) is an instinctive effort to increase end-expiratory pressures and prevent collapse of small airways and the development of atelectasis. Respiratory crackles are uncommon in infants and usually suggest development of a respiratory tract infection. Wheezes may be heard, particularly if there is a large left-to-right shunt.

Infants with heart failure often show increased tachypnea, fatigue, and diaphoresis during feeding.[56] Weight gain is slow owing to high energy requirements and low calorie intake. Diaphoresis occurs (because of increased sympathetic tone) particularly over the head and neck. There may be repeated lower respiratory tract infections. Peripheral perfusion usually is poor, with cool extremities; tachycardia is common (resting heart rate >150 beats/minute); and the respiratory rate is increased (resting rate >50 breaths/minute).[56]

Diagnosis and Treatment

Diagnosis of heart failure in infants and children is based on symptomatology, chest radiographic films, electrocardiographic findings, echocardiographic techniques to assess cardiac structures and ventricular function (i.e., end-systolic and end-diastolic diameters), arterial blood gases to determine intracardiac shunting and ventilation–perfusion inequalities, and other laboratory studies to determine anemia and electrolyte imbalances.

Treatment of heart failure in infants and children includes measures aimed at improving cardiac function and eliminating excess intravascular fluid. Oxygen delivery must be supported and oxygen demands controlled or minimized. Whenever possible, the cause of the disorder is corrected (e.g., medical treatment of sepsis and anemia, surgical correction of congenital heart defects). With congenital anomalies that are amenable to surgery, medical treatment often is needed for a time before surgery and usually is continued in the immediate postoperative period. For some children, only medical management can be provided.

Medical management of heart failure in infants and children is similar to that in the adult, although it is tailored to the special developmental needs of the child. Inotropic agents such as digitalis often are used to increase cardiac contractility. Diuretics may be given to reduce preload and vasodilating medications used to manipulate the afterload. Medication doses must be carefully tailored to control for the child's weight and conditions such as reduced renal function. Daily weighing and accurate measurement of intake and output are imperative during acute episodes of failure. Most children feel better in the semiupright position. An infant seat is useful for infants with chronic heart failure. Activity restrictions usually are designed to allow children to be as active as possible within the limitations of their heart disease. Infants with heart failure often have problems feeding. Small, frequent feedings usually are more successful

than larger, less frequent feedings. Severely ill infants may lack sufficient strength to suck and may need to be tube fed.

The treatment of heart failure in children should be designed to allow optimal physical and psychosocial development. It requires the full involvement of the parents, who often are the primary care providers; therefore, parent education and support are essential.

Heart Failure in the Elderly

Heart failure is one of the most common causes of disability in the elderly and is the most frequent hospital discharge diagnosis for the elderly. Among the factors that have contributed to the increased numbers of older people with heart failure are the improved therapies for ischemic and hypertensive heart disease.[59] Thus, persons who would have died from acute myocardial disease 20 years ago are now surviving, but with residual heart damage. Advances in treatment of other diseases have also contributed indirectly to the rising prevalence of heart failure in the older population. In contrast to the etiology in middle-aged persons with heart failure, factors other than systolic failure contribute to heart failure in the elderly. Preserved left ventricular function may be seen in 40% to 80% of older persons with heart failure.[59]

There are a number of changes associated with aging that contribute to the development of heart failure in the elderly.[59–61] First, reduced responsiveness to β-adrenergic stimulation limits the heart's capacity to maximally increase heart rate and contractility during an increase in activity or stress. A second major effect of aging is increased vascular stiffness, which leads to a progressive increase in systolic blood pressure with advancing age, which in turn contributes to the development of left ventricular hypertrophy and altered diastolic filling. Third, in addition to increased vascular stiffness, the heart itself becomes stiffer and less compliant with age. The changes in diastolic stiffness result in important alterations in diastolic filling and atrial function. A reduction in ventricular filling not only affects cardiac output, but also produces an elevation in diastolic pressure that is transmitted back to the left atrium, where it stretches the muscle wall and predisposes to atrial ectopic beats and atrial fibrillation. The fourth major effect of cardiovascular aging is altered myocardial metabolism at the level of the mitochondria. Although older mitochondria may be able to generate sufficient ATP to meet the normal energy needs of the heart, they may be less able to respond under stress.

Manifestations

The manifestations of heart failure in the elderly often are masked by other disease conditions.[1,2] Nocturia or nocturnal incontinence is an early symptom but may be caused by other conditions such as prostatic hypertrophy. Lower extremity edema may reflect venous insufficiency. Impaired perfusion of the gastrointestinal tract is a common cause of anorexia and profound loss of lean body mass. Loss of lean body mass may be masked by edema. Exertional dyspnea, orthopnea, and impaired exercise tolerance are cardinal symptoms of heart failure in both younger and older persons with heart failure. However, with increasing age, which is often accompanied by a more sedentary lifestyle, exertional dyspnea becomes less prominent. Instead of dyspnea, the prominent sign may be restlessness.

Physical signs of heart failure, such as elevated jugular venous pressure, hepatic congestion, and pulmonary crackles, occur less commonly in the elderly, in part because of the increased incidence of diastolic failure, in which signs of right-sided heart failure are late manifestations and a third heart sound is typically absent.[60] Instead, behavioral changes and altered cognition such as short-term memory loss and impaired problem solving are more common. With exacerbation of heart failure, the elderly often present with acute delirium and dementia. Depression is common in the elderly with heart failure and shares the symptoms of sleep disturbances, cognitive changes, and fatigue.

The elderly also maintain a precarious balance between the managed symptom state and acute symptom exacerbation. During the managed symptom state, they are relatively symptom free while adhering to their treatment regimen. Acute symptom exacerbation, often requiring emergency medical treatment, can be precipitated by seemingly minor conditions such as poor adherence to sodium restriction, infection, or stress. Failure to promptly seek medical care is a common cause of progressive acceleration of symptoms.

Diagnosis and Treatment

The diagnosis of heart failure in the elderly is based on the history, physical examination, chest radiograph, and electrocardiographic findings.[62] However, the presenting symptoms of heart failure often are difficult to evaluate. Symptoms of dyspnea on exertion are often interpreted as a sign of "getting older" or attributed to deconditioning from other diseases. Ankle edema is not unusual in the elderly because of decreased skin turgor and the tendency of the elderly to be more sedentary with the legs in a dependent position.

Treatment of heart failure in the elderly involves many of the same methods as in younger persons, with medication dose adaptations to reduce age-related adverse and toxic events. ACE inhibitors may be particularly beneficial to preserve cognitive and functional capacities. Activities are restricted to a level that is commensurate with the cardiac reserve. Seldom is bed rest recommended or advised. Bed rest causes rapid deconditioning of skeletal muscles and increases the risk of complications such as orthostatic hypotension and thromboemboli. Instead, carefully prescribed exercise programs can help to maintain activity tolerance. Even walking around a room usually is preferable to continuous bed rest.

In summary, the mechanisms of heart failure in children and the elderly are similar to those in adults. However, the causes and manifestations may differ because of age. In

children, heart failure is seen most commonly during infancy and immediately after heart surgery. It can be caused by congenital and acquired heart defects and is characterized by fatigue, effort intolerance, cough, anorexia, abdominal pain, and impaired growth. Treatment of heart failure in children includes correction of the underlying cause whenever possible. For congenital anomalies that are amenable to surgery, medical treatment often is needed for a time before surgery and usually is continued in the immediate postoperative period. For many children, only medical management can be provided.

In the elderly, age-related changes in cardiovascular functioning contribute to heart failure but are not in themselves sufficient to cause heart failure. The manifestations of heart failure often are different and superimposed on other disease conditions; therefore, heart failure often is more difficult to diagnose in the elderly than in younger persons. Because the elderly are more susceptible to adverse and toxic medication reactions, medication doses need to be adapted and more closely monitored.

REVIEW EXERCISES

1. A 75-year-old woman with long-standing hypertension and angina due to coronary heart disease presents with ankle edema, nocturia, increased shortness of breath with activity, and a chronic nonproductive cough. Her blood pressure is 170/80 and her heart rate 92. Electrocardiography and chest radiography indicate the presence of left ventricular hypertrophy.

A. Relate the presence of uncontrolled hypertension and coronary artery disease to the development of heart failure in this woman.
B. Explain the significance of left ventricular hypertrophy in terms of both a compensatory mechanism and a pathologic mechanism in the progression of heart failure.
C. Use Figure 20-2 to explain this woman's symptoms, including shortness of breath and nonproductive cough.

2. A 26-year-old man is admitted to the emergency department after an automobile injury with excessive blood loss. He is alert and anxious, his skin is cool and moist, his heart rate is 135, and his blood pressure is 100/85. He is receiving intravenous fluids, which were started at the scene of the accident by an emergency medical technician. He has been typed and cross-matched for blood transfusions and a urinary catheter has been inserted to monitor his urinary output. His urinary output has been less than 10 mL since admission and his blood pressure has dropped to 85/70. Efforts to control his bleeding have been unsuccessful and he is being prepared for emergency surgery.

A. Use information regarding the compensatory mechanisms in circulatory shock to explain this man's presenting symptoms, including urinary output.
B. Use Figure 20-9 to hypothesize about this man's blood loss and maintenance of blood pressure.
C. The treatment of hypovolemic shock is usually directed at maintaining the circulatory volume through fluid resuscitation rather than maintaining the blood pressure through the use of vasoactive medications. Explain.

REFERENCES

1. Hunt S.A., Abraham W.T., Chin M.H., et al. (2009). Focused update incorporation into ACC/AHA 2005 guidelines for diagnosis and management of chronic heart failure in the adult. *Circulation* 119, e119–e479.
2. Arnold J.M.O., Liu P., Demers C., et al. (2006). Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Canadian Journal of Cardiology* 22, 23–45.
3. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 103–115, 264, 278–288). Philadelphia: Elsevier Saunders.
4. Klabunde R.E. (2005). *Cardiovascular physiology concepts*. Philadelphia: Lippincott Williams & Wilkins.
5. Opie L.H. (2005). Mechanisms of cardiac contraction and relaxation. In Zipes D.P., Libbey P., Bonow R.O., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (7th ed., pp. 457–489). Philadelphia: Elsevier Saunders.
6. Carroll J.D., Hess O.M. (2005). Assessment of normal and abnormal cardiac function. In Zipes D.P., Libbey P., Bonow R.O., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (7th ed., pp. 491–507). Philadelphia: Elsevier Saunders.
7. Wu E.B., Yu C.M. (2005). Management of diastolic heart failure: A practical review of pathophysiology and treatment trial data. *International Journal of Clinical Practice* 59, 1239–1246.
8. Fletcher L., Thomas D. (2001). Congestive heart failure: Understanding the pathophysiology and management. *Journal of the American Academy of Nurse Practitioners* 13, 249–257.
9. Givertz M.M., Colucci W.S., Braunwald E. (2005). Clinical aspects of heart failure: Pulmonary edema, high-output failure. In Zipes D.P., Libbey P., Bonow R.O., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (7th ed., pp. 539–568). Philadelphia: Elsevier Saunders.
10. Aurigemma G.P., Gaasch W.H. (2004). Diastolic heart failure. *New England Journal of Medicine* 351, 1095–1105.
11. Haney S., Sur D., Xu Z. (2005). Diastolic heart failure: A review and primary care perspective. *Journal of the American Board of Family Practice* 18, 189–195.
12. Colucci W.C. (2005). Pathophysiology of heart failure. In Zipes D.P., Libbey P., Bonow R.O., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (7th ed., pp. 509–568). Philadelphia: Elsevier Saunders.
13. Budev M.M., Arroliga A.C., Wiedemann H.P., et al. (2003). Cor pulmonale: An overview. *Seminars in Respiratory Critical Care Medicine* 23, 233–243.
14. Francis G.S., Tang W.H.W. (2003). Pathophysiology of congestive heart failure. *Reviews in Cardiovascular Medicine* 4(Suppl 2), S14–S20.
15. Adams K.F. (2004). Pathophysiologic role of the renin-angiotensin-aldosterone and sympathetic nervous system in HF. *American Journal of Health-System Pharmacy* 61(Suppl 2), S4–S13.

16. Weber K.T. (2001). Aldosterone in congestive heart failure. *New England Journal of Medicine* 345, 1689–1697.
17. Struthers A.D. (2005). Pathophysiology of heart failure following myocardial infarction. *Heart* 91, 14–16.
18. Levin E.R., Gardner D.G., Samson W.K. (1998). Natriuretic peptides. *New England Journal of Medicine* 339, 321–328.
19. Nathisuwan S., Talbert R.L. (2002). A review of vasopeptidase inhibitors: A new modality in the treatment of hypertension and chronic heart failure. *Pharmacotherapy* 22, 27–42.
20. Spieker L.E., Lüscher T.F. (2003). Will endothelin receptor antagonists have a role in heart failure? *Medical Clinics of North America* 87, 459–474.
21. Ergul A. (2002). Endothelin-1 and endothelin receptor antagonists as potential cardiovascular therapeutic agents. *Pharmacotherapy* 22, 54–65.
22. Hunter J.J., Chien K.R. (1999). Signaling pathways for cardiac hypertrophy and failure. *New England Journal of Medicine* 341, 1276–1284.
23. Brack T. (2003). Cheyne-Stokes respiration in patients with congestive heart failure. *Swiss Medical Weekly* 133, 605–610.
24. Crijns H.J., Tjeerdsma G., De Kam P.J., et al. (2000). Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic HF. *European Heart Journal* 21, 1238–1245.
25. Gheorghiade M., Zannad F., Sopko G., et al. (2005). Acute heart failure syndrome: Current state and framework for future research. *Circulation* 112, 3958–3968.
26. Mebaxaa A., Gheorghliade M., Piña I.L. (2008). Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Critical Care Medicine* 36(1 Suppl), S129–S139.
27. Chen H.H., Schrier R.W. (2006). Pathophysiology of volume overload in acute heart failure syndromes. *American Journal of Medicine* 119(12A), S11–S26.
28. Kale P., Fang J.C. (2008). Devices in acute heart failure. *Critical Care Medicine* 36(1 Suppl), S121–S128.
29. Bridges E.J. (2005). Hemodynamic monitoring. In Woods S.L., Froelicher E.S.S., Motzer S.U., et al. (Eds.), *Cardiac nursing* (5th ed., pp. 478–526). Philadelphia: Lippincott Williams & Wilkins.
30. Katzung B.G., Parmley W.W. (2007). Drugs used in heart failure. In Katzung B.G. (Ed.), *Basic and clinical pharmacology* (10th ed., pp. 198–210). New York: McGraw-Hill Medical.
31. Albert N.M. (2003). Cardiac resynchronization therapy through biventricular pacing in patients with HF and ventricular dyssynchrony. *Critical Care Nurse* 23(June Suppl), 2–13.
32. Wheeldon D.R. (2003). Mechanical circulatory support: State of the art and future perspectives. *Perfusion* 8, 233–243.
33. Patel N.D., Barreiro C.J., Williams J.A., et al. (2005). Surgical ventricular remodeling for patients with clinically advanced congestive HF and severe left ventricular dysfunction. *Journal of Heart and Lung Transplantation* 24, 2202–2210.
34. Holmes C.L., Walley K.R. (2003). The evaluation and management of shock. *Clinical Chest Medicine* 24, 775–789.
35. Aymong E.D., Ramanathan K., Buller C.E. (2007). Pathophysiology of cardiogenic shock complicating acute myocardial infarction. *Medical Clinics of North America* 91, 701–712.
36. Topalian S., Ginsberg F., Parrillo J.E. (2008). Cardiogenic shock. *Critical Care Medicine* 36(1), S66–S74.
37. Antman E.M. (2005). ST-elevation myocardial infarction: Management. In Zipes D.P., Libbey P., Bonow R.O., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (7th ed., pp. 1200–1201). Philadelphia: Elsevier Saunders.
38. Kelley D.M. (2005). Hypovolemic shock. *Critical Care Nursing Quarterly* 28(1), 2–19.
39. Dutton R.P. (2007). Current concepts in hemorrhagic shock. *Anesthesiology Clinics* 25, 23–34.
40. Landry D.W., Oliver J.A. (2001). The pathogenesis of vasodilatory shock. *New England Journal of Medicine* 345, 588–595.
41. Lieberman P. (2006). Anaphylaxis. *Medical Clinics of North America* 90, 77–95.
42. Brown S.G.A. (2007). The pathophysiology of shock in anaphylaxis. *Immunology and Allergy Clinics of North America* 27, 165–175.
43. Ellis A.K., Day J.H. (2003). Diagnosis and management of anaphylaxis. *Canadian Medical Association Journal* 169, 307–312.
44. Stankiewicz J., Rua W., Gorski P. (1995). Latex allergy. *International Journal of Occupational Medicine and Environmental Health* 8, 139–312.
45. Nguyen H.B., Rivers E.P., Abrahamian F.M. (2006). Severe sepsis and septic shock: Review of the literature and emergency department management guidelines. *Annals of Emergency Medicine* 48, 28–54.
46. Russell J.A. (2006). Management of sepsis. *New England Journal of Medicine* 355, 1699–1711.
47. Dellinger R.P., Levy M.M., Cariet J.M., et al. (2008). Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine* 36(1), 296–327.
48. Gullo A., Bianco N., Berlot G. (2006). Management of severe sepsis and septic shock: Challenges and recommendations. *Critical Care Clinics* 22, 489–501.
49. Djillali A., Bellissant E., Cavaillon J-M. (2005). Septic shock. *Lancet* 365, 63–78.
50. Vincent J.L., Taccone F., Schmit X. (2007). Classification, incidence, and outcomes of sepsis and multiple organ failure. *Contributions to Nephrology* 156, 64–74.
51. Smith J.J., Kampine J.P. (1980). *Circulatory physiology* (p. 298). Baltimore: Williams & Wilkins.
52. Abraham E. (2003). Neutrophils and acute lung injury. *Critical Care Medicine* 31, S195–S199.
53. Rubenfeld, G.D., Herridge M.S. (2007). Epidemiology and outcomes of acute lung injury. *Chest* 131, 554–562.
54. Levi M., Ten Cate H.T. (1999). Disseminated intravascular coagulation. *New England Journal of Medicine* 341, 586–592.
55. Balk R.A. (2000). Pathogenesis and management of multiple organ dysfunction or failure in acute sepsis and septic shock. *Critical Care Clinics* 16, 337–352.
56. Bernstein D. (2007). Heart failure. In Behrman R.E., Kliegman R.M., Nelson W., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1582–1587). Philadelphia: Saunders Elsevier.
57. Kay J.D., Colan S.D., Graham T.P. (2001). Congestive heart failure in pediatric patients. *American Heart Journal* 142, 923–928.
58. O'Laughlin M.P. (1999). Congestive heart failure in children. *Pediatric Clinics of North America* 46, 263–273.
59. Thomas S., Rich M.W. (2007). Epidemiology, pathophysiology, and prognosis of heart failure in the elderly. *Clinics in Geriatric Medicine* 23, 1–10.
60. Rich M.W. (2006). Heart failure in older adults. *Medical Clinics of North America* 90, 863–885.
61. Schwartz J.B., Zipes D.P. (2005). Cardiovascular disease in the elderly. In Zipes D.P., Libbey P., Bonow R.O., et al. (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (7th ed., pp. 1925–1949). Philadelphia: Elsevier Saunders.
62. Abdelhafiz A.H. (2002). Heart failure in older people: Causes, diagnosis, and treatment. *Age and Aging* 31, 29–36.

UNIT 6

Respiratory Function

Structural Organization of the Respiratory System
- *Conducting Airways*
  - Nasopharyngeal Airways
  - Laryngotracheal Airways
  - Tracheobronchial Tree
- *Lungs and Respiratory Airways*
  - Alveolar Structures
  - Pulmonary and Bronchial Circulations
  - Innervation
- *Pleura*

Exchange of Gases Between the Atmosphere and the Lungs
- *Basic Properties of Gases*
- *Ventilation and the Mechanics of Breathing*
  - Respiratory Pressures
  - The Chest Cage and Respiratory Muscles
  - Lung Compliance
  - Airflow During Breathing
- *Lung Volumes*
- *Pulmonary Function Studies*
- *Efficiency and Work of Breathing*

Exchange and Transport of Gases
- *Ventilation*
  - Distribution of Ventilation
  - Dead Air Space
- *Perfusion*
  - Distribution of Blood Flow
  - Hypoxia-Induced Vasoconstriction
  - Shunt
- *Mismatching of Ventilation and Perfusion*
- *Diffusion*
- *Oxygen and Carbon Dioxide Transport*
  - Oxygen Transport
  - Carbon Dioxide Transport

Control of Breathing
- *Respiratory Center*
- *Regulation of Breathing*
  - Chemoreceptors
  - Lung Receptors
- *Cough Reflex*
- *Dyspnea*

Chapter 21

Control of Respiratory Function

The primary function of the respiratory system is gas exchange, with oxygen from the air being transferred to the blood and carbon dioxide from the blood being eliminated into the atmosphere. In addition to gas exchange, the lungs serve as a host defense by providing a barrier between the external environment and the inside of the body. And finally, the lungs are metabolic organs that synthesize and metabolize different substances. The content in this chapter focuses on the structure and function of the respiratory system as it relates to the exchange of gases. The function of the red blood cell in the transport of oxygen is discussed in Chapter 13.

Structural Organization of the Respiratory System

The respiratory system consists of the air passages, the two lungs and the blood vessels that supply them, and the structures that provide a ventilator mechanism, that is, the rib cage, respiratory muscles, and diaphragm. Functionally, the respiratory system can be divided into two parts: the *conducting airways*, through which air moves as it passes between the atmosphere and the lungs, and the *respiratory tissues* of the lungs, where gas exchange takes place.

The lungs are soft, spongy, cone-shaped organs located side by side in the chest cavity (Fig. 21-1). They are separated from each other by the *mediastinum* (i.e., the space between the lungs) and its contents—the heart,

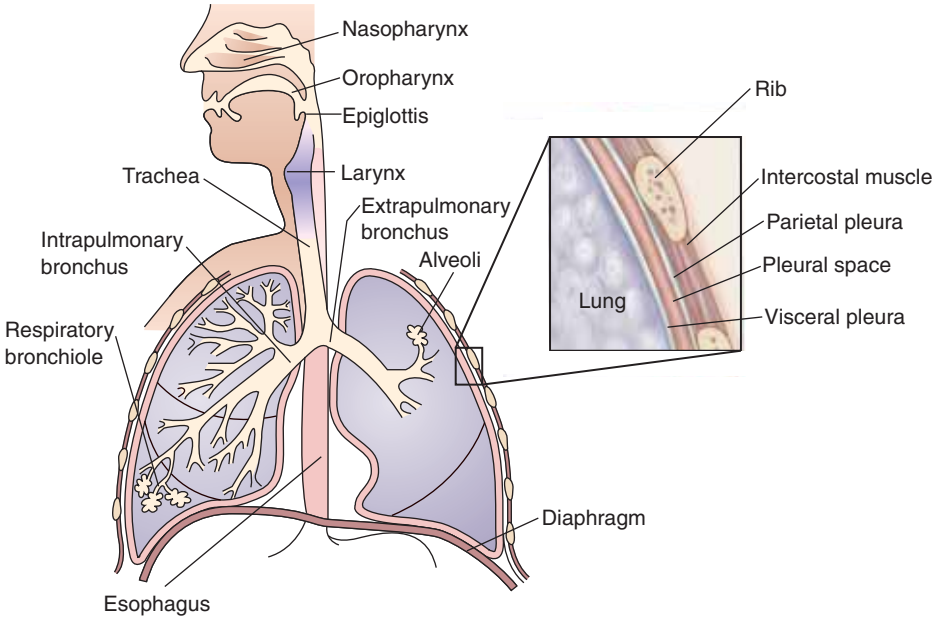


FIGURE 21-1. Structures of the respiratory system. The structures of the pleura are shown in the *inset*.

blood vessels, lymph nodes, nerve fibers, thymus gland, and esophagus. The upper part of the lung, which lies against the top of the thoracic cavity, is called the *apex*, and the lower part, which lies against the diaphragm, is called the *base*. The lungs are divided into lobes: three in the right lung and two in the left.

Conducting Airways

The conducting airways consist of the nasal passages, mouth and pharynx, larynx, trachea, bronchi, and bronchioles (Fig. 21-1). The air we breathe is warmed, filtered, and moistened as it moves through these structures. Heat is transferred to the air from the blood flowing through the walls of the respiratory passages; the mucociliary blanket removes foreign materials; and water from the mucous membranes is used to moisten the air.

The wall of conducting airways consists of three major components: a mucosal lining composed of epithelial and connective tissue, an underlying smooth muscle layer, and a supporting connective tissue layer (Fig. 21-2). Most of the conducting airways are lined with a ciliated pseudostratified columnar epithelium, containing a mosaic of mucus-secreting glands, ciliated cells with hairlike projections, and serous glands that secrete a watery fluid containing antibacterial enzymes. In addition, some less common cell types are interspersed in different parts of the airways. The epithelial layer gradually becomes thinner as it moves from the pseudostratified epithelium of the bronchi to cuboidal epithelium of the bronchioles and then to squamous epithelium of the alveoli.

The mucus produced by the epithelial cells in the conducting airways forms a layer called the *mucociliary blanket* that protects the respiratory system by entrapping dust, bacteria, and other foreign particles that enter the airways. The cilia, which constantly are in motion, move the mucociliary blanket with its entrapped particles in an escalator-like fashion toward the oropharynx, from which it is expectorated or swallowed. The function of cilia in clearing the lower airways and alveoli is optimal at normal oxygen levels and is impaired in situations of low and high oxygen levels. It is also impaired by drying conditions, such as breathing heated but unhumidified indoor air during the winter months. Cigarette smoking slows down or paralyzes the motility of the cilia. This slowing allows the residue from tobacco smoke, dust, and other particles to accumulate in the lungs, decreasing the efficiency of this pulmonary defense system. As discussed in Chapter 23, these changes are thought to contribute to the development of chronic bronchitis and emphysema.

The air in the conducting airways is kept moist by water contained in the mucous layer of the upper airways

Conducting and Respiratory Airways

- Respiration requires ventilation, or movement of gases into and out of the lungs; perfusion, or movement of blood through the lungs; and diffusion of gases between the lungs and the blood.
- Ventilation depends on the conducting airways, including the nasopharynx and oropharynx, larynx, and tracheobronchial tree, which move air into and out of the lungs but do not participate in gas exchange.
- Gas exchange takes place in the respiratory airways of the lungs, where gases diffuse across the alveolar-capillary membrane as they are exchanged between the air in the lungs and the blood that flows through the pulmonary capillaries.

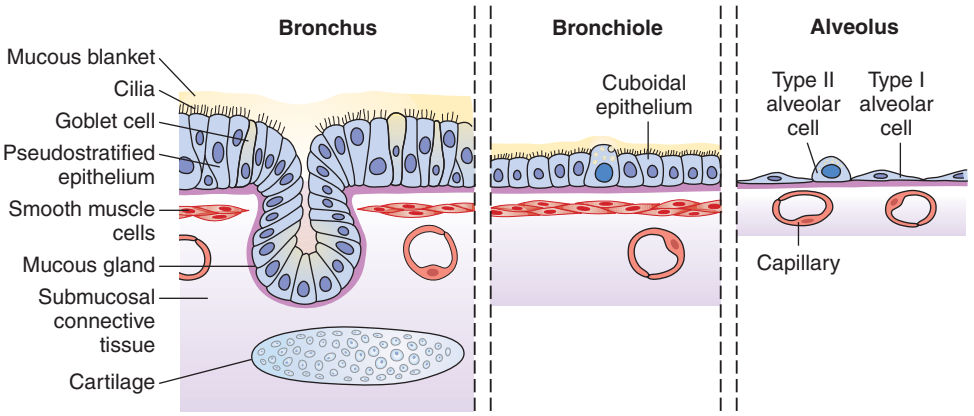


FIGURE 21-2. Airway wall structure: bronchus, bronchiole, and alveolus. The bronchial wall contains pseudostratified epithelium, smooth muscle cells, mucous glands, connective tissue, and cartilage. In smaller bronchioles, a simple epithelium is found, cartilage is absent, and the wall is thinner. The alveolar wall is designed for gas exchange, rather than structural support.

and tracheobronchial tree. The capacity of the air to contain water vapor without condensation increases as the temperature rises. Thus, the air in the alveoli, which is maintained at body temperature, usually contains considerably more water vapor than the atmospheric-temperature air that we breathe. The difference between the water vapor contained in the air we breathe and that found in the alveoli is drawn from the moist surface of the mucous membranes that line the conducting airways and is a source of insensible water loss (see Chapter 8). Under normal conditions, approximately 1 pint of water is used each day to humidify the air we breathe. During fever, the water vapor in the lungs increases, causing more water to be lost through the respiratory tract. In addition, fever usually is accompanied by an increase in respiratory rate so that more air passes through the airways, withdrawing moisture from its mucosal surface. As a result, respiratory secretions thicken, preventing free movement of the cilia and impairing the protective function of the mucociliary defense system. This is particularly true in persons whose water intake is inadequate.

Nasopharyngeal Airways

The nose is the preferred route for the entrance of air into the respiratory tract during normal breathing. As air passes through the nasal passages, it is filtered, warmed, and humidified. The outer nasal passages are lined with coarse hairs, which filter and trap dust and other large particles from the air. The upper portion of the nasal cavity is lined with a mucous membrane that contains a rich network of small blood vessels; this portion of the nasal cavity supplies warmth and moisture to the air we breathe.

The mouth serves as an alternative airway when the nasal passages are plugged or when there is a need for the exchange of large amounts of air, as occurs during exercise. The oropharynx extends posteriorly from the soft palate to the epiglottis. The oropharynx is the only opening between the nose and mouth and the lungs. Both swallowed food on its way to the esophagus and air on its way to the larynx pass through it. Obstruction of the oropharynx leads to immediate cessation of ventilation. Neural control of the tongue and pharyngeal muscles may be impaired in coma and certain types of neurologic disease. In these conditions, the tongue falls back into the pharynx and obstructs the airway, particularly if the person is lying on his or her back. Swelling of the pharyngeal structures caused by injury, infection, or severe allergic reaction also predisposes a person to airway obstruction, as does the presence of a foreign body.

Laryngotracheal Airways

The larynx connects the oropharynx with the trachea. The walls of the larynx are supported by rigid cartilaginous structures that prevent collapse during inspiration. The functions of the larynx can be divided into two categories: those associated with speech and those associated with protecting the lungs from substances other than air. The larynx is located in a strategic position between the upper airways and the lungs and sometimes is referred to as the "watchdog of the lungs."

The cavity of the larynx is divided into two pairs of two-by-two folds of mucous membrane stretching from front to back with an opening in the midline (Fig. 21-3).

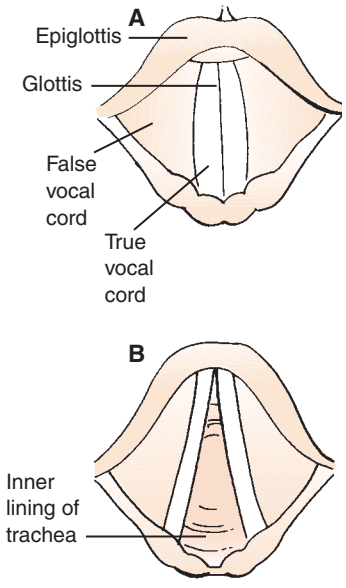


FIGURE 21-3. Epiglottis and vocal cords viewed from above with **(A)** glottis closed and **(B)** glottis open.

The upper pair of folds, called the *vestibular folds*, has a protective function. The lower pair of folds has cord-like margins; they are termed the *vocal folds* because their vibrations are required for making vocal sounds. The true vocal folds and the elongated opening between them is called the *glottis*. A complex set of muscles controls the opening and closing of the glottis. Speech involves the intermittent release of expired air and opening and closing of the glottis. The epiglottis, which is located above the vocal folds, is a large, leaf-shaped piece of cartilage that is covered with epithelium. During swallowing, the free edges of the epiglottis move downward to cover the larynx, thus routing liquids and foods into the esophagus.

In addition to opening and closing the glottis for speech, the vocal folds of the larynx can perform a sphincter function in closing off the airways. When confronted with substances other than air, the laryngeal muscles contract and close off the airway. At the same time, the cough reflex is initiated as a means of removing a foreign substance from the airway. If the swallowing mechanism is partially or totally paralyzed, food and fluids can enter the airways instead of the esophagus when a person attempts to swallow. These substances are not easily removed, and when they are pulled into the lungs, they can cause a serious inflammatory condition called *aspiration pneumonia*.

Tracheobronchial Tree

The tracheobronchial tree, which consists of the trachea, bronchi, and bronchioles, can be viewed as a system of branching tubes (Fig. 21-4A). It is similar to a tree whose branches become smaller and more numerous as they divide. There are approximately 23 levels of branching, beginning with the conducting airways and ending with the respiratory airways, where gas exchange takes place (Fig. 21-4B). The walls of the tracheobronchial tree are composed of several layers: an inner mucosal layer, a submucosal layer, and an outer adventitial layer. These layers vary at different levels of the tracheobronchial tree.

The trachea, or windpipe, is a continuous tube that connects the larynx and the major bronchi of the lungs. The walls of the trachea are supported by horseshoe- or C-shaped rings of hyaline cartilage, which prevent it from collapsing when the pressure in the thorax becomes negative (Fig. 21-5). The open part of the C-shaped ring, which abuts the esophagus, is connected by smooth muscle. Since this portion of the trachea is not rigid, the esophagus can expand anteriorly as swallowed food passes through it.

The trachea divides into two branches, forming the right and left main or primary bronchi (Fig. 21-6A). Between the main bronchi is a keel-like ridge called the *carina* (Fig. 21-6B). The mucosa of the carina is highly

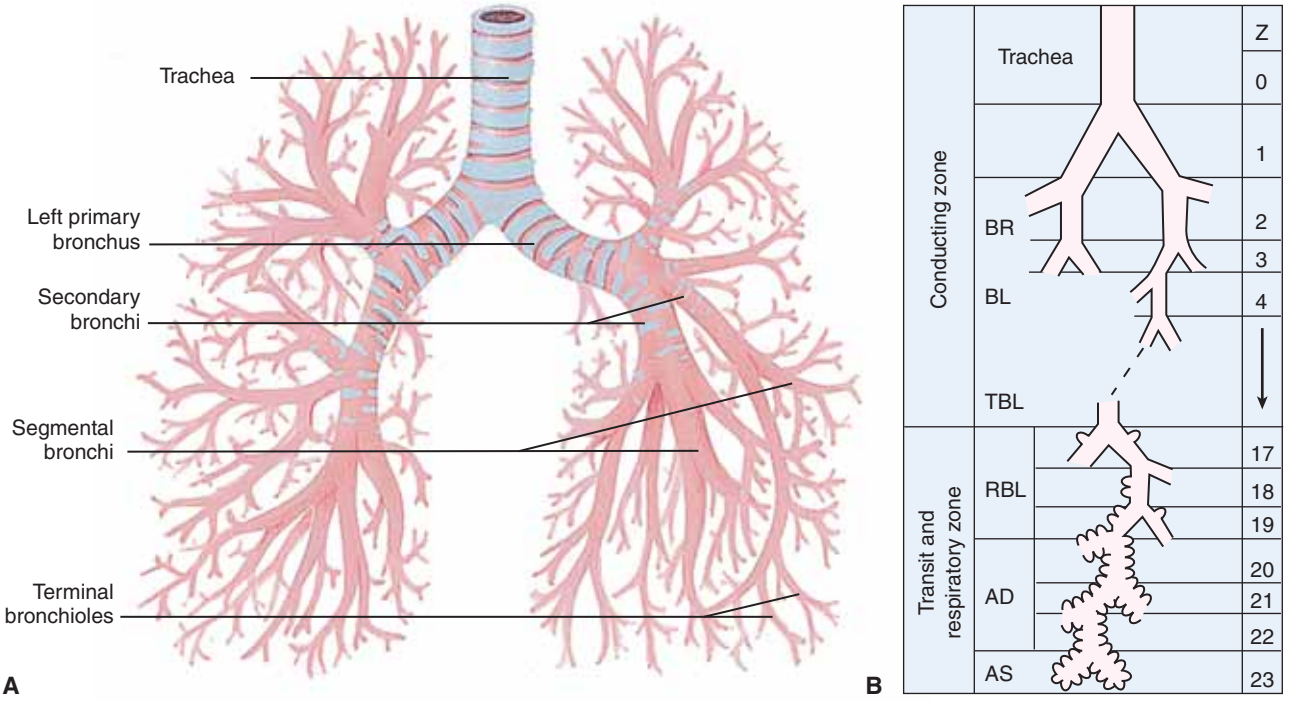


FIGURE 21-4. **(A)** Conducting and respiratory air pathways inferior to the larynx. (Anatomic Chart Company. *Atlas of human anatomy* [p. 175]. Springhouse PA: Springhouse.) **(B)** Idealization of the human airways. The first 16 generations of branching (Z) make up the conducting airways, and the last seven constitute the respiratory zone (or transitional and respiratory zone). AD, alveolar ducts; AS, alveolar sacs; BL, bronchiole; BR, bronchus; RBL, respiratory bronchiole; TBL, terminal bronchiole. (From Weibel E.R. [1962]. *Morphometry of the human lung* [p. 111]. Berlin: Springer-Verlag.)

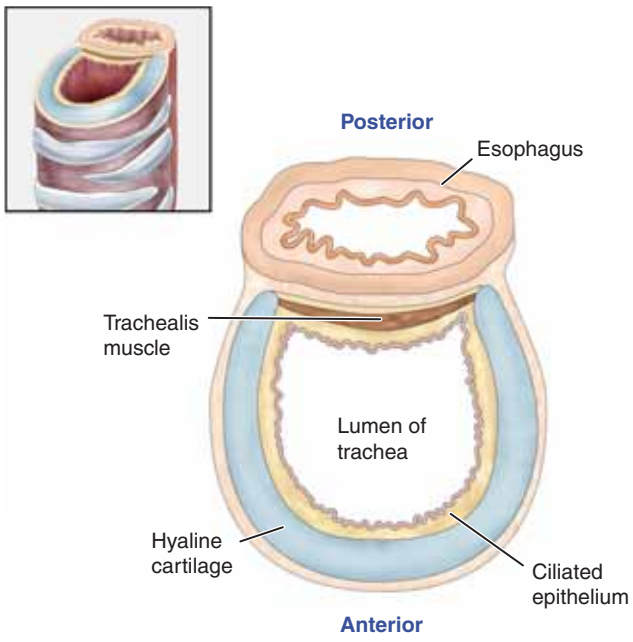


FIGURE 21-5. Cross-section of the trachea, illustrating its relationship to the esophagus, the position of the supporting hyaline cartilage rings in its wall, and the trachealis muscle connecting the free ends of the cartilage rings.

sensitive; violent coughing is initiated when a foreign object (e.g., suction catheter) makes contact with it. The structure of the primary bronchi is similar to that of the trachea in that these airways are lined with a mucosal surface and supported by cartilaginous rings. Each primary bronchus, accompanied by the pulmonary arteries, veins, and lymph vessels, enters the lung through a slit called the *hilus*.

On entering the lungs, each primary bronchus divides into secondary or lobular bronchi that supply each of the lobes of the lung—three in the right lung and two in the left. The right middle lobe bronchus is of relatively small diameter and length and sometimes bends sharply near its bifurcation. It is surrounded by a collar of lymph nodes that drain the middle and the lower lobe and is particularly subject to obstruction. The secondary bronchi, in turn, divide to form the segmental bronchi, which supply the bronchopulmonary segments of the lung. These segments are identified according to their location in the lung (e.g., the apical segment of the right upper lobe) and are the smallest named units in the lung. Lung lesions such as atelectasis and pneumonia often are localized to a particular bronchopulmonary segment. The structure of the secondary and segmental bronchi is similar to that of the primary bronchi, except

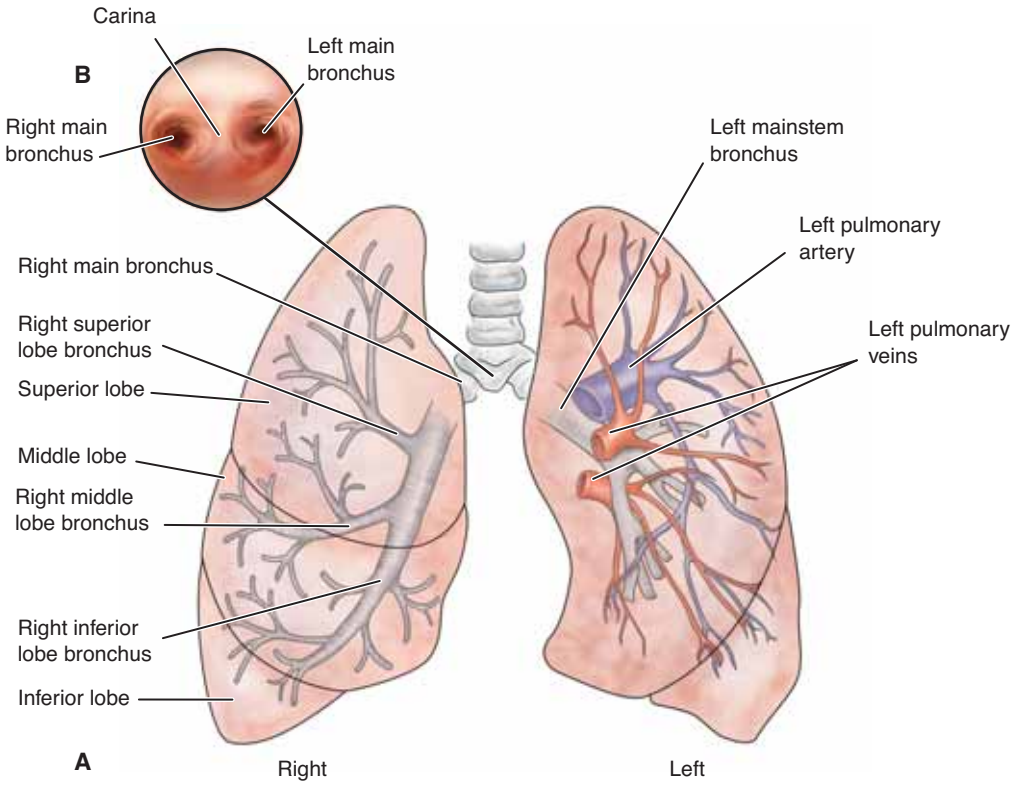


FIGURE 21-6. **(A)** Anterior view of respiratory structures including the lobes of the lung, the larynx, the trachea, and the main bronchi on the left and the main pulmonary artery and vein on the right. **(B)** The carina that is located at the bifurcation of right and left mainstem bronchi.

the C-shaped cartilage rings are replaced by irregular plates of hyaline cartilage that completely surround the lumina of the bronchi and there are two layers of smooth muscle spiraling in opposite directions.

The segmental bronchi continue to branch, forming smaller bronchi, until they become the terminal bronchioles, the smallest of the conducting airways. As these bronchi branch and become smaller, their wall structure changes. The cartilage gradually decreases and there is an increase in smooth muscle and elastic tissue (with respect to the thickness of the wall). By the time the bronchioles are reached, there is no cartilage present and their walls are composed mainly of smooth muscle and elastic fibers. Bronchospasm, or contraction of these muscles, causes narrowing of the bronchioles and impairs air flow. The elastic fibers, which radiate from the adventitia of the bronchial wall and connect with elastic fibers arising from other parts of the bronchial tree, exert tension on the bronchial walls; by pulling uniformly in all directions, they help maintain airway patency.

Lungs and Respiratory Airways

The lungs are the functional structures of the respiratory system. In addition to their gas exchange function, they inactivate vasoactive substances such as bradykinin, convert angiotensin I to angiotensin II, and serve as a reservoir for blood storage. Heparin-producing cells are particularly abundant in the capillaries of the lung, where small clots may be trapped.

The gas exchange function of the lung takes place in the lobules of the lungs. Each lobule, which is the smallest functional unit of the lung, is supplied by a terminal bronchiole, an arteriole, pulmonary capillaries, and a venule (Fig. 21-7). Gas exchange takes place in the terminal respiratory bronchioles and the alveolar ducts and sacs. Blood enters the lobules through a pulmonary artery and exits through a pulmonary vein. Lymphatic structures surround the lobule and aid in the removal of plasma proteins and other particles from the interstitial spaces.

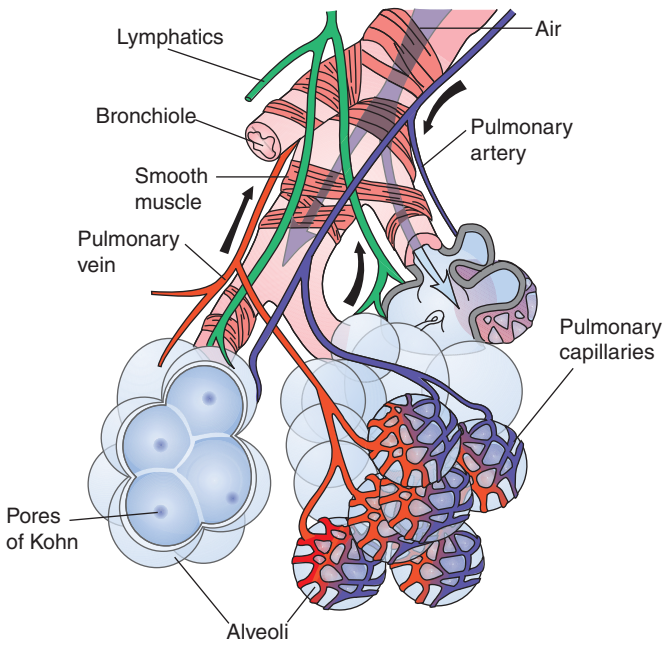


FIGURE 21-7. Lobule of the lung, showing the bronchial smooth muscle fibers, pulmonary blood vessels, and lymphatics.

Alveolar Structures

The alveoli are the terminal air spaces of the respiratory tract and the actual sites of gas exchange between the air and the blood. Each alveolus is a small outpouching of respiratory bronchioles, alveolar ducts, and alveolar sacs (Fig. 21-7). The alveolar sacs are cup-shaped, thin-walled structures that are separated from each other by thin alveolar septa. A single network of capillaries occupies most of the septa, so blood is exposed to air on both sides. There are approximately 300 million alveoli in the adult lung, with a total surface area of approximately 50 to 100 m^2. Unlike the bronchioles, which are tubes with their own separate walls, the alveoli are interconnecting spaces that have no separate walls. As a result of this arrangement, there is a continual mixing of air in the alveolar structures. Small holes in the alveolar walls, the pores of Kohn, also contribute to the mixing of air.

The alveolar epithelium is composed of two types of cells: type I and type II alveolar cells (Fig. 21-8). The alveoli also contain brush cells and macrophages. The brush cells, which are few in number, are thought to act as receptors that monitor the air quality of the lungs. The macrophages, which are present in both the alveolar lumen and the septum of the alveoli, function to remove offending material from the lung.

Type I Alveolar Cells. The type I alveolar cells, also known as *type I pneumocytes*, are extremely thin squamous cells with a thin cytoplasm and flattened nucleus that occupy about 95% of the surface area of the alveoli. They are joined to one another and to other cells by occluding junctions. These junctions form an effective barrier between the air and the components of the alveolar wall. Type I alveolar cells are not capable of regeneration.

Type II Alveolar Cells. The type II alveolar cells, also called *type II pneumocytes*, are secretory cells that produce the surface-active agent called *surfactant*. These cuboidal cells, which are found interspersed among the type I cells, tend to bulge into the air spaces (see Fig. 21-8). Type II cells are as numerous as type I cells, but because of their different shape, they cover only about 5% of the alveolar surface area. In addition to secreting surfactant, type II alveolar cells are the progenitor cells for type I cells. Following lung injury, they proliferate and restore both type I and type II alveolar cells.

The surfactant molecules produced by the type II alveolar cells reduce the surface tension at the air–epithelium interface and they modulate the immune functions of the lung. Recent research has identified four types of surfactant, each with a different molecular structure: surfactant protein A (SP-A), B (SP-B), C (SP-C), and D (SP-D). SP-B and SP-C reduce the surface tension at the air–epithelium interface and increase lung compliance and ease of lung

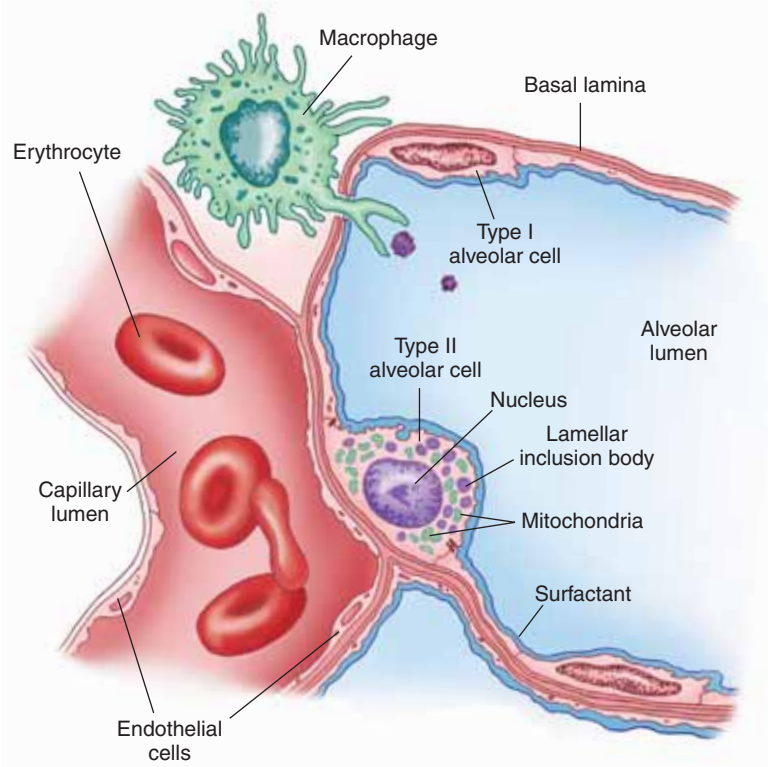


FIGURE 21-8. Schematic illustration of type I and type II alveolar cells and their relationship to the alveoli and pulmonary capillaries. Type I alveolar cells comprise most of the alveolar surface. The type II alveolar cells, which produce surfactant, are located at the corners between adjacent alveoli. Also shown are the endothelial cells, which line the pulmonary capillaries, and an alveolar macrophage.

inflation. SP-B is particularly important to the generation of the surface-reducing film that makes lung expansion possible (to be discussed). SP-A and SP-D do not reduce surface tension, but contribute to host defenses that protect against pathogens that have entered the lung. They are members of the collectin family that function as a part of the innate immune system (see Chapter 15). Collectively they opsonize pathogens, including bacteria and viruses, to facilitate phagocytosis by macrophages. They also regulate the production of inflammatory mediators. Evidence also suggests that SP-A and SP-D are directly bacteriocidal, meaning they can kill bacteria in the absence of immune system effector cells.

Alveolar Macrophages. The alveolar macrophages, which are present in both the connective tissue of the septum and in the air spaces of the alveolus, are responsible for the removal of offending substances from the alveoli. In the air spaces, they scavenge the surface to remove inhaled particulate matter, such as dust and pollen. Some macrophages move up the bronchial tree in the mucus and are disposed of by swallowing or coughing when they reach the pharynx. Others enter the septal connective tissue, where, filled with phagocytosed materials, they remain for life. Thus, at autopsy, urban dwellers, as well as smokers, usually show many alveolar macrophages filled with carbon and other polluting particles from the environment. The alveolar macrophages also phagocytose insoluble infectious agents such as *Mycobacterium tuberculosis*. The activated macrophages then aggregate to form a fibrin-encapsulated granuloma, called a *tubercle*, that serves to contain the infection. The tubercle bacillus can remain dormant in this stage or be reactivated years later, when the person's immunologic tolerance wanes as the result of conditions such as immunosuppressive therapy or acquired immunodeficiency disease (AIDS; see Chapter 16).

Pulmonary and Bronchial Circulations

The lungs are provided with a dual blood supply: the pulmonary and bronchial circulations. The pulmonary circulation arises from the pulmonary artery and provides for the gas exchange function of the lungs (see Fig. 21-7). Deoxygenated blood leaves the right heart through the pulmonary artery, which divides into a left pulmonary artery that enters the left lung and a right pulmonary artery that enters the right lung. Return of oxygenated blood to the heart occurs by way of the pulmonary veins, which empty into the left atrium. It is important to note that this is the only part of the circulation in which arteries carry deoxygenated blood and veins carry oxygenated blood.

The bronchial circulation supplies the blood supply for the conducting airways and the supporting structures of the lung. It also has a secondary function of warming and humidifying incoming air as it moves through the conducting airways. The bronchial arteries arise from the thoracic aorta and enter the lungs with the major bronchi, dividing and subdividing along with the bronchi as they move out into the lung, supplying them and other lung structures with oxygen. The blood from the capillaries in the bronchial circulation drains into the bronchial veins, with the blood from the larger bronchial

veins emptying into the vena cava and blood from the smaller bronchial veins emptying into the pulmonary veins. Because the bronchial circulation does not participate in gas exchange, this blood is deoxygenated. As a result, it dilutes the oxygenated blood returning to the left side of the heart by way of the pulmonary veins.

The bronchial blood vessels are the only ones that can undergo angiogenesis (formation of new vessels) and develop collateral circulation when vessels in the pulmonary circulation are obstructed, as in pulmonary embolism. The development of new blood vessels helps to keep lung tissue alive until the pulmonary circulation can be restored.

Innervation

The lung is innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system. The parasympathetic fibers are derived from the vagal nerves, and the sympathetic fibers from the upper thoracic and cervical ganglia; together they form the pulmonary plexuses in the region of the hilus before entering the lung. Fibers from the plexus follow the major bronchi and blood vessels into the lung to innervate bronchial smooth muscle cells, blood vessels, and epithelial cells (including the goblet and submucosal glands). There is no voluntary motor innervation of the lung, nor are there pain fibers. Pain fibers are found only in the pleura.

Stimulation of the parasympathetic nervous system leads to airway constriction, blood vessel dilation, and increased glandular secretion. Parasympathetic fibers contain excitatory (cholinergic) motor neurons that respond to acetylcholine. Parasympathetic stimulation through the vagus nerve is responsible for the slightly constricted smooth muscle tone in the airways of the lung under normal resting conditions. Stimulation of the sympathetic nervous system causes airway dilation, blood vessel constriction, and inhibition of glandular secretion. Neurotransmitters of the sympathetic innervation of the lung include the catecholamines norepinephrine and epinephrine.

Pleura

A thin, transparent, double-layered serous membrane, called the *pleura*, lines the thoracic cavity and encases the lungs (see Fig. 21-1). The outer parietal layer lines the pulmonary cavities and adheres to the thoracic wall, the mediastinum, and the diaphragm. The inner visceral pleura closely covers the lung and is adherent to all its surfaces. It is continuous with the parietal pleura at the hilus of the lung, where the major bronchus and pulmonary vessels enter and leave the lung. A thin film of serous fluid separates the two pleural layers, allowing the two layers to glide over each other and yet hold together, so there is no separation between the lungs and the chest wall. The pleural cavity is a potential space in which serous fluid or inflammatory exudate can accumulate. The term *pleural effusion* is used to describe an abnormal collection of fluid in the pleural cavity.

In summary, the respiratory system consists of the airways and the lungs. Functionally, the airways of the respiratory system can be divided into two parts: the conducting airways, through which air moves as it passes into and out of the lungs, and the respiratory tissues, where gas exchange actually takes place. The conducting airways include the nasal passages, mouth and nasopharynx, larynx, and tracheobronchial tree. Air is warmed, filtered, and humidified as it passes through these structures.

The lungs are the functional structures of the respiratory system. In addition to their gas exchange function, they inactivate vasoactive substances such as bradykinin, convert angiotensin I to angiotensin II, and serve as a reservoir for blood. The lobules, which are the functional units of the lung, consist of the terminal bronchioles and alveoli where gas exchange takes place. There are two types of alveolar cells: type I alveolar cells, which provide the surface area for the gas exchange function of the lung, and type II alveolar cells, which secrete the surface-active agent surfactant.

The lungs are provided with a dual blood supply: the pulmonary circulation provides for the gas exchange function of the lungs and the bronchial circulation supplies blood to the conducting airways and supporting structures of the lung. Innervation of the lungs occurs by way of the sympathetic and parasympathetic divisions of the autonomic nervous system. Parasympathetic innervation causes airway constriction and an increase in respiratory secretions, whereas sympathetic innervation causes bronchial dilation and a decrease in respiratory tract secretions.

The lungs are encased in a thin, transparent, double-layered serous membrane called the *pleura*. A thin film of serous fluid separates the outer parietal and inner visceral pleural layers, allowing the two layers to glide over each other and yet hold together, so there is no separation between the lungs and the chest wall. The pleural cavity is a potential space in which serous fluid or inflammatory exudate can accumulate.

Exchange of Gases Between the Atmosphere and the Lungs

Basic Properties of Gases

The air we breathe is made up of a mixture of gases, mainly nitrogen and oxygen. These gases exert a combined pressure called the *atmospheric pressure*. The pressure at sea level is defined as 1 atmosphere, which is equal to 760 millimeters of mercury (mm Hg) or 14.7 pounds per square inch (PSI). When measuring respiratory pressures, atmospheric pressure is assigned a value of 0. This means that a respiratory pressure of +15 mm Hg is 15 mm Hg above atmospheric pressure, and a respiratory pressure of –15 mm Hg is 15 mm Hg less than atmospheric

pressure. Respiratory pressures often are expressed in centimeters of water (cm H_2O) because of the small pressures involved (1 mm Hg = 1.35 cm H_2O pressure).

The pressure exerted by a single gas in a mixture is called the *partial pressure*. The capital letter "P" followed by the chemical symbol of the gas (e.g., PO_2) is used to denote its partial pressure. The law of partial pressures states that the total pressure of a mixture of gases, as in the atmosphere, is equal to the sum of the partial pressures of the different gases in the mixture. If the concentration of oxygen at 760 mm Hg (1 atmosphere) is 20%, its partial pressure is 152 mm Hg (760 × 0.20).

Water vapor is different from other types of gases; its partial pressure is affected by temperature but not atmospheric pressure. The relative humidity refers to the percentage of moisture in the air compared with the amount that the air can hold without causing condensation (100% saturation). Warm air holds more moisture than cold air. This is the reason that precipitation in the form of rain or snow commonly occurs when the relative humidity is high and there is a sudden drop in atmospheric temperature. The air in the alveoli, which is 100% saturated at normal body temperature, has a water vapor pressure of 47 mm Hg. The water vapor pressure must be included in the sum of the total pressure of the gases in the alveoli (i.e., the total pressure of the other gases in the alveoli is 760 − 47 = 713 mm Hg).

Air moves between the atmosphere and the lungs because of a pressure difference or gradient. According to the laws of physics, the pressure of a gas varies inversely with the volume of its container, provided the temperature remains constant. If equal amounts of a gas are placed in two different-size containers, the pressure of the gas in the smaller container will be greater than the pressure in the larger container. The movement of gases is always from the container with the greater pressure to the one with the lesser pressure. The chest cavity can be viewed as a volume container. During inspiration, air moves into the lungs as the size of the chest cavity increases, and during expiration, air moves out as the size of the chest cavity decreases.

Ventilation and the Mechanics of Breathing

Ventilation is concerned with the movement of gases into and out of the lungs. It relies on a system of open airways and a change in pressure that is created as the respiratory muscles change the size of the chest cage. The degree to which the lungs inflate and deflate depends on the movement of the chest cage and pressures created by respiratory muscles, the resistance that the air encounters as it moves through the airways, and the compliance or ease with which the lungs can be inflated.

Respiratory Pressures

The pressure inside the airways and alveoli of the lungs is called the *intrapulmonary pressure* or *alveolar pressure*. The gases in this area of the lungs are in communication with atmospheric pressure (Fig. 21-9). When the glottis is open and air is not moving into or out of the lungs, as occurs just before inspiration or expiration, the intrapulmonary pressure is zero or equal to atmospheric pressure.

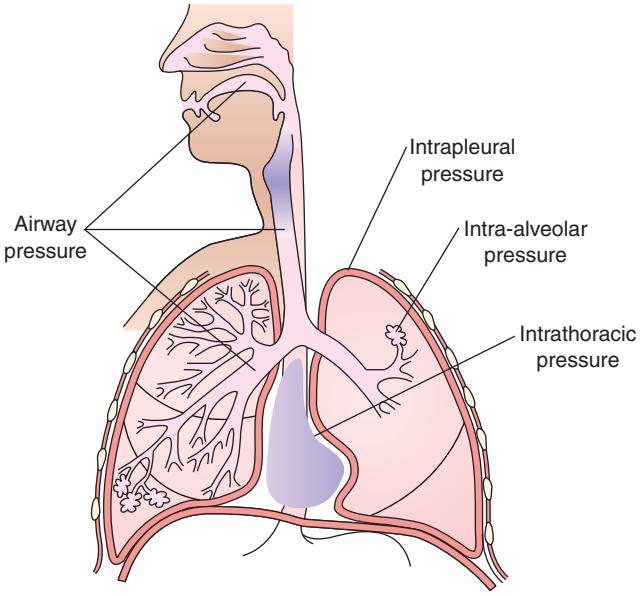


FIGURE 21-9. Partitioning of respiratory pressures.

The pressure in the pleural cavity is called the *intrapleural pressure*. The intrapleural pressure is always negative in relation to alveolar pressure in the normally inflated lung, approximately −4 mm Hg between breaths when the glottis is open and the alveolar spaces are open

Ventilation and Gas Exchange

- Ventilation refers to the movement of gases into and out of the lungs through a system of open airways and along a pressure gradient resulting from a change in chest volume.
- During inspiration, air is drawn into the lungs as the respiratory muscles expand the chest cavity; during expiration, air moves out of the lungs as the chest muscles recoil and the chest cavity becomes smaller.
- The ease with which air is moved into and out of the lung depends on the resistance of the airways, which is inversely related to the fourth power of the airway radius, and lung compliance, or the ease with which the lungs can be inflated.
- The minute volume, which is determined by the metabolic needs of the body, is the amount of air that is exchanged each minute. It is the product of the tidal volume or amount of air exchanged with each breath multiplied by the respiratory rate.

to the atmosphere. The lungs and the chest wall have elastic properties, each pulling in the opposite direction. If removed from the chest, the lungs would contract to a smaller size, and the chest wall, if freed from the lungs, would expand. The opposing forces of the chest wall and lungs create a pull against the visceral and parietal layers of the pleura, causing the pressure in the pleural cavity to become negative. During inspiration, the elastic recoil of the lungs increases, causing intrapleural pressure to become more negative than during expiration. Without the negative intrapleural pressure holding the lungs against the chest wall, their elastic recoil properties would cause them to collapse. Although the intrapleural pressure of the inflated lung is always negative in relation to alveolar pressure, it may become positive in relation to atmospheric pressure (e.g., during forced expiration and coughing).

The *intrathoracic pressure* is the pressure in the thoracic cavity. It is essentially equal to intrapleural pressure and is the pressure to which the lungs, heart, and great vessels are exposed. Forced expiration against a closed glottis (Valsalva maneuver) compresses the air in the thoracic cavity and produces marked increases in intrathoracic and intrapleural pressures.

The Chest Cage and Respiratory Muscles

The lungs and major airways share the chest cavity with the heart, great vessels, and esophagus. The chest cavity is a closed compartment bounded on the top by the neck muscles and at the bottom by the diaphragm. The outer walls of the chest cavity are formed by 12 pairs of ribs, the sternum, the thoracic vertebrae, and the intercostal muscles that lie between the ribs. Mechanically, ventilation or the act of breathing depends on the fact that the chest cavity is a closed compartment whose only opening to the exterior is the trachea.

Ventilation consists of inspiration and expiration. During *inspiration*, the size of the chest cavity increases, the intrathoracic pressure becomes more negative, and air is drawn into the lungs. *Expiration* occurs as the elastic components of the chest wall and lung structures that were stretched during inspiration recoil, causing the size of the chest cavity to decrease and the pressure in the chest cavity to increase (Fig. 21-10).

The diaphragm is the principal muscle of inspiration. When the diaphragm contracts, the abdominal contents are forced downward and the chest expands from top to bottom (see Fig. 21-10). During normal levels of inspiration, the diaphragm moves approximately 1 cm, but this can be increased to 10 cm on forced inspiration. The diaphragm is innervated by the phrenic nerve roots, which arise from the cervical level of the spinal cord, mainly from C4 but also from C3 and C5. Persons with spinal cord injury above this level require mechanical ventilation. Paralysis of one side of the diaphragm causes the chest to move up on that side rather than down during inspiration because of the negative pressure in the chest. This is called *paradoxical movement*.

The external intercostal muscles, which also aid in inspiration, connect to the adjacent ribs and slope downward and forward (Fig. 21-11). When they contract, they raise the ribs and rotate them slightly so that the sternum is pushed forward; this enlarges the chest from side to side and from front to back. The intercostal muscles receive their innervation from nerves that exit the central nervous system at the thoracic level of the spinal cord. Paralysis of these muscles usually does not have a serious effect on respiration because of the effectiveness of the diaphragm.

The accessory muscles of inspiration include the scalene muscles and the sternocleidomastoid muscles. The scalene muscles elevate the first two ribs, and the sternocleidomastoid muscles raise the sternum to increase the size of the chest cavity. These muscles contribute little to quiet breathing but contract vigorously during exercise. For the accessory muscles to assist in ventilation, they must be stabilized in some way. For example, persons with bronchial asthma often brace their arms against a firm object during an attack as a means of stabilizing their shoulders so that the attached accessory muscles can exert their full effect on ventilation. The head commonly is bent backward so that the scalene and sternocleidomastoid muscles can elevate the ribs more effectively. Other muscles that play a minor role in inspiration are the alae nasi, which produce flaring of the nostrils during obstructed breathing.

Expiration is largely passive. It occurs as the elastic components of the chest wall and lung structures that

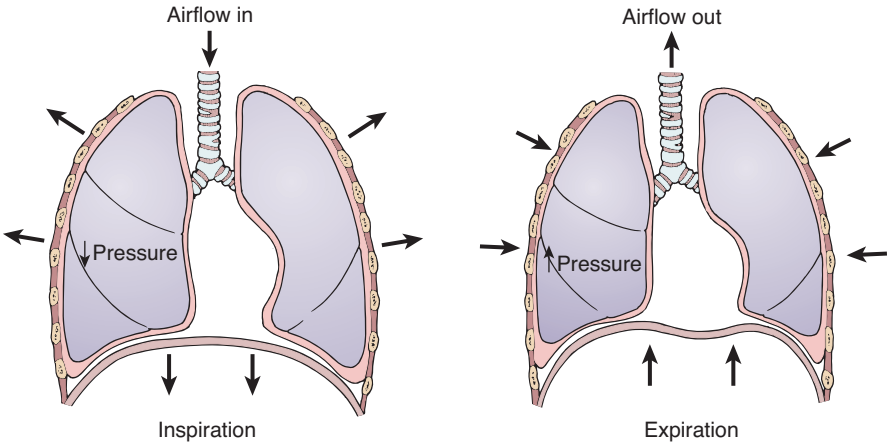


FIGURE 21-10. Movement of the diaphragm and changes in chest volume and pressure during inspiration and expiration. During inspiration, contraction of the diaphragm and expansion of the chest cavity produce a decrease in intrathoracic pressure, causing air to move into the lungs. During expiration, relaxation of the diaphragm and chest cavity produces an increase in intrathoracic pressure, causing air to move out of the lungs.

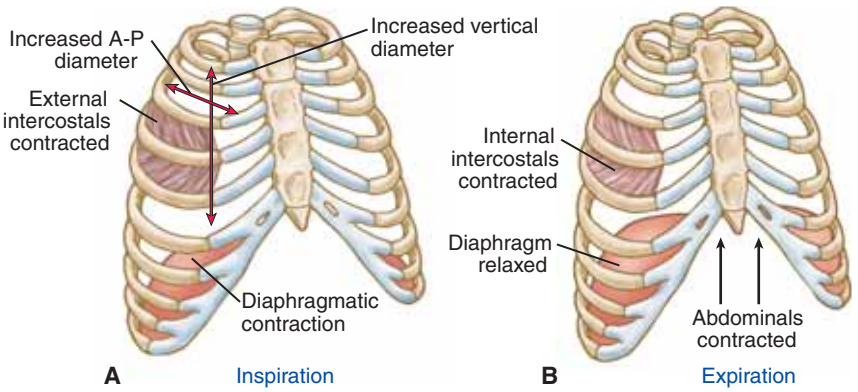


FIGURE 21-11. Expansion and contraction of the chest cage during expiration and inspiration, demonstrating especially diaphragmatic contraction, elevation of the rib cage, and function of the **(A)** external and **(B)** internal intercostals.

were stretched during inspiration recoil, causing air to leave the lungs as the intrathoracic pressure increases. When needed, the abdominal and the internal intercostal muscles can be used to increase expiratory effort (see Fig. 21-11). The increase in intra-abdominal pressure that accompanies the forceful contraction of the abdominal muscles pushes the diaphragm upward and results in an increase in intrathoracic pressure. The internal intercostal muscles move inward, which pulls the chest downward, increasing expiratory effort.

Lung Compliance

Lung compliance refers to the ease with which the lungs can be inflated. Compliance can be appreciated by comparing the ease of blowing up a balloon that has been previously blown up with a new balloon that is stiff and noncompliant. Specifically, lung compliance is a measure of the change in lung volume that occurs with a change in intrapulmonary pressure. The normal compliance of both lungs in the average adult is approximately 200 mL/cm H_2O. This means that every time the intrapulmonary pressure increases by 1 cm/H_2O, the lung volume expands by 200 mL. It would take more pressure to move the same amount of air into a noncompliant lung.

Lung compliance is determined by the elastic properties of the lung, its water content, and surface tension. It also depends on the compliance of the thoracic or chest cage. It is diminished by conditions that reduce the natural elasticity of the lung, increase the surface tension in the alveoli, or impair the flexibility of the thoracic cage. Lung tissue is made up of elastin and collagen fibers. The elastin fibers are easily stretched and increase the ease of lung inflation, whereas the collagen fibers resist stretching and make lung inflation more difficult. In lung diseases such as interstitial lung disease and pulmonary fibrosis, the lungs become stiff and noncompliant as the elastin fibers are replaced with the collagen fibers of scar tissue. Pulmonary congestion and edema produce a reversible decrease in pulmonary compliance by increasing the water content of the lung.

Elastic recoil describes the ability of the elastic components of the lung to recoil to their original position after having been stretched. Overstretching lung tissues, as occurs with emphysema, causes the elastic components of the lung to lose their recoil, making the lung more compliant and easier to inflate but more difficult to deflate because of its inability to recoil.

Surface Tension. An important factor in lung compliance is the *surface tension* in the alveoli. The alveoli are lined with a thin film of liquid, and it is at the interface between this liquid film and the alveolar air that surface tension develops. This is because the forces that hold the liquid molecules together are stronger than those that hold the air molecules together. In the alveoli, excess surface tension causes the liquid film to contract, making lung inflation more difficult.

The units of surface tension are those of force per unit length. The relationship between the pressure within a sphere such as an alveolus and the tension in the wall can be described using the law of Laplace (pressure = 2 × surface tension/radius). If the surface tension were equal throughout the lungs, the alveoli with the smallest radii would have the greatest pressure, and this would cause them to empty into the larger alveoli (Fig. 21-12A). The reason this does not occur is because of special surface tension-lowering molecules, called *surfactant*, that line the inner surface of the alveoli.

Pulmonary surfactant is a complex mixture of phospholipids, neutral lipids, and proteins that are synthesized in the previously discussed type II alveolar cells. Substances that are termed *surfactants* consist of two parts, with opposing properties that are irreversibly bound to each other. One part is polar and seeks aqueous fluid or hydrophilic (water-attracting) surfaces; the other is nonpolar and seeks oil, air, or hydrophobic (water-repelling) surfaces (Fig. 21-12B). Pulmonary surfactant forms a monolayer with its hydrophilic surface binding to liquid film on the surface of the alveoli and its hydrophobic surface facing outward toward the gases in the alveolar air. It is this monolayer that interrupts the surface tension that develops at the air–liquid interface in the alveoli.

Pulmonary surfactant, particularly SP-B, exerts several important effects on lung inflation: it lowers the surface tension and it increases lung compliance and ease of lung inflation. Without surfactant, lung inflation would be extremely difficult. In addition, it helps to keep the alveoli dry and prevent pulmonary edema. This is because water is pulled out of the pulmonary capillaries into the alveoli when increased surface tension causes the alveoli to contract.

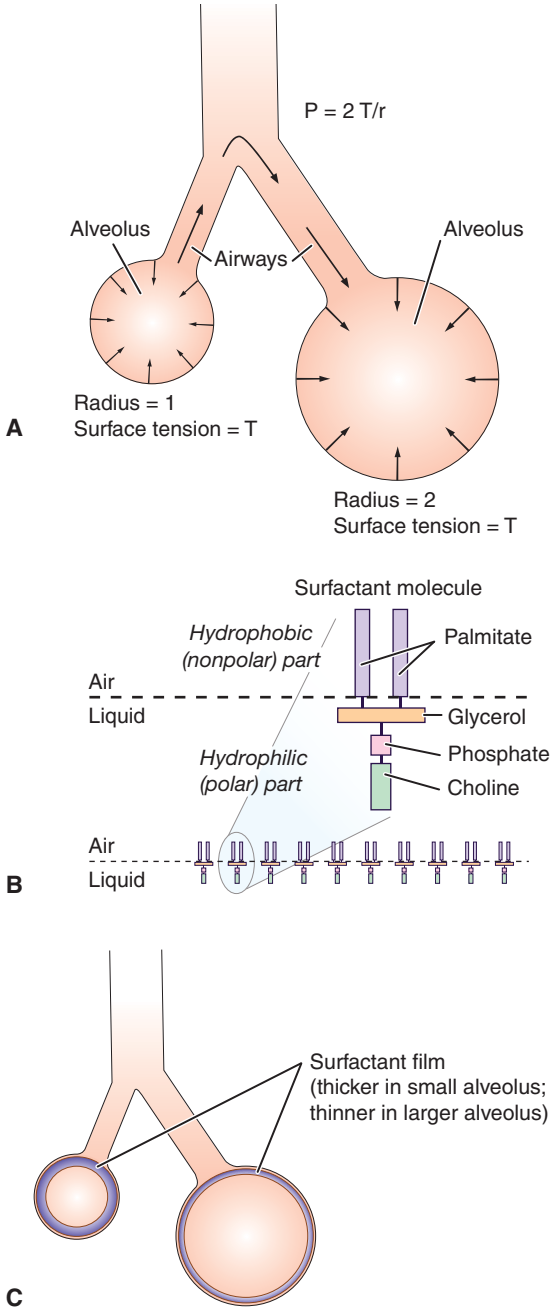


FIGURE 21-12. **(A)** The effect of the surface tension (forces generated at the fluid–air interface) and radius on the pressure and movement of gases in the alveolar structures. According to the law of Laplace (P = 2 T/r, P = pressure, T = tension, r = radius), the pressure generated within the sphere is inversely proportional to the radius. Air moves from the alveolus with a small radius and higher pressure to the alveolus with the larger radius and lower pressure. **(B)** The surfactant molecules with their hydrophilic heads (that attach to the fluid lining of the alveolus) and their hydrophobic tails (that are oriented toward the air interface. **(C)** The surfactant molecules form a monolayer (shaded in *blue*) that disrupts the intermolecular forces and lowers the surface tension more in the smaller alveolus with its higher concentration of surfactant than in the larger alveolus with its lower concentration of surfactant.

Surfactant also stabilizes the inflation of alveoli by changing its density in relation to alveolar size, with surfactant molecules becoming more tightly compressed in small alveoli with their higher surface tension and less compressed in larger alveoli with their lower surface tension (see Fig. 21-12C). At low lung volumes, when the molecules are tightly compressed, some surfactant is squeezed out of the surface to form micelles. On expansion, the surfactant in these micelles is used to spread a new film on the alveolar surface lining. In surgical and bed-ridden patients, shallow and quiet breathing often impairs the spreading of surfactant. Encouraging these patients to cough and deep breathe enhances the spreading of surfactant, allowing for a more even distribution of ventilation and prevention of atelectasis.

The type II alveolar cells that produce surfactant do not begin to mature until the 26th to 27th week of gestation; consequently, many premature infants have difficulty producing sufficient amounts of surfactant. This can lead to alveolar collapse and severe respiratory distress. This condition, called *infant respiratory distress syndrome*, is the single most common cause of respiratory disease in premature infants. Recombinant forms of surfactant are now available for use in treatment of the disorder (see Chapter 22). The synthesis of surfactant can also be impaired in the adult. This usually occurs as the result of severe injury or infection and can contribute to the development of a condition called *the acute respiratory distress syndrome* (see Chapter 23).

Airflow During Breathing

The volume of air that moves into and out of the gas exchange portion of the lungs is directly related to the pressure difference between the lungs and the atmosphere and inversely related to the resistance that the air encounters as it moves through the conducting airways.

Airway Resistance. Airway resistance is the ratio of the pressure driving inspiration or expiration to airflow. The French physician Jean Léonard Marie Poiseuille first described the pressure-flow characteristics of laminar flow in a straight circular tube, a correlation that has become known as *Poiseuille law*. According to Poiseuille law, the resistance to flow is inversely related to the fourth power of the radius ($R = 1/r^4$). If the radius is reduced by one half, the resistance increases 16-fold ($2 \times 2 \times 2 \times 2 = 16$).

Airway resistance differs in large (e.g., trachea and bronchi), medium-sized (e.g., segmental), and small (e.g., bronchioles) airways. Therefore, the total airway resistance is equal to the sum of the resistances in these three types of airways. The site of most of the resistance along the bronchial tree is in the large bronchi, with the smallest airways contributing very little to the total airway resistance. This is because most of these airways are arranged in parallel and their resistances are added as reciprocals (i.e., total combined resistance = 1/R + 1/R, etc.). While the resistance of each individual bronchiole may be relatively high, their great number results in a large total cross-sectional area, causing their total combined

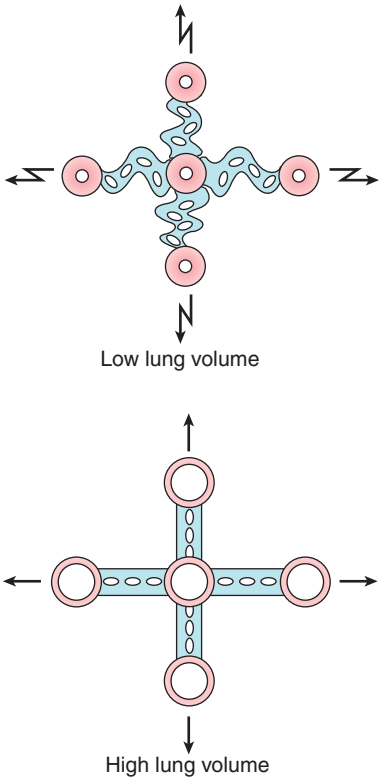


FIGURE 21-13. Interaction of tissue forces on airways during low and high lung volumes. At low lung volumes, the tissue forces promote folding or collapsing and place less tension on the airways, which become smaller; during high lung volumes, the tissue forces stretch and pull the airways open.

airway resistance to be low. Many airway diseases, such as emphysema and chronic bronchitis, begin in the small airways. Early detection of these diseases is often difficult because a considerable amount of damage must be present before the usual diagnostic measurements of airway resistance can detect them.

Airway resistance is greatly affected by lung volumes, being less during inspiration than during expiration. This is because elastic-type fibers connect the outside of the airways to the surrounding lung tissues. As a result, these airways are pulled open as the lungs expand during inspiration, and they become narrower as the lungs deflate during expiration (Fig. 21-13). This is one of the reasons why persons with conditions that increase airway resistance, such as bronchial asthma, usually have less difficulty during inspiration than during expiration.

Airway resistance is also affected by the bronchial smooth muscle tone that controls airway diameter. The smooth muscles in the airway, from the trachea down to the terminal bronchioles, are under autonomic nervous system control. As discussed earlier in the chapter, stimulation of the parasympathetic nervous system causes bronchial constriction as well as increased mucous secretion, whereas sympathetic stimulation has the opposite effect.

Laminar and Turbulent Airflow. Depending on the velocity and pattern of flow, airflow can be laminar or turbulent. Both laminar and turbulent flow cause resistance to air movement in the airways. *Laminar*, or *streamlined, airflow* occurs at low flow rates in which the air stream is parallel to the sides of the airway. With laminar flow, the air at the periphery must overcome the resistance to flow, and as a result, the air in the center of the airway moves faster. In the bronchial tree with its many branches, laminar airflow probably occurs only in the very small airways, where the velocity of flow is low. Because the small airways contribute little resistance to airflow, they constitute a silent zone (to be discussed). *Turbulent airflow* is disorganized flow in which the molecules of the gas move laterally, collide with one another, and change their velocities. Whether turbulence develops depends on the radius of the airways, the interaction of the gas molecules, and the velocity of airflow. It is most likely to occur when the radius of the airways is large and the velocity of flow is high. Turbulent flow occurs regularly in the trachea. Turbulence of airflow accounts for the respiratory sounds that are heard during chest auscultation (i.e., listening to chest sounds using a stethoscope).

Airway Compression During Forced Expiration. Airway resistance does not change much during normal quiet breathing; however, it is significantly increased during forced expiration, such as in vigorous exercise. The marked changes that occur during forced expiration are the result of airway compression. Airflow through the collapsible airways in the lungs depends on the distending airway (intrapulmonary) pressures that hold the airways open and the external (intrapleural or intrathoracic) pressures that surround and compress the airways. The difference between these two pressures (intrathoracic pressure minus airway pressure) is called the *transpulmonary pressure*. For airflow to occur, the distending pressure inside the airways must be greater than the compressing pressure outside the airways. During forced expiration, the transpulmonary pressure is decreased because of a disproportionate increase in the intrathoracic pressure compared with airway pressure. The resistance that air encounters as it moves out of the lungs causes a further drop in airway pressure. If this drop in airway pressure is sufficiently great, the surrounding intrathoracic pressure will compress the collapsible airways (i.e., those that lack cartilaginous support), causing airflow to be interrupted and air to be trapped in the terminal airways (Fig. 21-14).

Although this type of airway compression usually is seen only during forced expiration such as occurs with vigorous exercise in persons with normal respiratory function, it may occur during normal breathing in persons with lung diseases. For example, in conditions that increase airway resistance, such as asthma or chronic obstructive lung disease, the pressure drop along the smaller airways is magnified, and an increase in intra-airway pressure is needed to maintain airway patency. Measures such as pursed-lip breathing increase airway pressure and improve expiratory flow rates in persons with obstructive lung diseases (discussed in Chapter 23). This is also the rationale for using positive end-expiratory pressure in persons who are being mechanically ventilated. Infants who are having trouble breathing often grunt to increase their expiratory airway pressures and keep their airways open.

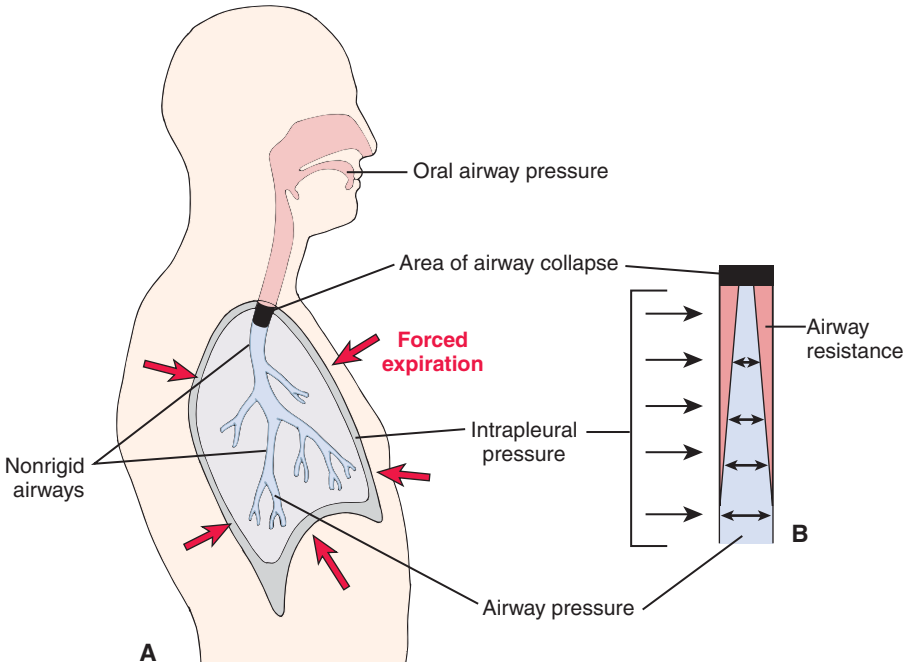


FIGURE 21-14. Mechanism that limits maximal expiratory flow rate. **(A)** Airway patency and airflow in the nonrigid airways of the lungs rely on a transpulmonary pressure gradient in which airway pressure is greater than intrapleural pressure. **(B)** Airway resistance normally produces a drop in airway pressure as air moves out of the lungs. The increased intrapleural pressure that occurs with forced expiration produces airway collapse in the nonrigid airways at the point where intrapleural pressure exceeds airway pressure.

Lung Volumes

Lung volumes, or the amount of air exchanged during ventilation, can be subdivided into three components: (1) the tidal volume (TV), (2) the inspiratory reserve volume (IRV), and (3) the expiratory reserve volume (ERV). The TV, usually about 500 mL, is the amount of air that moves into and out of the lungs during a normal breath (Fig. 21-15). The IRV is the maximum amount of air that can be inspired in excess of the normal TV, and the ERV is the maximum amount that can be exhaled in excess of the normal TV. Approximately 1200 mL of air always remains in the lungs after forced expiration; this air is the *residual volume* (RV). The RV increases with age because there is more trapping of air in the lungs at the end of expiration. The lung volumes can be measured using an instrument called a *spirometer*.

Lung capacities include two or more lung volumes. The *vital capacity* (VC) equals the IRV plus the TV plus the ERV and is the amount of air that can be exhaled from the point of maximal inspiration. The *inspiratory capacity* (IC) equals the TV plus the IRV. It is the amount of air a person can breathe in beginning at the normal expiratory level. The *functional residual capacity* (FRC) is the sum of the RV and ERV; it is the volume of air that remains in the lungs at the end of normal expiration. The *total lung capacity* (TLC) is the sum of all the volumes in the lungs. The RV cannot be measured with the spirometer because this air cannot be expressed from the lungs. It is measured by indirect methods, such as the helium dilution methods, the nitrogen washout methods, or body plethysmography. Lung volumes and capacities are summarized in Table 21-1.

Pulmonary Function Studies

The previously described lung volumes and capacities are anatomic or static measures, determined by spirometry and measured without relation to time. The spirometer

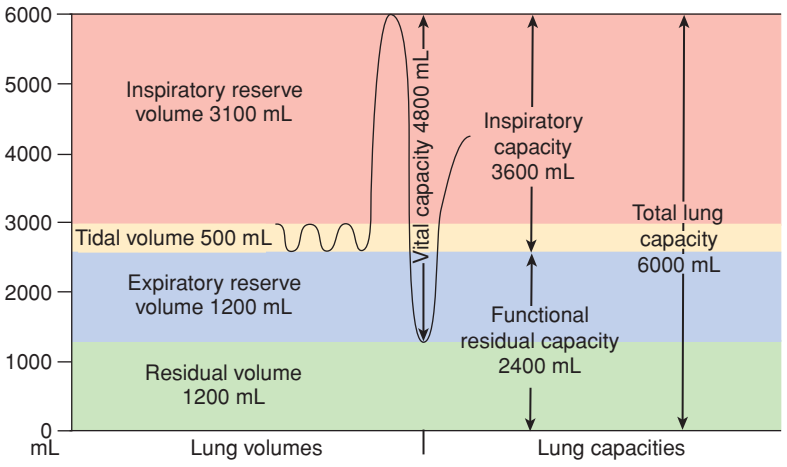


FIGURE 21-15. Spirometry recoding of respiratory volumes (*left*) and diagram of lung capacities (*right*). The tidal volume (TV, yellow) is the volume of air inhaled and exhaled during normal breathing; the inspiratory reserve volume (IRV, pink), the maximal volume of air that can be forcefully inhaled in excess of the TV; the expiratory reserve volume (ERV, blue), the maximal volume of air that can be exhaled in excess of the TV; and the residual volume (RV, green), the air that continues to remain in the lung after maximal respiratory effort. The inspiratory capacity (IC) is the sum of the IRV and the TV; the functional residual capacity (FRC), the sum of the IRV, TV, and ERV; and the total lung capacity (TLC) the sum of all the volumes. The vital capacity (VC, not shown) is the IRV, TV, and ERV.

TABLE 21-1 Lung Volumes and Capacities

Volume	Symbol	Measurement
Tidal volume (about 500 mL at rest)	TV	Amount of air that moves into and out of the lungs with each breath
Inspiratory reserve volume (about 3000 mL)	IRV	Maximum amount of air that can be inhaled from the point of maximal expiration
Expiratory reserve volume (about 1100 mL)	ERV	Maximum volume of air that can be exhaled from the resting end-expiratory level
Residual volume (about 1200 mL)	RV	Volume of air remaining in the lungs after maximal expiration. This volume cannot be measured with the spirometer; it is measured indirectly using methods such as the helium dilution method, the nitrogen washout technique, or body plethysmography.
Functional residual capacity (about 2300 mL)	FRC	Volume of air remaining in the lungs at end-expiration (sum of RV and ERV)
Inspiratory capacity (about 3500 mL)	IC	Sum of IRV and TV
Vital capacity (about 4600 mL)	VC	Maximal amount of air that can be forcibly exhaled from the point of maximal inspiration
Total lung capacity (about 5800 mL)	TLC	Total amount of air that the lungs can hold; it is the sum of all the volume components after maximal inspiration. This value is about 20% to 25% less in females than in males.

also is used to measure dynamic lung function (i.e., ventilation with respect to time); these tests often are used in assessing pulmonary function (Table 21-2). The *maximum voluntary ventilation* measures the volume of air that a person can move into and out of the lungs during maximum effort lasting for a specific period of time. This measurement usually is converted to liters per minute. Two other useful tests are the *forced vital capacity* (FVC) and the *forced expiratory volume* (FEV). The FVC involves full inspiration to total lung capacity followed by forceful maximal expiration. Obstruction of airways produces an FVC that is lower than that observed with more slowly performed vital capacity measurements. The FEV is the expiratory volume achieved in a given time period. The $FEV_{1.0}$ is the forced expiratory volume that can be exhaled in 1 second. The $FEV_{1.0}$ frequently is expressed as a percentage of the FVC. The $FEV_{1.0}$ and FVC are used in the diagnosis of obstructive lung disorders.

Efficiency and Work of Breathing

The *minute volume*, or total ventilation, is the amount of air that is exchanged in 1 minute. It is determined by the metabolic needs of the body. The minute volume is equal to the TV multiplied by the respiratory rate. During normal activity it is about 6000 mL (500 mL TV × respiratory rate of 12 breaths per minute). The efficiency of breathing is determined by matching the TV and respiratory rate in a manner that provides an optimal minute volume while minimizing the work of breathing.

The work of breathing is determined by the amount of effort required to move air through the conducting

TABLE 21-2 Pulmonary Function Tests

Test	Symbol	Measurement*
Maximal voluntary ventilation	MVV	Maximum amount of air that can be breathed in a given time
Forced vital capacity	FVC	Maximum amount of air that can be rapidly and forcefully exhaled from the lungs after full inspiration. The expired volume is plotted against time.
Forced expiratory volume achieved in 1 second	$FEV_{1.0}$	Volume of air expired in the first second of FVC
Percentage of forced vital capacity	$(FEV_{1.0}/FVC\%) \times 100$	Volume of air expired in the first second, expressed as a percentage of FVC
Forced midexpiratory flow rate	$FEF_{25\%–75\%}$	The forced midexpiratory flow rate determined by locating the points on the volume-time curve recording obtained during FVC corresponding to 25% and 75% of FVC and drawing a straight line through these points. The slope of this line represents the average midexpiratory flow rate.
Forced inspiratory flow rate	$FIF_{25\%–75\%}$	FIF is the volume inspired from RV at the point of measurement. $FIF_{25\%–75\%}$ is the slope of a line between the points on the volume pressure tracing corresponding to 25% and 75% of the inspired volume.

*By convention, all the lung volumes and rates of flow are expressed in terms of body temperature and pressure and saturated with water vapor (BTPS), which allows for a comparison of the pulmonary function data from laboratories with different ambient temperatures and altitudes.

airways and by the ease of lung expansion or compliance. Because expansion of the lungs is difficult for persons with stiff and noncompliant lungs, they usually find it easier to breathe if they keep their TV low and breathe at a more rapid rate (e.g., 300 mL × 20 breaths/min = 6000 mL) to achieve their minute volume and meet their oxygen needs. In contrast, persons with obstructive airway disease usually find it less difficult to inflate their lungs but expend more energy in moving air through the airways. As a result, these persons tend to take deeper breaths and breathe at a slower rate (e.g., 600 mL × 10 breaths/min = 6000 mL) to achieve their oxygen needs.

In summary, the movement of air between the atmosphere and the lungs follows the laws of physics as they relate to gases. The air in the alveoli contains a mixture of gases, including nitrogen, oxygen, carbon dioxide, and water vapor. With the exception of water vapor, each gas exerts a pressure that is determined by the atmospheric pressure and the concentration of the gas in the mixture. Water vapor pressure is affected by temperature but not atmospheric pressure. Air moves into the lungs along a pressure gradient. The pressure inside the airways and alveoli of the lungs is called *intrapulmonary* (or *alveolar*) *pressure,* the pressure in the pleural cavity is called *intrapleural pressure,* and the pressure in the thoracic cavity is called *intrathoracic pressure.*

Breathing is the movement of gases between the atmosphere and the lungs. It requires a system of open airways and pressure changes resulting from the action of the respiratory muscles in changing the volume of the chest cage. The diaphragm is the principal muscle of inspiration, assisted by the external intercostal muscles. The scalene and sternocleidomastoid muscles elevate the ribs and act as accessory muscles for inspiration. Expiration is largely passive, aided by the elastic recoil of the respiratory muscles that were stretched during inspiration. Lung compliance describes the ease with which the lungs can be inflated. It reflects the elasticity of the lung tissue and the surface tension in the alveoli. Surfactant molecules, produced by type II alveolar cells, reduce the surface tension in the lungs, thereby increasing lung compliance. Airway resistance refers to the impediment to flow that the air encounters as it moves through the airways. It differs with airway size, being greatest in the medium-sized bronchi and lowest in the smaller bronchioles.

Lung volumes and lung capacities reflect the amount of air that is exchanged during normal and forced breathing. Lung volumes and lung capacities can be measured using a spirometer. Pulmonary function studies are used to assess ventilation with respect to time. The minute volume, which is determined by the metabolic needs of the body, is the amount of air that is exchanged in 1 minute (i.e., respiratory rate × tidal volume). The efficiency and work of breathing are determined by factors such as impaired lung compliance and airway diseases that increase the work involved in maintaining the minute volume.

Exchange and Transport of Gases

The primary functions of the lungs are oxygenation of the blood and removal of carbon dioxide. Pulmonary gas exchange is conventionally divided into three processes: (1) ventilation or the flow of gases into and out of the alveoli of the lungs, (2) perfusion or flow of blood in the adjacent pulmonary capillaries, and (3) diffusion or transfer of gases between the alveoli and the pulmonary capillaries.

Ventilation

Ventilation refers to the exchange of gases in the respiratory system. There are two types of ventilation: pulmonary and alveolar. *Pulmonary ventilation* refers to the total exchange of gases between the atmosphere and the lungs. *Alveolar ventilation* is the exchange of gases within the gas exchange portion of the lungs. Ventilation requires a system of open airways and a pressure difference that moves air into and out of the lungs. It is affected by body position and lung volume as well as by disease conditions that affect the heart and respiratory system.

Distribution of Ventilation

The distribution of ventilation between the base (bottom) and apex (top) of the lung varies with body position and reflects the effects of gravity on intrapleural pressure and lung compliance. Compliance reflects the change in volume that occurs with a change in intrapleural pressure. It is less in fully expanded alveoli, which have difficulty accommodating more air, and greater in alveoli that are less inflated and can more easily expand to accommodate more air. In the seated or standing position, gravity exerts a downward pull on the lung, causing intrapleural pressure at the apex of the lung to become more negative. As a result, the alveoli at the apex of the lung are more fully expanded and less compliant than those at the base of the lung. The same holds true for lung expansion in the dependent portions of the lung in the supine or lateral position. In the supine position, ventilation in the lowermost (posterior) parts of the lung exceeds that in the uppermost (anterior) parts. In the lateral position (i.e., lying on the side), the dependent lung is better ventilated.

The distribution of ventilation also is affected by lung volumes. During full inspiration (high lung volumes) in the seated or standing position, the airways are pulled open and air moves into the more compliant portions of the lower lung. At low lung volumes, the opposite occurs. At functional residual capacity, the intrapleural pressure at the base of the lung exceeds airway pressure, compressing the airways so that ventilation is greatly reduced. In contrast, the airways in the apex of the lung remain open, and this area of the lung is well ventilated.

Even at low lung volumes, some air remains in the alveoli of the lower portion of the lungs, preventing their collapse. According to the law of Laplace (discussed previously), the pressure needed to overcome the tension in the wall of a sphere or an elastic tube is inversely related to its radius; therefore, the small airways close first, trapping

some air in the alveoli. This trapping of air may be increased in older persons and persons with chronic lung disease (e.g., emphysema) owing to a loss in the elastic recoil properties of the lungs. In these persons, airway closure occurs at the end of normal instead of low lung volumes, trapping larger amounts of air with a resultant increase in the residual lung volume.

Dead Air Space

Dead space refers to the air that must be moved with each breath but does not participate in gas exchange. The movement of air through dead space contributes to the work of breathing but not to gas exchange. There are two types of dead space: that contained in the conducting airways, called the *anatomic dead space*, and that contained in the respiratory portion of the lung, called the *alveolar dead space*. The volume of the anatomic airway dead space (i.e., air in the nose, pharynx, trachea, and bronchi) is fixed at approximately 150 to 200 mL, depending on body size. The creation of a tracheostomy (surgical opening in the trachea) decreases anatomic dead space ventilation because air does not have to move through the nasal and oral airways. Alveolar dead space, normally about 5 to 10 mL, constitutes alveolar air that does not participate in gas exchange. When alveoli are ventilated but deprived of blood flow, they do not contribute to gas exchange and thereby constitute alveolar dead space.

The *physiologic dead space* includes both the anatomic dead space and the alveolar dead air space. In persons with normal respiratory function, physiologic dead space is about the same as anatomic dead space. Only in lung disease does physiologic dead space increase. Alveolar ventilation is equal to the minute ventilation minus the physiologic dead space ventilation.

Perfusion

The term *perfusion* is used to describe the flow of blood through the pulmonary capillary bed. The primary function of the pulmonary circulation is to move deoxygenated blood through the gas exchange portion of the lung. The pulmonary circulation serves several important functions in addition to gas exchange. It filters all the blood that moves from the right to the left side of the circulation, removes most of the thromboemboli that might form, and serves as a reservoir of blood for the left side of the heart.

The gas exchange function of the lungs requires a continuous flow of blood through the respiratory portion of the lungs. Deoxygenated blood enters the lung through the pulmonary artery, which has its origin in the right side of the heart and enters the lung at the hilus, along with the primary bronchus. The pulmonary arteries branch in a manner similar to that of the airways. The small pulmonary arteries accompany the bronchi as they move down the lobules and branch to supply the capillary network that surrounds the alveoli (see Fig. 21-7). The oxygenated capillary blood is collected in the small pulmonary veins of the lobules, and then it moves to the larger veins to be collected in the four large pulmonary veins that empty into the left atrium.

The pulmonary blood vessels are thinner, are more compliant, and offer less resistance to flow than those in the systemic circulation, and the pressures in the pulmonary system are much lower (e.g., 22/8 mm Hg versus 120/70 mm Hg). The low pressure and low resistance of the pulmonary circulation accommodate the delivery of varying amounts of blood from the systemic circulation without producing signs and symptoms of congestion. The volume in the pulmonary circulation is approximately 500 mL, with approximately 100 mL of this volume located in the pulmonary capillary bed. When the input of blood from the right heart and output of blood to the left heart are equal, pulmonary blood flow remains constant. Small differences between input and output can result in large changes in pulmonary volume if the differences continue for many heartbeats. The movement of blood through the pulmonary capillary bed requires that the mean pulmonary arterial pressure be greater than the mean pulmonary venous pressure. Pulmonary venous pressure increases in left-sided heart failure, allowing blood to accumulate in the pulmonary capillary bed and cause pulmonary edema (see Chapter 20).

Distribution of Blood Flow

As with ventilation, the distribution of pulmonary blood flow is affected by body position and gravity. In the upright position, the distance of the upper apices of the lung above the level of the heart may exceed the perfusion capabilities of the mean pulmonary arterial pressure (approximately 12 mm Hg); therefore, blood flow in the upper part of the lungs is less than that in the base or bottom part of the lungs (Fig. 21-16). In the supine position, the lungs and the heart are at the same level, and blood flow to the apices and base of the lungs becomes more uniform. In this position, however, blood flow to the posterior or dependent portions (e.g., bottom of the lung when lying on the side) exceeds flow in the anterior or nondependent portions of the lungs.

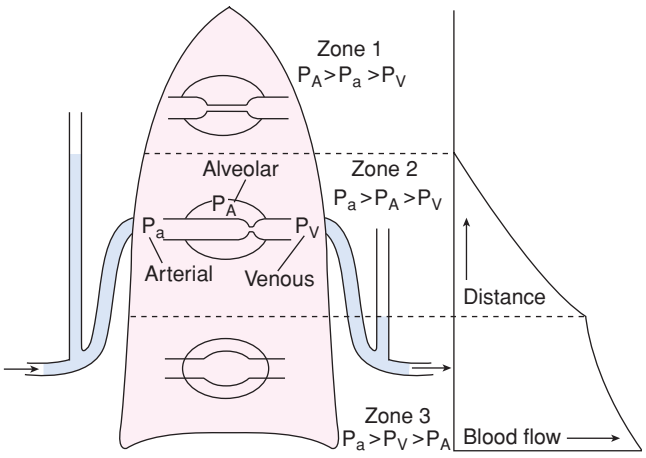


FIGURE 21-16. The uneven distribution of blood flow in the lung results from different pressures affecting the capillaries, which are affected by body position and gravity. (From West J.B. [2000]. *Respiratory physiology: The essentials* [p. 29]. Philadelphia: Lippincott Williams & Wilkins.)

Hypoxia-Induced Vasoconstriction

The blood vessels in the pulmonary circulation undergo marked vasoconstriction when they are exposed to hypoxia. When alveolar oxygen levels drop below 60 mm Hg, marked vasoconstriction may occur, and at very low oxygen levels, the local flow may be almost abolished. In regional hypoxia, as occurs with a localized airway obstruction (e.g., atelectasis), vasoconstriction is localized to a specific region of the lung. In this situation, vasoconstriction has the effect of directing blood flow away from the hypoxic regions of the lungs.

Generalized hypoxia causes vasoconstriction throughout all of the vessels of the lung. Generalized vasoconstriction occurs when the partial pressure of oxygen is decreased at high altitudes, or it can occur in persons with chronic hypoxia caused by lung disease. The vasoconstriction that accompanies prolonged hypoxia can lead to pulmonary hypertension and increased workload on the right heart. A low blood pH also produces vasoconstriction, especially when alveolar hypoxia is present (e.g., during circulatory shock).

Shunt

Shunt refers to blood that moves from the right to the left side of the circulation without being oxygenated. As with dead air space, there are two types of shunts: physiologic and anatomic. In an *anatomic shunt*, blood moves from the venous to the arterial side of the circulation without moving through the lungs. Anatomic intracardiac shunting of blood due to congenital heart defects is discussed in Chapter 19. In a *physiologic shunt*, there is mismatching of ventilation and perfusion within the lung, resulting in insufficient ventilation to provide the oxygen needed to oxygenate the blood flowing through the alveolar capillaries. Physiologic shunting of blood usually results from destructive lung disease that impairs ventilation or from heart failure that interferes with movement of blood through sections of the lungs.

Mismatching of Ventilation and Perfusion

The gas exchange properties of the lung depend on matching ventilation and perfusion, ensuring that equal amounts of air and blood are entering the respiratory portion of the lungs. Both dead air space and shunt produce a mismatching of ventilation and perfusion as depicted in Figure 21-17. With shunt (depicted on the left), there is perfusion without ventilation, resulting in a low ventilation–perfusion ratio. It occurs in conditions such as atelectasis in which there is airway obstruction (see Chapter 23). With dead air space (depicted on the right), there is ventilation without perfusion, resulting in a high ventilation–perfusion ratio. It occurs with conditions such as pulmonary embolism, which impairs blood flow to a part of the lung. The arterial blood leaving the pulmonary circulation reflects mixing of blood from normally ventilated and perfused areas of the lung as well as areas that are not ventilated (dead air space) or perfused (shunt). Many of the conditions that cause mismatching of ventilation and perfusion involve both dead air space and shunt. In chronic obstructive lung disease, for example, there may be impaired ventilation in one area of the lung and impaired perfusion in another area.

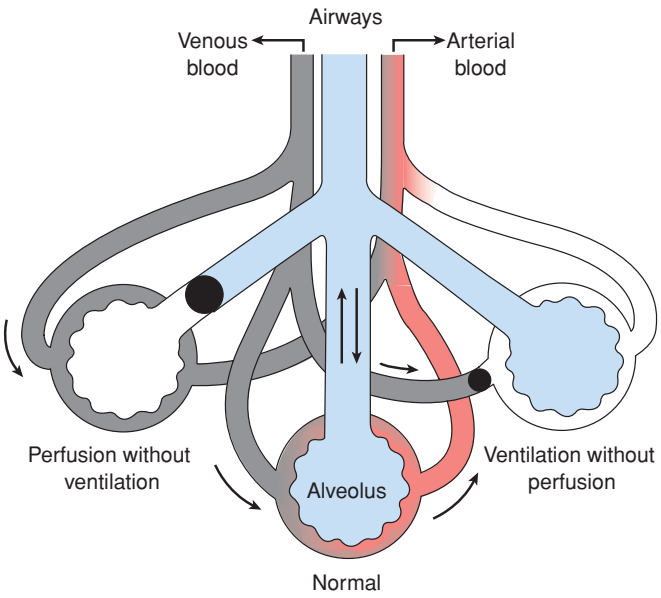


FIGURE 21-17. Matching of ventilation and perfusion. (*Center*) Normal matching of ventilation and perfusion; (*left*) perfusion without ventilation (i.e., shunt); (*right*) ventilation without perfusion (i.e., dead air space).

Matching of Ventilation and Perfusion

- Exchange of gases between the air in the alveoli and the blood in pulmonary capillaries requires a matching of ventilation and perfusion.
- Dead air space refers to the volume of air that is moved with each breath but does not participate in gas exchange. Anatomic dead space is that contained in the conducting airways that normally do not participate in gas exchange. Alveolar dead space results from alveoli that are ventilated but not perfused.
- Shunt refers to blood that moves from the right to the left side of the circulation without being oxygenated. With an anatomic shunt, blood moves from the venous to the arterial side of the circulation without going through the lungs. Physiologic shunting results from blood moving through unventilated parts of the lung.
- The blood oxygen level reflects the mixing of blood from alveolar dead space and physiologic shunting areas as it moves into the pulmonary veins.

Diffusion

Diffusion occurs in the respiratory portions of the lung and refers to the movement of gases across the alveolar–capillary membrane. Gas diffusion in the lung can be described by the *Fick law of diffusion*. The Fick law states that the volume of a gas ($\dot{V}$ gas) diffusing across the membrane per unit time is directly proportional to the difference in the pressure of the gas ($P_1 - P_2$), the surface area (SA) of the membrane, and the diffusion coefficient (D) of the gas, and is inversely proportional to the thickness (T) of the membrane (Fig. 21-18).

Several factors influence the diffusion of gases in the lung. The administration of high concentrations of oxygen increases the difference in partial pressure between the two sides of the membrane and increases the diffusion of the gas. Diseases that destroy lung tissue (i.e., surface area for diffusion) or increase the thickness of the alveolar–capillary membrane adversely influence the diffusing capacity of the lungs. The removal of one lung, for example, reduces the diffusing capacity by one half. The thickness of the alveolar–capillary membrane and the distance for diffusion are increased in persons with pulmonary edema or pneumonia. The characteristics of the gas and its molecular weight and solubility constitute the diffusion coefficient and determine how rapidly the gas diffuses through the respiratory membranes. For example, carbon dioxide diffuses 20 times more rapidly than oxygen because of its greater solubility in the respiratory membranes.

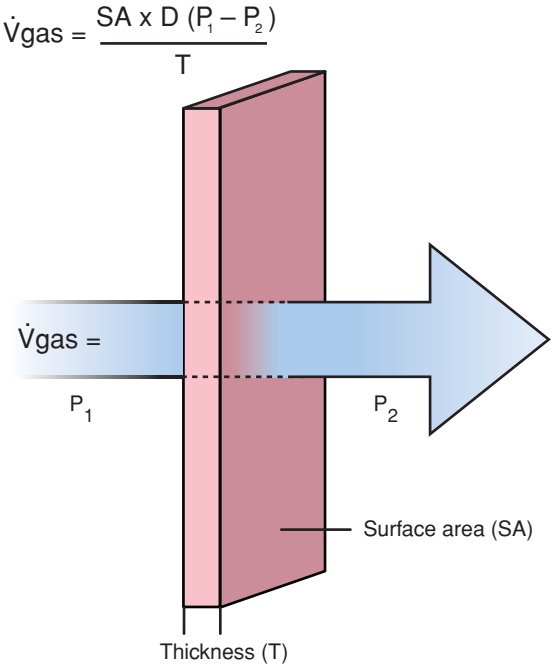


FIGURE 21-18. Fick laws of diffusion state that the diffusion of a gas ($\dot{V}$gas) across a sheet of tissue is directly related to the surface area (A) of the tissue, the diffusion constant (D) for the gas, and the partial pressure difference ($P_1 - P_2$) on either side of the tissue, and is inversely proportional to the thickness (T) of the tissue.

The diffusing capacity provides a measure of the rate of gas transfer in the lungs per partial pressure gradient. Because the initial alveolar–capillary difference for oxygen cannot be measured, carbon monoxide is used to determine the diffusing capacity. Carbon monoxide has several advantages: (1) its uptake is not limited by diffusion or blood flow, (2) there is essentially no carbon monoxide in venous blood, and (3) its affinity for hemoglobin is 210 times that of oxygen, ensuring that its partial pressure will remain essentially zero in the pulmonary capillary. The most common technique for making this measurement is the *single-breath test*. This test involves the inhalation of a single breath of dilute carbon monoxide (CO), followed by a breath-hold of 10 seconds. The diffusing capacity can be calculated using the lung volume and the percentage of CO in the alveoli at the beginning and end of the 10-second breath-hold.

Oxygen and Carbon Dioxide Transport

Although the lungs are responsible for the exchange of gases with the external environment, it is the blood that transports these gases between the lungs and body tissues. The blood carries oxygen and carbon dioxide in the physically dissolved state and in combination with hemoglobin. Carbon dioxide also is converted to bicarbonate and transported in that form.

Dissolved oxygen and carbon dioxide exert a partial pressure that is designated in the same manner as the partial pressure in the gas state. In the clinical setting, blood gas measurements are used to determine the partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) in the blood. Arterial blood commonly is used for measuring blood gases. Venous blood is not used because venous levels of oxygen and carbon dioxide reflect the metabolic demands of the tissues rather than the gas exchange function of the lungs. The PO_2 of arterial blood normally is above 80 mm Hg, and the PCO_2 is in the range of 35 to 45 mm Hg. Normally, the arterial blood gases are the same or nearly the same as the partial pressure of the gases in the alveoli. The arterial PO_2 often is written PaO_2, and the alveolar PO_2 as PAO_2, with the same types of designations being used for PCO_2. This text uses PO_2 and PCO_2 to designate both arterial and alveolar levels of the gases.

Oxygen Transport

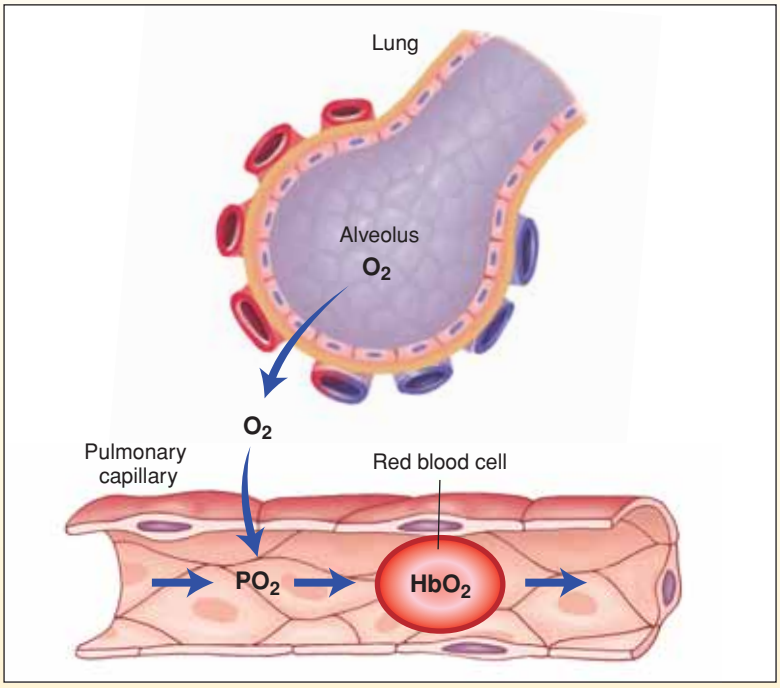
Oxygen is transported in two forms: (1) in chemical combination with hemoglobin and (2) in the dissolved state. Hemoglobin carries about 98% to 99% of oxygen in the blood and is the main transporter of oxygen. The remaining 1% to 2% of the oxygen is carried in the dissolved state. Only the dissolved form of oxygen (i.e., PO_2) passes through the capillary wall, diffuses through the cell membrane, and makes itself available for use in cell metabolism. The oxygen content of the blood (measured as mL of O_2 per deciliter [dL] or 100 mL of blood) includes the oxygen carried by hemoglobin and in the dissolved state.

UNDERSTANDING → Oxygen Transport

All body tissues rely on oxygen (O_2) that is transported in the blood to meet their metabolic needs. Oxygen is carried in two forms: dissolved and bound to hemoglobin. About 98% of O_2 is carried by hemoglobin and the remaining 2% is carried in the dissolved state. Dissolved oxygen is the only form that diffuses across cell membranes and produces a partial pressure (PO_2), which, in turn, drives diffusion. The transport of O_2 involves (1) transfer from the alveoli to the pulmonary capillaries in the lung, (2) hemoglobin binding and transport, and (3) the dissociation from hemoglobin in the tissue capillaries.

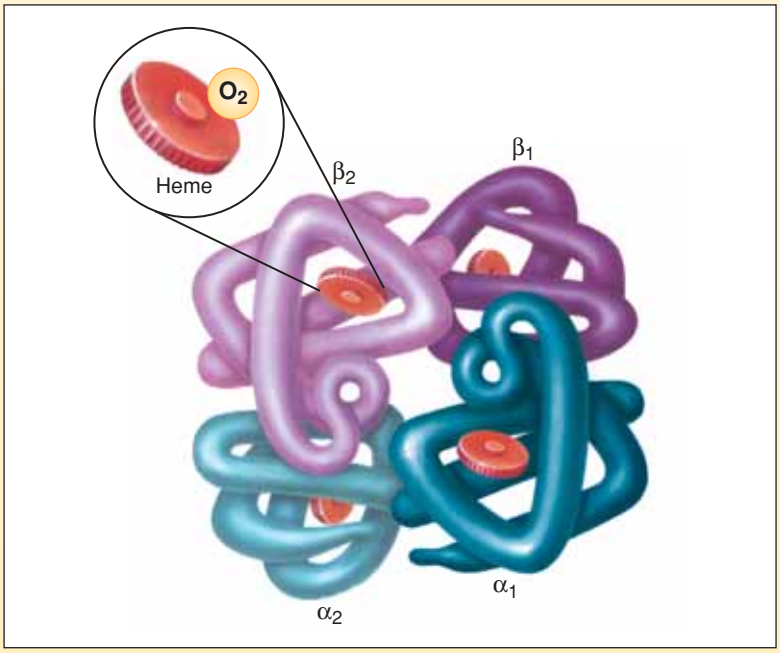
1

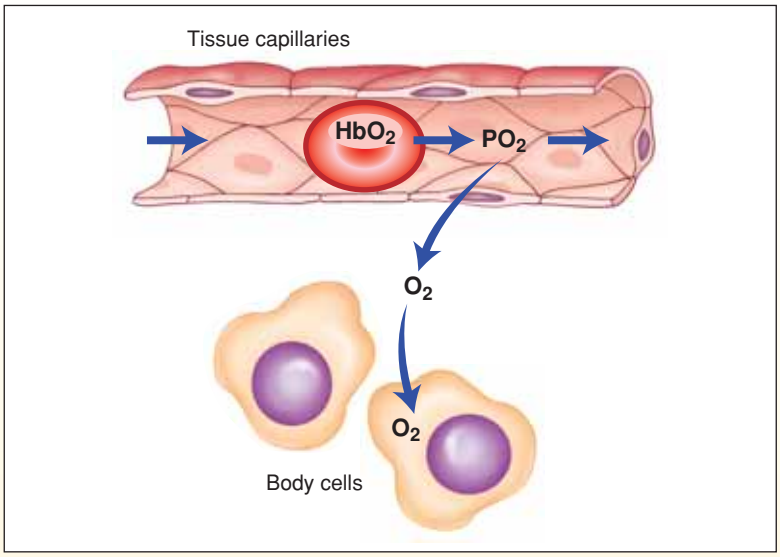
Alveoli-to-Capillary Transfer. In the lung, O_2 moves from the alveoli to the pulmonary capillaries as a dissolved gas. Its movement occurs along a concentration gradient, moving from the alveoli, where the PO_2 is about 100 mm Hg, to the venous end of the pulmonary capillaries with their lesser O_2 concentration and lower PO_2. The dissolved O_2 moves rapidly between the alveoli and the pulmonary capillaries, such that the PO_2 at the arterial end of the capillary is almost if not the same as that in the alveoli.



2

Hemoglobin Binding and Transport. Oxygen, which is relatively insoluble in plasma, relies on hemoglobin for transport in the blood. Once oxygen has diffused into the pulmonary capillary, it moves rapidly into the red blood cells and reversibly binds to hemoglobin to form HbO_2. The hemoglobin molecule contains four heme units, each capable of attaching an oxygen molecule. Hemoglobin is 100% saturated when all four units are occupied and is usually about 97% saturated in the systemic arterial blood. The capacity of the blood to carry O_2 is dependent both on hemoglobin levels and the ability of the lungs to oxygenate the hemoglobin.





Hemoglobin Transport. Hemoglobin is a highly efficient carrier of oxygen. Hemoglobin with bound oxygen is called *oxyhemoglobin*, and when oxygen is removed, it is called *deoxygenated* or *reduced hemoglobin*. Each gram of hemoglobin carries approximately 1.34 mL of oxygen when it is fully saturated. This means that a person with a hemoglobin level of 14 g/dL carries 18.8 mL of oxygen per dL (i.e., 1.34 × 14 g/dL hemoglobin) of blood.

In the lungs, oxygen moves across the alveolar–capillary membrane, through the plasma, and into the red blood cell, where it forms a loose and reversible bond with the hemoglobin molecule. In normal lungs, this process is rapid, so that even with a fast heart rate, the hemoglobin is almost completely saturated with oxygen during the short time it spends in the pulmonary capillaries. As the oxygen moves out of the capillaries in response to the needs of the tissues, the hemoglobin saturation, which usually is approximately 95% to 97% as the blood leaves the left side of the heart, drops to approximately 75% as the mixed venous blood returns to the right side of the heart.

Dissolved Oxygen. The partial pressure of oxygen represents the level of dissolved oxygen in plasma. The amount of dissolved oxygen that is carried in the plasma depends on its partial pressure and its solubility in the plasma. The PO_2 of the arterial blood normally ranges from 95 to 100 mm Hg when breathing room air at 1 atmosphere (760 mm Hg). The solubility of oxygen in plasma is fixed and very small. For every 1 mm Hg of PO_2 present, 0.03 mL of oxygen becomes dissolved in 1 dL of plasma. This means that at a normal arterial PO_2 of 95 mm Hg, about 0.29 mL of oxygen is dissolved in every dL of plasma. Therefore, the amount of oxygen transported in the dissolved state is very small, only about 3% of the total, as compared with the 97% transported by the hemoglobin.

Although the amount of oxygen carried in plasma under normal conditions is small, it can become a lifesaving mode of transport in cases of carbon monoxide poisoning, when most of the hemoglobin sites are occupied by carbon monoxide and are unavailable for transport of oxygen. The use of a hyperbaric chamber, in which 100% oxygen can be administered at high atmospheric pressures, increases the amount of oxygen that can be carried in the dissolved state.

Binding Affinity of Hemoglobin for Oxygen. The efficiency of the hemoglobin transport system depends on the ability of the hemoglobin molecule to bind oxygen in the lungs and release it as it is needed in the tissues. Oxygen that remains bound to hemoglobin cannot participate in tissue metabolism. The term *affinity* refers to hemoglobin's ability to bind oxygen. Hemoglobin binds oxygen more readily when its affinity is increased and releases it more readily when its affinity is decreased.

The hemoglobin molecule is composed of four polypeptide chains with an iron-containing heme group (see Chapter 13, Fig. 13-2). Because oxygen binds to the iron atom, each hemoglobin molecule can bind four molecules of oxygen when it is fully saturated. Oxygen binds cooperatively with the heme groups on the hemoglobin molecule. After the first molecule of oxygen binds to a heme group, the hemoglobin molecule undergoes a change in shape. As a result, the second and third molecules of oxygen bind more readily, and binding of the fourth molecule is even easier. In a like manner, the unloading of the first molecule of oxygen enhances the unloading of the next molecule and so on. Thus, the affinity of hemoglobin for oxygen changes with hemoglobin saturation.

Hemoglobin's affinity for oxygen is also influenced by pH, carbon dioxide concentration, and body temperature. It binds oxygen more readily under conditions of increased pH (alkalosis), decreased carbon dioxide concentration, and decreased body temperature and it releases it more readily under conditions of decreased pH (acidosis), increased carbon dioxide concentration, and fever. For example, increased tissue metabolism generates carbon dioxide and metabolic acids and thereby decreases the affinity of hemoglobin for oxygen. Heat also is a by-product of tissue metabolism, explaining the effect of fever on oxygen binding.

Red blood cells contain a metabolic intermediate called *2,3-diphosphoglycerate (2,3-DPG)* that also affects the affinity of hemoglobin for oxygen. An increase in 2,3-DPG enhances unloading of oxygen from hemoglobin at the tissue level. Conditions that increase 2,3-DPG include exercise, hypoxia that occurs at high altitude, and chronic lung disease.

The Oxygen–Hemoglobin Dissociation Curve. The relationship between the oxygen carried in combination with hemoglobin and the PO_2 of the blood is described by the *oxygen–hemoglobin dissociation curve*, which is shown in Figure 21-19. The *x* axis of the graph depicts the PO_2 or dissolved oxygen. It reflects the partial pressure of oxygen in the lungs (i.e., the PO_2 ranges from 95 to 100 mm Hg when breathing room air, but can rise to 200 mm Hg or higher when oxygen-enriched air is breathed). The *y* axis on the left depicts hemoglobin saturation or the amount of oxygen that is carried by hemoglobin. The right *y* axis depicts oxygen content or total amount of oxygen (i.e., mL O_2/dL) that is being carried in the blood.

The S-shaped oxygen dissociation curve has a flat top portion representing binding of oxygen to hemoglobin in the lungs and a steep portion representing its release into the tissue capillaries (Fig. 21-19A). The S shape of the curve reflects the effect that oxygen saturation has on the conformation of the hemoglobin molecule and its affinity for oxygen. At approximately 100 mm Hg PO_2, a plateau occurs, at which point the hemoglobin is approximately 98% saturated. Increasing the alveolar PO_2 above this level does not increase the hemoglobin saturation. Even at high altitudes, when the partial pressure of oxygen is considerably decreased, the hemoglobin remains relatively well saturated. At 60 mm Hg PO_2, for example, the hemoglobin is still approximately 89% saturated.

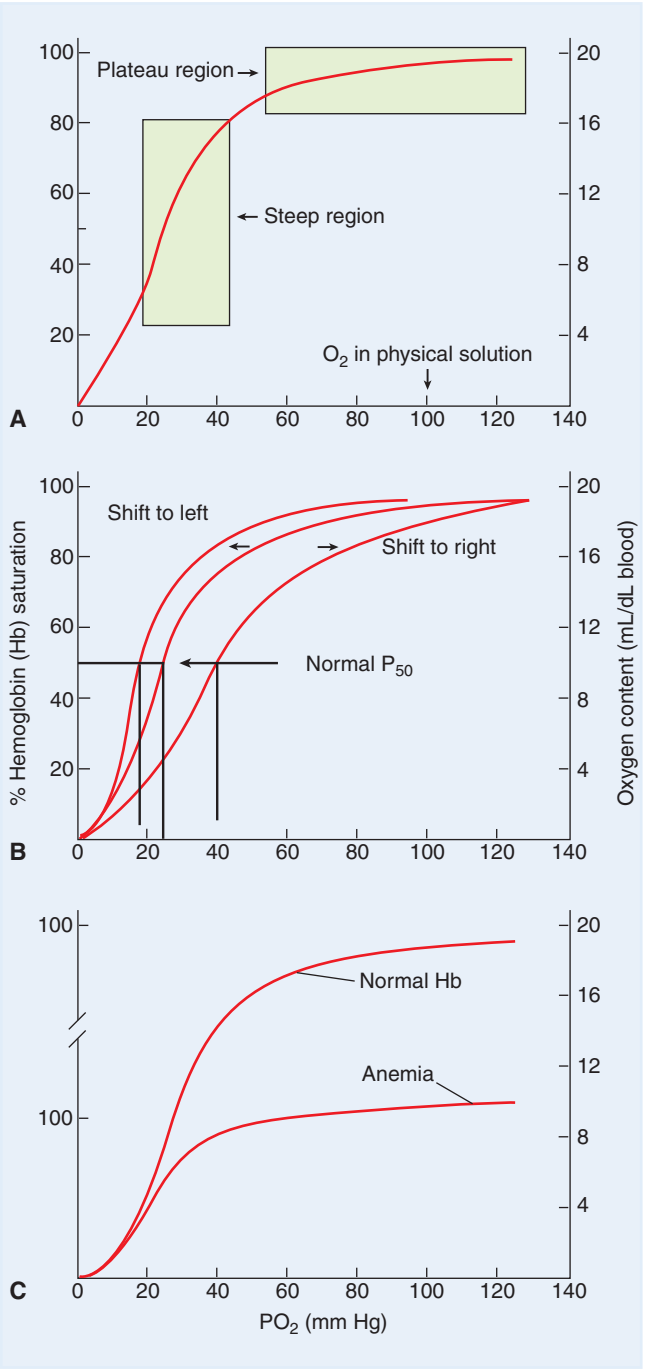


FIGURE 21-19. Oxygen–hemoglobin dissociation curve. **(A)** Left boxed area represents the steep portion of the curve where oxygen is released from hemoglobin (Hb) to the tissues, and the top boxed area the plateau of the curve where oxygen is loaded onto hemoglobin in the lung. P_{50} is the partial pressure of oxygen required to saturate 50% of hemoglobin with oxygen. **(B)** The effect of body temperature, arterial PCO_2, and pH on hemoglobin affinity for oxygen as indicated by a shift in the curve and position of the P_{50}. A shift of the curve to the right due to an increase in temperature or PCO_2 or a decrease in pH favors release of oxygen to the tissues. A decrease in temperature or PCO_2 or an increase in pH shifts the curve to the left. **(C)** Effect of anemia on the oxygen-carrying capacity of blood. The hemoglobin can be completely saturated, but the oxygen content of the blood is reduced. (Adapted from Rhoades R.A., Tanner G.A. [1996]. *Medical physiology.* Boston: Little, Brown.)

The steep portion of the dissociation curve—between 60 and 40 mm Hg—represents the removal of oxygen from hemoglobin as it moves through the tissue capillaries. This portion of the curve reflects the fact that there is considerable transfer of oxygen from hemoglobin to the tissues with only a small drop in PO_2, thereby ensuring a gradient for oxygen to move into body cells. The tissues normally remove approximately 5 mL of oxygen per dL of blood, and the hemoglobin of mixed venous blood is approximately 75% saturated as it returns to the right side of the heart. In this portion of the dissociation curve (saturation <75%), the rate at which oxygen is released from hemoglobin is determined largely by tissue uptake. During strenuous exercise, for example, the muscle cells may remove as much as 15 mL of oxygen per dL of blood from hemoglobin.

Hemoglobin can be regarded as a buffer system that regulates the delivery of oxygen to the tissues. In order to function as a buffer system, the affinity of hemoglobin for oxygen must change with the metabolic needs of the tissues. This change is represented by a shift to the right or left in the dissociation curve (Fig. 21-19B). A shift to the right indicates that the tissue PO_2 is greater for any given level of hemoglobin saturation and represents reduced affinity of the hemoglobin for oxygen at any given PO_2. It usually is caused by conditions that produce an increase in tissue metabolism, such as fever or acidosis, or by an increase in PCO_2. High altitude and conditions such as pulmonary insufficiency, heart failure, and severe anemia also cause the oxygen dissociation curve to shift to the right. A shift to the left in the oxygen dissociation curve represents an increased affinity of hemoglobin for oxygen and occurs in situations associated with a decrease in tissue metabolism, such as alkalosis, decreased body temperature, and decreased PCO_2 levels. The degree of shift can be determined by the P_{50}, or the partial pressure of oxygen that is needed to achieve a 50% saturation of hemoglobin. Returning to Figure 21-19B, the dissociation curve on the left has a P_{50} of approximately 20 mm Hg; the normal curve, a P_{50} of 26; and the curve on the right, a P_{50} of 39 mm Hg.

The oxygen content (measured in mL/dL of blood) represents the total amount of oxygen that is carried in the blood, including the dissolved oxygen and that carried by the hemoglobin (Fig. 21-19C). It is the oxygen content of the blood rather than the PO_2 or hemoglobin saturation that determines the amount of oxygen that is carried in the blood and delivered to the tissues. Thus, an anemic person may have a normal PO_2 and hemoglobin saturation level but decreased oxygen content because of the lower amount of hemoglobin for binding oxygen.

Carbon Dioxide Transport

Carbon dioxide is transported in the blood in three forms (see Chapter 8, Understanding Carbon Dioxide Transport): as dissolved carbon dioxide (10%), attached to hemoglobin (30%), and as bicarbonate (60%). Acid-base balance is influenced by the amount of dissolved carbon dioxide and the bicarbonate level in the blood.

As carbon dioxide is formed during the metabolic process, it diffuses out of cells into the tissue spaces and then into the capillaries. The amount of dissolved carbon dioxide that can be carried in plasma is determined by the partial pressure of the gas and its solubility coefficient (0.03 mL/dL/mm Hg PCO_2). Carbon dioxide is 20 times more soluble in plasma than oxygen. Thus, the dissolved state plays a greater role in transport of carbon dioxide compared with oxygen.

Most of the carbon dioxide diffuses into the red blood cells, where it either forms carbonic acid or combines with hemoglobin. *Carbonic acid* (H_2CO_3) is formed when carbon dioxide combines with water ($CO_2 + H_2O = H^+ + HCO_3^-$). The process is catalyzed by an enzyme called *carbonic anhydrase*, which is present in large quantities in red blood cells. Carbonic anhydrase increases the rate of the reaction between carbon dioxide and water approximately 5000-fold. Carbonic acid readily ionizes to form bicarbonate (HCO_3^-) and hydrogen (H^+) ions. The hydrogen ions combine with the hemoglobin, which is a powerful acid-base buffer, and the bicarbonate ion diffuses into plasma in exchange for a chloride ion. This exchange is made possible by a special bicarbonate-chloride carrier protein in the red blood cell membrane. As a result of the bicarbonate-chloride shift, the chloride and water content of the red blood cell is greater in venous blood than in arterial blood.

In addition to the carbonic anhydrase–mediated reaction with water, carbon dioxide reacts directly with hemoglobin to form *carbaminohemoglobin*. The combination of carbon dioxide with hemoglobin is a reversible reaction that involves a loose bond, which allows transport of carbon dioxide from tissues to the lungs, where it is released into the alveoli for exchange with the external environment. The release of oxygen from hemoglobin in the tissues enhances the binding of carbon dioxide to hemoglobin; in the lungs, the combining of oxygen with hemoglobin displaces carbon dioxide. The binding of carbon dioxide to hemoglobin is determined by the acidic nature of hemoglobin. Binding with carbon dioxide causes the hemoglobin to become a stronger acid. In the lungs, the highly acidic hemoglobin has lesser tendency to form carbaminohemoglobin, and carbon dioxide is released from hemoglobin into the alveoli. In the tissues, the release of oxygen from hemoglobin causes hemoglobin to become less acid, thereby increasing its ability to combine with carbon dioxide and form carbaminohemoglobin.

In summary, the primary functions of the lungs are oxygenation of the blood and removal of carbon dioxide. Pulmonary gas exchange is conventionally divided into three processes: ventilation or the flow of gases into the alveoli of the lungs; perfusion, or movement of blood through the adjacent pulmonary capillaries; and diffusion, or transfer of gases between the alveoli and the pulmonary capillaries.

Ventilation is the movement of air between the atmosphere and the lungs. Pulmonary ventilation refers to the total exchange of gases between the atmosphere and the lungs, and alveolar ventilation refers to ventilation in the gas exchange portion of the lungs. The distribution of

alveolar ventilation and pulmonary capillary blood flow varies with lung volume and body position. The efficiency of gas exchange requires matching of ventilation and perfusion so that equal amounts of air and blood enter the respiratory portion of the lungs. Two factors—dead air space and shunt—interfere with matching of ventilation and perfusion and do not contribute to gas exchange. Dead air space occurs when areas of the lungs are ventilated but not perfused. Shunt is the condition under which areas of the lungs are perfused but not ventilated.

The diffusion of gases in the lungs is influenced by four factors: the surface area available for diffusion; the thickness of the alveolar–capillary membrane, through which the gases diffuse; the differences in the partial pressure of the gas on either side of the membrane; and the diffusion characteristics of the gas.

The blood transports oxygen to the cells and returns carbon dioxide to the lungs. Oxygen is transported in two forms: in chemical combination with hemoglobin and physically dissolved in plasma (PO_2). Hemoglobin is an efficient carrier of oxygen, and approximately 97% of oxygen is transported in this manner. It is the oxygen content of the blood (the dissolved oxygen and that carried by the hemoglobin) rather than the PO_2 or hemoglobin saturation that determines the amount of oxygen that is carried in the blood and delivered to the tissues. Carbon dioxide is carried in three forms: carbaminohemoglobin (30%), dissolved carbon dioxide (10%), and bicarbonate (60%).

Control of Breathing

Unlike the heart, which has inherent rhythmic properties and can beat independently of the nervous system, the muscles that control respiration require continuous input from the nervous system. Movement of the diaphragm, intercostal muscles, sternocleidomastoid, and other accessory muscles that control ventilation is integrated by neurons located in the pons and medulla. These neurons are collectively referred to as the *respiratory center* (Fig. 21-20).

Respiratory Center

The respiratory center consists of two dense, bilateral aggregates of respiratory neurons involved in initiating inspiration and expiration and incorporating afferent impulses into motor responses of the respiratory muscles. The first, or dorsal, group of neurons in the respiratory center is concerned primarily with inspiration. These neurons control the activity of the phrenic nerves that innervate the diaphragm and drive the second, or ventral, group of respiratory neurons. They are thought to integrate sensory input from the lungs and airways into the ventilatory response. The second group of neurons, which contains inspiratory and expiratory neurons, controls the spinal motor neurons of the intercostal and abdominal muscles.

The pacemaker properties of the respiratory center result from the cycling of the two groups of respiratory

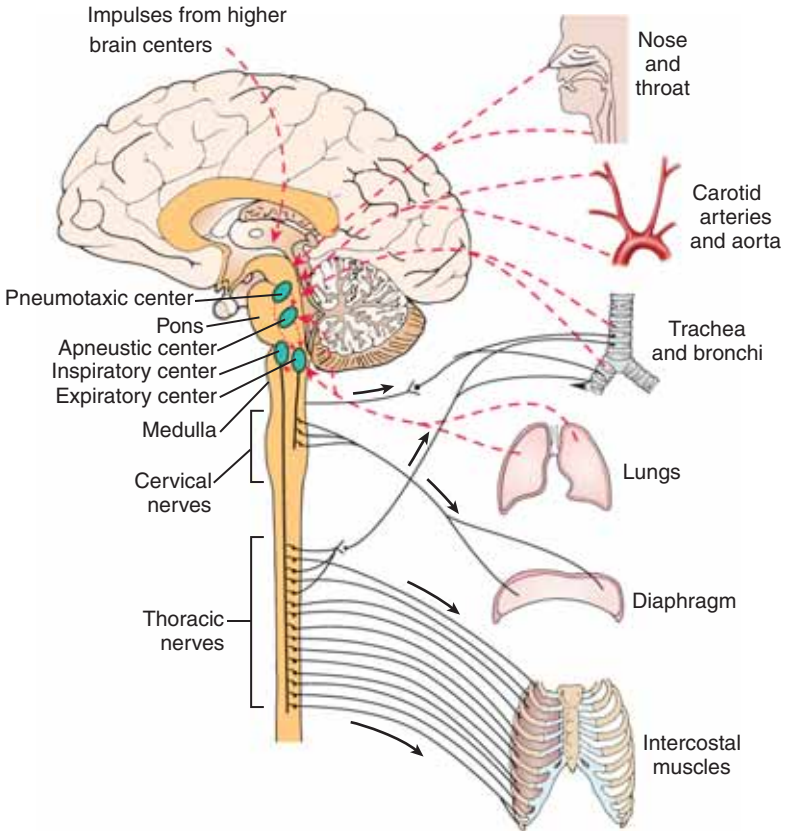


FIGURE 21-20. Schematic representation of activity in the respiratory center. Impulses traveling over afferent neurons (*dashed lines*) communicate with central neurons, which activate efferent neurons that supply the muscles of respiration. Respiratory movements can be altered by a variety of stimuli.

neurons: the *pneumotaxic center* in the upper pons and the *apneustic center* in the lower pons (Fig. 21-20). These two groups of neurons contribute to the function of the respiratory center in the medulla. The apneustic center has an excitatory effect on inspiration, tending to prolong inspiration. The pneumotaxic center switches inspiration off, assisting in the control of respiratory rate and inspiratory volume. Brain injury, which damages the connections between the pneumotaxic and apneustic centers, results in an irregular breathing pattern that consists of prolonged inspiratory gasps interrupted by expiratory efforts.

Axons from the neurons in the respiratory center cross in the midline and descend in the ventrolateral columns of the spinal cord. The tracts that control expiration and inspiration are spatially separated in the cord, as are the tracts that transmit specialized reflexes (i.e., coughing and hiccuping) and voluntary control of ventilation. Only at the level of the spinal cord are the respiratory impulses integrated to produce a reflex response.

Regulation of Breathing

The control of breathing has both automatic and voluntary components. The automatic regulation of ventilation is controlled by input from two types of sensors or receptors: chemoreceptors and lung and chest wall receptors. Chemoreceptors monitor blood levels of oxygen, carbon dioxide, and pH and adjust ventilation to meet the changing metabolic needs of the body. Lung receptors monitor breathing patterns and lung function. Receptors in the joints, tendons, and muscles of chest wall structures may also play a role in breathing, particularly when quiet breathing is called for or when breathing efforts are opposed by increased airway resistance or reduced lung compliance.

Voluntary regulation of ventilation integrates breathing with voluntary acts such as speaking, blowing, and singing. These acts, which are initiated by the motor and premotor cortex, cause a temporary suspension of automatic breathing. The automatic and voluntary components of respiration are regulated by afferent impulses that are transmitted to the respiratory center from a number of sources. Afferent input from higher brain centers is evidenced by the fact that a person can consciously alter the depth and rate of respiration. Fever, pain, and emotion exert their influence through lower brain centers. Vagal afferents from sensory receptors in the lungs and airways are integrated in the dorsal area of the respiratory center.

Chemoreceptors

The needs of body tissues for oxygen and the removal of carbon dioxide are regulated by chemoreceptors that monitor blood levels of these gases. Input from these sensors is transmitted to the respiratory center, and ventilation is adjusted to maintain the arterial blood gases within a normal range. There are two types of chemoreceptors: central and peripheral. The central chemoreceptors are located in the brain stem and the peripheral chemoreceptors in the carotid arteries and aorta.

Ventilatory drive is exquisitely sensitive to the PCO_2 levels of the blood perfusing the *central chemoreceptors*. These receptors are located in chemosensitive regions near the respiratory center in the medulla and are bathed in cerebrospinal fluid (CSF). Although the central chemoreceptors monitor carbon dioxide levels, the actual stimulus for these receptors is provided by hydrogen ions in the CSF. The CSF is separated from the blood by the blood-brain barrier, which permits free diffusion of carbon dioxide but not hydrogen ions. For this reason, changes in the pH of the blood have considerably less effect in stimulating ventilation than carbon dioxide, which stimulates the central chemoreceptors indirectly by changing the hydrogen ion concentration of the CSF. This occurs as the carbon dioxide that crosses the blood-brain barrier rapidly combines with water to form carbonic acid, which then dissociates into bicarbonate and hydrogen ions; with the hydrogen ions producing a direct stimulating effect on respiration. The central chemoreceptors are extremely sensitive to short-term changes in blood PCO_2 levels. An increase in the PCO_2 of the blood produces an increase in ventilation that reaches its peak within a minute or so and then declines if the PCO_2 level remains elevated. Thus, persons with chronically elevated blood PCO_2 levels no longer respond to this stimulus increased ventilation but rely on the stimulus provided by a decrease in arterial PO_2 levels that is sensed by the peripheral chemoreceptors.

The *peripheral chemoreceptors*, which are located in the bifurcation of the common carotid arteries and in the arch of the aorta, monitor arterial PO_2 levels. Although the peripheral chemoreceptors also monitor changes in PCO_2 and pH, they play a much more important role in monitoring PO_2 levels. These receptors exert little control over ventilation until the PO_2 has dropped below 60 mm Hg. Thus, hypoxia is the main stimulus for ventilation in persons with chronically elevated levels of carbon dioxide. If these patients are given oxygen therapy at a level sufficient to increase the PO_2 above that needed to stimulate the peripheral chemoreceptors, their ventilation may be seriously depressed.

Lung Receptors

Lung receptors monitor the status of breathing in terms of airway resistance and lung expansion. There are three types of lung receptors: stretch, irritant, and juxtacapillary receptors.

Stretch receptors are located in the smooth muscle layers of the conducting airways. They respond to changes in pressure in the walls of the airways. When the lungs are inflated, these receptors inhibit inspiration and promote expiration. They are important in establishing breathing patterns and minimizing the work of breathing by adjusting respiratory rate and TV to accommodate changes in lung compliance and airway resistance.

The *irritant receptors* are located between the airway epithelial cells. They are stimulated by noxious gases, cigarette smoke, inhaled dust, and cold air. Stimulation of the irritant receptors leads to airway constriction and a pattern of rapid, shallow breathing. This pattern of

breathing probably protects respiratory tissues from the damaging effects of toxic inhalants. It also is thought that the mechanical stimulation of these receptors may ensure more uniform lung expansion by initiating periodic sighing and yawning. It is possible that these receptors are involved in the bronchoconstriction response that occurs in some persons with bronchial asthma.

The *juxtacapillary* or *J receptors* are located in the alveolar wall, close to the pulmonary capillaries. It is thought that these receptors sense lung congestion. These receptors may be responsible for the rapid, shallow breathing that occurs with pulmonary edema, pulmonary embolism, and pneumonia.

Cough Reflex

Coughing is a neurally mediated reflex that protects the lungs from the accumulation of secretions and from entry of irritating and destructive substances. It is one of the primary defense mechanisms of the respiratory tract. The cough reflex is initiated by receptors located in the tracheobronchial wall; these receptors are extremely sensitive to irritating substances and to the presence of excess secretions. Afferent impulses from these receptors are transmitted through the vagus to the medullary center, which integrates the cough response.

Coughing requires the rapid inspiration of a large volume of air (usually about 2.5 L), followed by rapid closure of the glottis and forceful contraction of the abdominal and expiratory muscles. As these muscles contract, intrathoracic pressures are elevated to levels of 100 mm Hg or more. The rapid opening of the glottis at this point leads to an explosive expulsion of air.

Many conditions can interfere with the cough reflex and its protective function. The reflex is impaired in persons whose abdominal or respiratory muscles are weak. This problem can be caused by disease conditions that lead to muscle weakness or paralysis, by prolonged inactivity, or as an outcome of surgery involving these muscles. Bed rest interferes with expansion of the chest and limits the amount of air that can be taken into the lungs in preparation for coughing, making the cough weak and ineffective. Disease conditions that prevent effective closure of the glottis and laryngeal muscles interfere with production of the marked increase in intrathoracic pressure that is needed for effective coughing. For example, the presence of a nasogastric tube may prevent closure of the upper airway structures and may fatigue the receptors for the cough reflex that are located in the area. The cough reflex also is impaired when there is depressed function of the medullary centers in the brain that integrate the cough reflex. Interruption of the central integration aspect of the cough reflex can arise as a result of disease of this part of the brain or the action of drugs that depress the cough center.

Although the cough reflex is a protective mechanism, frequent and prolonged coughing can be exhausting and painful and can have undesirable effects on the cardiovascular and respiratory systems and on the elastic tissues of the lungs. This is particularly true in young children and elderly persons.

Dyspnea

Dyspnea is a subjective sensation or a person's perception of difficulty in breathing that includes the perception of labored breathing and the reaction to that sensation. The terms *dyspnea*, *breathlessness*, and *shortness of breath* often are used interchangeably. Dyspnea is observed in at least three major cardiopulmonary disease states: primary lung diseases such as pneumonia, asthma, and emphysema; heart disease that is characterized by pulmonary congestion; and neuromuscular disorders such as myasthenia gravis and muscular dystrophy that affect the respiratory muscles. Although dyspnea commonly is associated with respiratory disease, it also occurs during exercise, particularly in untrained persons.

The cause of dyspnea is unknown. Four types of mechanisms have been proposed to explain the sensation: stimulation of lung receptors; increased sensitivity to changes in ventilation perceived through central nervous system mechanisms; reduced ventilatory capacity or breathing reserve; and stimulation of neural receptors in the muscle fibers of the intercostals and diaphragm and of receptors in the skeletal joints. The first of the suggested mechanisms is stimulation of lung receptors. These receptors are stimulated by the contraction of bronchial smooth muscle, the stretch of the bronchial wall, pulmonary congestion, and conditions that decrease lung compliance. The second category of proposed mechanisms focuses on central nervous system mechanisms that transmit information to the cortex regarding respiratory muscle weakness or a discrepancy between the increased effort of breathing and inadequate respiratory muscle contraction. The third type of mechanism focuses on a reduction in ventilatory capacity or breathing reserve. A reduction in breathing reserve (i.e., maximum voluntary ventilation not being used during a given activity) to less than 65% to 75% usually correlates well with dyspnea. The fourth possible mechanism is stimulation of muscle and joint receptors in the respiratory musculature because of a discrepancy in the tension generated by these muscles and the TV that results. These receptors, once stimulated, transmit signals that bring about an awareness of the breathing discrepancy. Like other subjective symptoms, such as fatigue and pain, dyspnea is difficult to quantify because it relies on a person's perception of the problem.

The most common method for measuring dyspnea is a retrospective determination of the level of daily activity at which a person experiences dyspnea. Several scales are available for this use. One of these uses four dimensions (dyspnea, fatigue, emotional function, breathing mastery) of dyspnea to evaluate disability. The visual analog scale may be used to assess breathing difficulty that occurs with a given activity, such as walking a certain distance. The visual analog scale consists of a line (often 10 cm in length) with descriptors such as "easy to breathe" on one end and "very difficult to breathe" on the other. The person being assessed selects a point on the scale that describes his or her perceived dyspnea. It also can be used to assess dyspnea over time.

The treatment of dyspnea depends on the cause. For example, persons with impaired respiratory function may require oxygen therapy, and those with pulmonary

edema may require measures to improve heart function. Methods to decrease anxiety, breathing retraining, and energy conservation measures may be used to decrease the subjective sensation of dyspnea.

In summary, the respiratory system requires continuous input from the nervous system. Movement of the diaphragm, intercostal muscles, and other respiratory muscles is controlled by neurons of the respiratory center located in the pons and medulla. The control of breathing has both automatic and voluntary components. The automatic regulation of ventilation is controlled by two types of receptors: lung receptors, which protect respiratory structures, and chemoreceptors, which monitor the gas exchange function of the lungs by sensing changes in blood levels of carbon dioxide, oxygen, and pH. There are three types of lung receptors: stretch receptors, which monitor lung inflation; irritant receptors, which protect against the damaging effects of toxic inhalants; and J receptors, which are thought to sense lung congestion. There are two groups of chemoreceptors: central and peripheral. The central chemoreceptors are the most important in sensing changes in carbon dioxide levels, and the peripheral chemoreceptors function in sensing arterial blood oxygen levels.

Voluntary respiratory control is needed for integrating breathing and actions such as speaking, blowing, and singing. These acts, which are initiated by the motor and premotor cortex, cause temporary suspension of automatic breathing. The cough reflex protects the lungs from the accumulation of secretions and from the entry of irritating and destructive substances; it is one of the primary defense mechanisms of the respiratory tract. Dyspnea is a subjective sensation of difficulty in breathing that is seen in cardiac, pulmonary, and neuromuscular disorders that affect the respiratory muscles. It can also occur during strenuous work and exercise in healthy persons.

REVIEW EXERCISES

1. Use the solubility coefficient for oxygen and the oxygen–hemoglobin dissociation curve depicted in Figure 21-19 to answer the following questions:

A. What is the hemoglobin saturation at a high altitude in which the barometric pressure is 500 mm Hg (consider oxygen to represent 21% of the total gases)?

B. It is usually recommended that the hemoglobin saturation of persons with chronic lung disease be maintained at about 89% when they are receiving supplemental low-flow oxygen. What would their PO_2 be at this level of hemoglobin saturation, and what is the rationale for keeping the PO_2 at this level?

C. What is the oxygen content of a person with a hemoglobin level of 6 g/dL who is breathing room air?

D. What is the oxygen content of a person with carbon monoxide poisoning who is receiving 100% oxygen at 3 atmospheres pressure in a hyperbaric chamber? Consider that most of the person's hemoglobin is saturated with carbon monoxide.

BIBLIOGRAPHY

Berne R.M., Levy M.N., Koeppen B.M., et al. (2004). *Physiology* (5th ed., pp. 443–520). Philadelphia: Elsevier Saunders.

Carrieri-Kohlman V., Stulbarg M. (2003). Dyspnea. In Carrieri-Kohlman V., Linsey A.M., West C.M. *Pathophysiological phenomena in nursing.* (3rd ed., pp. 175–207). Philadelphia: Saunders.

Cole F.S. (2003). Surfactant protein B: Unambiguously necessary for adult pulmonary function. *American Journal of Physiology: Lung and Cell Molecular Physiology* 285, L540–L545.

Crapo R.O. (1994). Pulmonary function testing. *New England Journal of Medicine* 331, 25–30.

DeTroyer A., Kirkwood P.A., Wilson T.A. (2005). Respiratory action of inspiratory muscles. *Physiology Reviews* 85, 717–756.

Ganong W.F. (2005). *Review of medical physiology* (22nd ed., pp. 647–697). New York: Lange Medical Books/McGraw-Hill.

Guyton A., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 471–522). Philadelphia: Elsevier Saunders.

Hills B.A. (1999). An alternative view of the role(s) of surfactant and the alveolar model. *Journal of Applied Physiology* 87(5), 1567–1583.

Junqueira L.C., Carneiro J., Kelly R.O. (2005). *Basic histology* (11th ed., pp. 340–357). New York: Appleton & Lange.

Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 97–135). Philadelphia: Lippincott Williams & Wilkins.

Prabhakar N.R., Peng Y-J. (2004). Peripheral chemoreceptors in health and disease. *Journal of Applied Physiology* 96, 359–366.

Rhoades R.A., Tanner G.A. (2003). *Medical physiology* (2nd ed., pp. 309–375). Philadelphia: Lippincott Williams & Wilkins.

Ross M.H., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 612–644). Philadelphia: Lippincott Williams & Wilkins.

West J.B. (2008). *Respiratory physiology: The essentials* (8th ed.). Philadelphia: Lippincott Williams & Wilkins.

Whitsett J.A., Weaver T.E. (2002). Hydrophobic surfactant proteins in lung function and disease. *New England Journal of Medicine* 347(26), 2141–2148.

Wright J.R. (2005). Immunoregulatory functions of surfactant proteins. *Nature Reviews Immunology* 5(1), 58–68.

Respiratory Tract Infections
The Common Cold
Rhinosinusitis
Clinical Features
Influenza
Etiology
Pathogenesis
Clinical Features
Influenza Immunization
Pneumonias
Classification
Acute Bacterial (Typical) Pneumonia
Primary Atypical Pneumonia
Tuberculosis
Etiology
Pathogenesis
Primary Tuberculosis
Secondary Tuberculosis
Diagnosis and Treatment
Fungal Infections
Types of Infections
Clinical Features
Cancer of the Lung
Types of Lung Cancer
Small Cell Lung Cancer
Non–Small Cell Lung Cancers
Clinical Features
Manifestations
Diagnosis and Treatment
Respiratory Disorders in Children
Lung Development
Ventilation in the Neonate
Airway Resistance
Lung Volumes and Gas Exchange
Control of Ventilation
Alterations in Breathing Patterns
Respiratory Disorders in the Neonate
Respiratory Distress Syndrome
Bronchopulmonary Dysplasia
Respiratory Infections in Children
Upper Airway Infections
Lower Airway Infections
Signs of Impending Respiratory Failure

Chapter 22

Respiratory Tract Infections, Neoplasms, and Childhood Disorders

Respiratory illnesses represent one of the more common reasons for visits to the physician, admission to the hospital, and forced inactivity among all age groups. The common cold, although not usually serious, results in missed work and school days. Pneumonia and influenza are ranked as the eighth leading cause of death in the United States.[1] Tuberculosis remains one of the deadliest diseases in the world. In addition to microbial pathogens, cigarette smoking contributes significantly to disorders of the respiratory tract, including lung cancer. The content in this chapter is divided into three sections: respiratory tract infections, cancer of the lung, and respiratory disorders in children.

Respiratory Tract Infections

Respiratory tract infections can involve the upper respiratory tract (i.e., nose, oropharynx, and larynx), the lower respiratory tract (i.e., lower airways and lungs), or the upper and lower airways. The discussion in this section of the chapter focuses on the common cold, rhinosinusitis, influenza, pneumonia, tuberculosis, and fungal infections of the lung. Acute respiratory infections in children are discussed in the last section of the chapter.

The respiratory tract is susceptible to infectious processes caused by many different types of microorganisms. For the most part, the signs and symptoms of respiratory tract infections depend on the function of the structure involved, the severity of the infectious process, and the person's age and general health status.

Viruses are the most frequent cause of respiratory tract infections. They can cause infections ranging from a self-limited cold to life-threatening pneumonia. Moreover, viral infections can damage the bronchial epithelium, obstruct airways, and lead to secondary bacterial infections. Each viral species has its own pattern of

respiratory tract involvement. The rhinoviruses grow best at 33°C and remain strictly confined to the upper respiratory tract.[2] The influenza virus can infect both the upper and lower respiratory tracts. Other microorganisms, such as bacteria (e.g., pneumococci, staphylococci), mycobacteria (e.g., *Mycobacterium tuberculosis*), fungi (e.g., *Histoplasma capsulatum* [histoplasmosis], *Coccidioides immitis* [coccidioidomycosis], and *Blastomyces dermatitidis* [blastomycosis]), and opportunistic organisms (e.g., *Pneumocystis jiroveci* [formerly *Pneumocystis carinii*]), produce infections of the lung, many of which produce significant morbidity and mortality.

The Common Cold

The common cold is a viral infection of the upper respiratory tract. It occurs more frequently than any other respiratory tract infection. Most adults have two to three colds per year, whereas the average school child may have up to 12 per year.[3] The condition usually begins with a sore and scratchy throat followed by profuse and water rhinorrhea, nasal congestion, sneezing, and coughing. Other cold symptoms include malaise, fatigue, headache, hoarseness, sinus congestion, and myalgia. Fever is a common sign in children but is an infrequent finding in adults.[3] The disease process is usually self-limited, lasting approximately 7 days.

Initially thought to be caused by either a single "cold virus" or a group of them, the common cold is now recognized to be associated with a number of viruses.[3,4] The most common of these are the rhinoviruses, parainfluenza viruses, respiratory syncytial virus, coronaviruses, and adenoviruses. The season of the year and the person's age and prior exposure are important factors in the type of virus causing the infection and the type of symptoms that occur. For example, outbreaks of colds due to rhinoviruses are most common in early fall and late spring, those due to respiratory syncytial virus peak in the winter and spring months, and infections due to the adenoviruses and coronaviruses are more frequent during the winter and spring months. Infections resulting from the respiratory syncytial virus and parainfluenza viruses are most common and severe in children younger than 3 years of age. Infections occur less frequently and with milder symptoms with increasing age. Parainfluenza viruses often produce lower respiratory symptoms with first infections, but less severe upper respiratory symptoms with reinfections. The rhinoviruses are the most common cause of colds in persons between 5 and 40 years of age. There are more than 100 serotypes of rhinoviruses.[4] Although people acquire lifetime immunity to an individual serotype, it would take a long time to become immune to all serotypes.

The "cold viruses" are rapidly spread from person to person. Children are the major reservoir of cold viruses, often acquiring a new virus from another child in school or day care. The fingers are the greatest source of spread, and the nasal mucosa and conjunctival surface of the eyes are the most common portals for entry of the virus. The most highly contagious period is during the first 3 days after the onset of symptoms, and the incubation period is approximately 5 days. Cold viruses have been found to survive for more than 5 hours on the skin and hard surfaces, such as plastic countertops.[4,5] Aerosol spread of colds through coughing and sneezing is much less important than the spread by fingers picking up the virus from contaminated surfaces and carrying it to the nasal membranes and eyes.[5] This suggests that careful attention to hand washing is one of the most important preventive measures for avoiding the common cold.

Because the common cold is an acute and self-limited illness in persons who are otherwise healthy, symptomatic treatment with rest and antipyretic drugs is usually all that is needed. Antibiotics are ineffective against viral infections and are not recommended.[6] Over-the-counter (OTC) remedies are available for treating the common cold. Antihistamines are popular OTC drugs because of their action in drying nasal secretions. However, there is no evidence that they shorten the duration of the cold.[6] They may dry up bronchial secretions and worsen the cough. They are not recommended for use in children. Decongestant drugs (i.e., sympathomimetic agents) are available in OTC nasal sprays, drops, and oral cold medications. These drugs constrict the blood vessels in the swollen nasal mucosa and reduce nasal swelling. Rebound nasal swelling can occur with indiscriminate use of nasal drops and sprays. Oral preparations containing decongestants may cause systemic vasoconstriction and elevation of blood pressure when given in doses large enough to relieve nasal congestion, and they should be avoided by persons with hypertension, heart disease, hyperthyroidism, diabetes mellitus, or other health problems.[3]

Rhinosinusitis

The term *rhinitis* refers to an inflammation of the nasal passages and *sinusitis* to an inflammation of the paranasal sinuses. Although it has not been universally accepted, the suggestion has been made that the term *rhinosinusitis* is a more accurate term for what is commonly referred to as *sinusitis*, because the mucosa of the nasal cavities and paranasal sinuses are lined with a continuous mucous membrane layer and sinusitis rarely occurs in the absence of infectious or allergic rhinitis.[7]

The paranasal sinuses are air-filled extensions of the respiratory part of the nasal cavities into the frontal, ethmoid, sphenoid, and maxilla bones (Fig. 22-1A). The sinuses, which are named for the bones in which they are found, are connected by narrow openings or *ostia* with the superior, middle, and inferior nasal turbinates of the nasal cavity.[8] The anterior ethmoid, frontal, and maxillary sinuses all drain into the nasal cavity through a relatively convoluted and narrow passage called the *ostiomeatal complex* (see Fig. 22-1B). The *sphenoidal sinuses* drain from a separate complex between the septum and the superior turbinate (see Fig. 22-1C).

The most common causes of rhinosinusitis are conditions that obstruct the narrow ostia that drain the sinuses.[8–10] Most commonly, rhinosinusitis develops

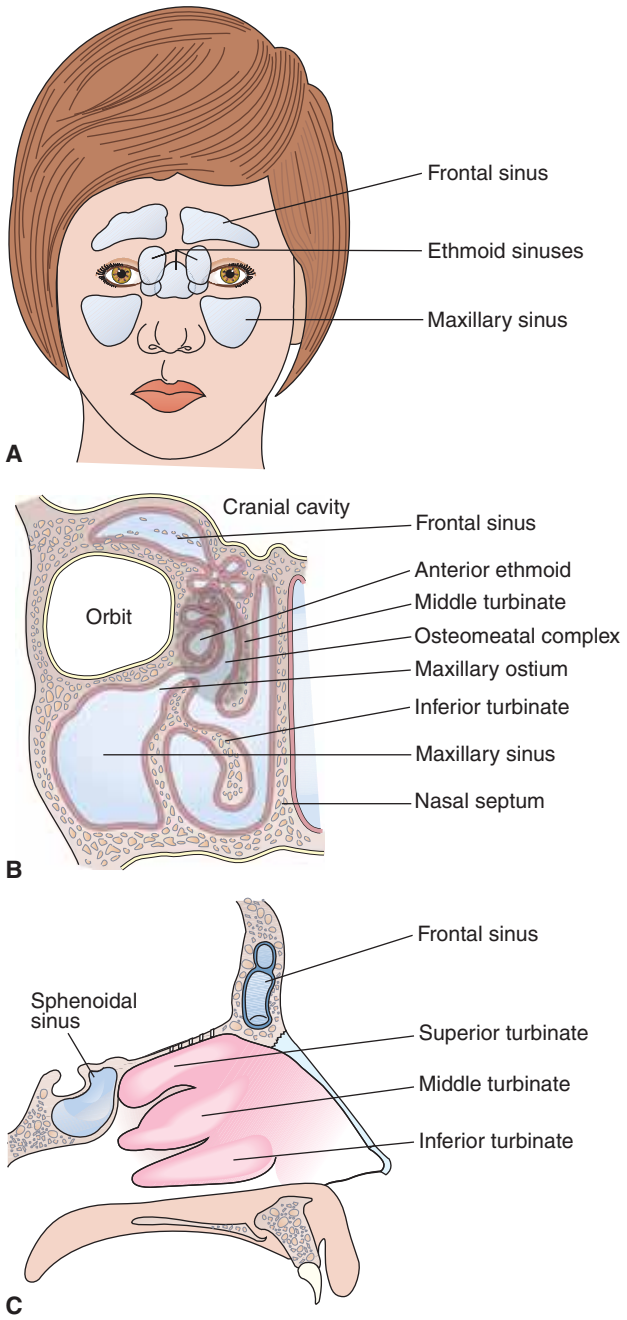


FIGURE 22-1. Paranasal sinuses. **(A)** Frontal view showing the frontal, ethmoid, and maxillary sinuses. **(B)** Cross-section of nasal cavity (anterior view). The shaded area is the osteomeatal complex, which is the final common pathway for drainage of the anterior ethmoid, frontal, and maxillary sinuses. **(C)** Lateral wall, left nasal cavity showing the frontal sphenoidal sinuses and the superior, middle, and inferior turbinates.

when a viral upper respiratory tract infection or allergic rhinitis obstructs the ostiomeatal complex and impairs the mucociliary clearance mechanism. Nasal polyps also can obstruct the sinus openings and facilitate sinus infection. Infections associated with nasal polyps can be self-perpetuating because constant irritation from the infection can facilitate polyp growth. Barotrauma caused by changes in barometric pressure, as occurs in airline pilots and flight attendants, may lead to impaired sinus ventilation and clearance of secretions. Swimming, diving, and abuse of nasal decongestants are other causes of sinus irritation and impaired drainage. Maxillary sinusitis may result from dental infection, and teeth that are tender should be carefully examined for signs of an abscess.

Clinical Features

Rhinosinusitis can be classified as acute, subacute, or chronic.[7–9] Acute rhinosinusitis may last from 5 to 7 days in the case of acute viral rhinosinusitis and up to 4 weeks in the case of acute bacterial rhinosinusitis. Recurrent acute rhinosinusitis is defined as four or more episodes of acute disease within a 12-month period. Subacute rhinosinusitis lasts from 4 weeks to less than 12 weeks, whereas chronic rhinosinusitis lasts beyond 12 weeks.

Acute rhinosinusitis may be of viral, bacterial, or viral–bacterial etiology. In most cases, bacterial infection is preceded by a viral upper respiratory infection, which in turn leads to inflammation and obstruction of the ostiomeatal complex. Rhinovirus is the most common viral pathogen. *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis* make up the majority of community-acquired bacterial pathogens.[7–10] In contrast to acute infections, the pathogens found in chronic rhinosinusitis are usually a mixture of aerobic and anaerobic bacteria, including *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and anaerobic gram-negative bacilli.[9,10] Although the mechanisms that contribute to the chronicity of the disorder are uncertain, mucociliary dysfunction, mucostasis, hypoxia, and release of microbial products are thought to play a role. Allergies may also play an important role in the pathogenesis of chronic rhinosinusitis.[11] In immunocompromised persons, such as those with human immunodeficiency virus (HIV) infection, the sinuses may become infected with gram-negative species and opportunistic fungi.[9,10] In persons in this group, particularly those with leukopenia, the disease may have a fulminant and even fatal course.

Manifestations. The symptoms of acute viral rhinosinusitis often are difficult to differentiate from those of the common cold and allergic rhinitis (discussed in Chapter 16). They include facial pain, headache, purulent nasal discharge, decreased sense of smell, and fever. A history of a preceding common cold and the presence of purulent nasal drainage, pain on bending, unilateral maxillary pain, and pain in the teeth are common findings with involvement of the maxillary sinuses. The symptoms of acute viral rhinosinusitis usually resolve within 5 to 7 days without medical treatment. Acute bacterial rhinosinusitis is suggested by symptoms that worsen after 5 to 7 days or persist beyond 10 days, or symptoms that are out of proportion to those usually associated with a viral upper respiratory tract infection.[9,10]

Persons who are immunocompromised, such as those with leukemia, aplastic anemia, a bone marrow transplant, or HIV infection, may present with fever of unknown origin, rhinorrhea, or facial edema. Often, other signs of inflammation such as purulent drainage are absent.

In persons with chronic rhinosinusitis, the only symptoms may be those such as nasal obstruction, a sense of fullness in the ears, postnasal drip, hoarseness, chronic cough, and loss of taste and smell.[7,9] Sinus pain often is absent; instead, the person may complain of a headache that is dull and constant. Persons with chronic rhinosinusitis may have superimposed bouts of acute rhinosinusitis. The epithelial changes that occur during acute and subacute forms of rhinosinusitis usually are reversible, but the mucosal changes that occur with chronic rhinosinusitis may be irreversible.

Diagnosis and Treatment. The diagnosis of rhinosinusitis usually is based on symptom history and a physical examination that includes inspection of the nose and throat. Headache due to sinusitis needs to be differentiated from other types of headache. Sinusitis headache usually is exaggerated by bending forward, coughing, or sneezing. Physical examination findings in acute bacterial sinusitis include turbinate edema, nasal crusts, purulent drainage, and failure of transillumination of the maxillary sinuses.[12] Transillumination is done in a completely darkened room by placing a flashlight against the skin overlying the infraorbital rim, directing the light inferiorly, having the person open his or her mouth, and observing the hard palate for light transmission. Sinus radiographs and computed tomography (CT) scans may be used. CT scans usually are reserved for diagnosis of chronic rhinosinusitis or to exclude complications. Magnetic resonance imaging (MRI) is expensive and usually reserved for cases of suspected neoplasms or fungal sinusitis.

Treatment of rhinosinusitis depends on cause and includes appropriate use of antibiotics, intranasal corticosteroids, mucolytic agents, and symptom relief measures.[8–10,12] Antibiotics are usually reserved for persons with severe or persistent symptoms and specific findings of bacterial infection.[10] Intranasal corticosteroids frequently are prescribed for persons with both allergies and rhinosinusitis.[11] The treatment of acute rhinosinusitis includes measures to promote adequate drainage by reducing nasal congestion. The topical α-adrenergic decongestants may be used on a short-term (3 days) basis in older children and adults for this purpose.[8] The use of antihistamines is controversial, particularly for acute rhinosinusitis, because they can dry up secretions and thereby decrease drainage. Mucolytic agents such as guaifenesin may be used to thin secretions. Intranasal corticosteroids may be used to decrease inflammation in persons with chronic and allergic rhinitis or rhinosinusitis. Nonpharmacologic measures include saline nasal sprays and steam inhalations.

Surgical intervention directed at correcting obstruction of the ostiomeatal openings may be indicated in persons with chronic rhinosinusitis that is resistant to other forms of therapy. Indications for surgical intervention include obstructive nasal polyps and obstructive nasal deformities.

Complications. Because of the sinuses' proximity to the brain and orbital wall, sinusitis can lead to intracranial and orbital wall complications. Intracranial complications are seen most commonly with infection of the frontal and ethmoid sinuses because of their proximity to the dura and drainage of the veins from the frontal sinus into the dural sinus. Orbital complications can range from edema of the eyelids to orbital cellulitis and subperiosteal abscess formation. Facial swelling over the involved sinus, abnormal extraocular movements, protrusion of the eyeball, periorbital edema, or changes in mental status may indicate intracranial complications and require immediate medical attention.[9]

Influenza

Influenza is one of the most important causes of acute upper respiratory tract infection in humans. Until the advent of acquired immunodeficiency syndrome (AIDS), it was the last uncontrolled pandemic killer of humans. In the United States, epidemics of influenza typically occur during the winter months and are associated with approximately 36,000 deaths.[13] Rates of infection are highest among children, but rates of serious illness and death are highest among persons who are 65 years of age or older.

Etiology

Influenza is caused by viruses belonging to the Orthomyxoviridae family, whose members are characterized by a segmented, single-stranded ribonucleic acid (RNA) genome.[13–16] There are three distinct types of influenza viruses, types A, B, and C. Influenza A and B are the types of influenza viruses that cause epidemics. Influenza C does not cause influenza epidemics, but causes mild upper respiratory infections in children and adults. Influenza A viruses are further categorized into subtypes based on two surface antigens: hemagglutinin (HA) and neuraminidase (NA) activity (Fig. 22-2). HA is an attachment protein that allows the virus to enter epithelial cells in the respiratory tract, and NA facilitates viral replication and release from the cell.[16] There are 15 known HAs (H1 to H15) and 9 NAs (N1 to N9) that define the specific subtypes of influenza A.[14] Influenza B viruses are not categorized into subtypes.[13] Immunity to the surface HA and NA antigens reduces the likelihood and severity of infection with the influenza virus.

Epidemics and pandemics result from the ability of the influenza virus to develop new HA and NA subtypes against which the population is not protected.[14,15] The genetic diversity of influenza A is fostered by its segmented genomic structure and ability to infect and replicate in humans and many avian and animal species, including swine. Epidemics of influenza A occur when minor changes in the amino acids of HA and NA, called an *antigenic drift,* generate a new subtype to which the

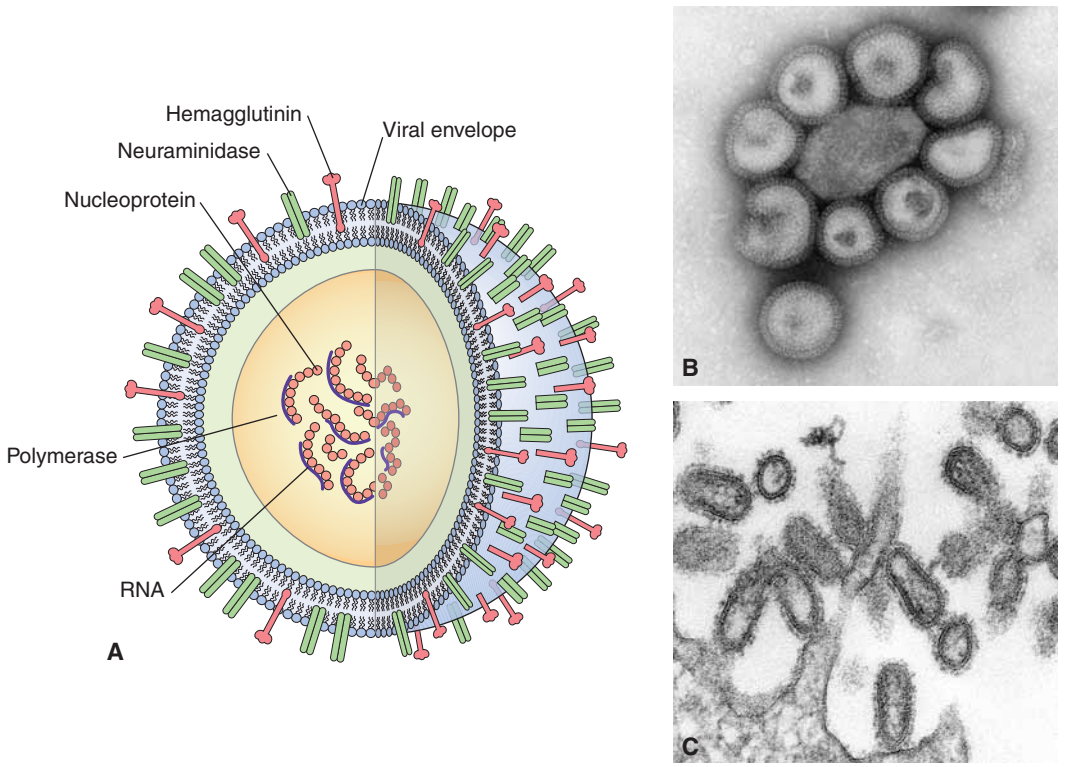


FIGURE 22-2. Influenza type A virus. **(A)** Model of the RNA influenza A virus, showing the hemagglutinin and neuraminidase envelope glycoproteins that provide access to host cells. **(B)** Negative-stained transmission electron micrograph (TEM) depicting the ultrastructural details of a number of influenza viral particles, or "virions." **(C)** TEM revealing ultrastructural features of the 1918 influenza pandemic virus virions. (B and C Courtesy Public Image Library, Centers for Disease Control and Prevention. [Online] Available: http://phil.cdc.gov/phil/home.asp.)

population is only partially protected by cross-reacting antibodies. Pandemics occur when a process called an *antigenic shift* causes both the HA and NA antigens to be replaced through recombination of the RNA segments with those of animal viruses, making all individuals susceptible to the new influenza virus.

As with many viral respiratory tract infections, influenza is more contagious than bacterial respiratory tract infections. In contrast to the rhinoviruses, transmission occurs by inhalation of droplet nuclei rather than touching contaminated objects. Most infected people develop symptoms of the disease, increasing the likelihood of contagion through spread of infectious droplets. Young children are most likely to become infected and also to spread the infection. The incubation period for influenza is 1 to 4 days, with an average of 2 days.[13] Persons become contagious starting 1 day before their symptoms begin and remain infectious through approximately 5 days after illness onset. Children can be infectious for greater than 10 days, and young children can shed virus for up to 6 days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months.

Pathogenesis

The influenza viruses can cause three types of infections: an uncomplicated upper respiratory infection (rhinotracheitis), viral pneumonia, and a respiratory viral infection followed by a bacterial infection. Influenza initially establishes upper airway infection. In doing this, the virus first targets and kills mucus-secreting, ciliated, and other epithelial cells, leaving gaping holes between the underlying basal cells and allowing extracellular fluid to escape. This is the reason for the rhinorrhea or "runny nose" that is characteristic of this phase of the infection. If the virus spreads to the lower respiratory tract, the infection can cause severe shedding of bronchial and alveolar cells. In addition to compromising the natural defenses of the respiratory tract, influenza infection promotes bacterial adhesion to epithelial cells.

Clinical Features

In the early stages, the symptoms of influenza often are indistinguishable from other viral infections. There is an abrupt onset of fever and chills; malaise; muscle aching; headache; profuse, watery nasal discharge; nonproductive cough; and sore throat.[13,14] One distinguishing feature of an influenza viral infection is the rapid onset, sometimes in as little as minutes, of profound malaise. The symptoms of uncomplicated rhinotracheitis usually peak by days 3 to 5 and disappear by days 7 to 10. Weakness, cough, and malaise may persist for weeks after clinical resolution of influenza. Young children with influenza

viral infection can have initial symptoms mimicking bacterial sepsis with high fevers and febrile convulsions.

Viral pneumonia occurs as a complication of influenza, most frequently in the elderly or in persons with cardiopulmonary disease, but has been reported in pregnant women and in healthy, immunocompetent people.[17] It typically develops within 1 day after onset of influenza and is characterized by rapid progression of fever, tachypnea, tachycardia, cyanosis, and hypotension. The clinical course of influenza pneumonia progresses rapidly. It can cause hypoxemia and death within a few days of onset. Survivors often develop diffuse pulmonary fibrosis.

Secondary complications typically include sinusitis, otitis media, bronchitis, and bacterial pneumonia.[16] Persons in whom secondary bacterial pneumonia develops usually report that they were beginning to feel better when they experienced a return of fever, shaking chills, pleuritic chest pain, and productive cough. The most common causes of secondary bacterial pneumonia are *S. pneumoniae, S. aureus, H. influenzae,* and *M. catarrhalis.* This form of pneumonia commonly produces less cyanosis and tachypnea and is usually milder than primary influenza pneumonia. Influenza-related deaths can result from pneumonia as well as exacerbations of cardiopulmonary conditions and other disease. Reye syndrome (fatty liver with encephalitis) is a rare complication of influenza, particularly in young children who have been given aspirin as an antipyretic agent.[16]

Diagnosis and Treatment. The appropriate treatment of people with influenza depends on accurate and timely diagnosis. The early diagnosis can reduce the inappropriate use of antibiotics and provide the opportunity for use of an antiviral drug. Rapid diagnostic tests, which are available for use in outpatient settings, allow health care providers to diagnose influenza more accurately, consider treatment options more carefully, and monitor the influenza type and its prevalence in their community.[16]

The goals of treatment for influenza are designed to limit the infection to the upper respiratory tract. The symptomatic approach for treatment of uncomplicated influenza rhinotracheitis focuses on rest, keeping warm, and drinking large amounts of liquids. Analgesics and cough medications can also be used. Rest decreases the oxygen requirements of the body and reduces the respiratory rate and the chance of spreading the virus from the upper to lower respiratory tract. Keeping warm helps maintain the respiratory epithelium at a core body temperature of 37°C (98.6°F) or higher if fever is present, thereby inhibiting viral replication, which is optimal at 35°C (96°F). Drinking large amounts of liquids ensures that the function of the epithelial lining of the respiratory tract is not further compromised by dehydration. Antiviral medications may be indicated in some persons. Antibacterial antibiotics should be reserved for bacterial complications. The use of aspirin to treat fever should be avoided in children because of the risk of Reye syndrome.

Four antiviral drugs are available for treatment of influenza: amantadine, rimantadine, zanamivir, and oseltamivir. The first-generation antiviral drugs amantadine and rimantadine are no longer used because of the high incidence of resistance.[13,16] Zanamivir (Relenza) and oseltamivir (Tamiflu) are inhibitors of NA, the viral glycoprotein that is necessary for viral replication and release. These drugs, which have been approved for treatment of acute uncomplicated influenza infection, are effective against both influenza A and B viruses. Zanamivir is administered intranasally and oseltamivir is administered orally. Zanamivir can cause bronchospasm and is not recommended for persons with asthma or chronic obstructive lung disease. To be effective, the antiviral drugs should be initiated within 36 hours after onset of symptoms.[16]

Influenza Immunization

Because influenza is so highly contagious, prevention relies primarily on vaccination. Currently, there are two types of influenza vaccines available: the trivalent inactivated influenza vaccine (TIIV) and the live, attenuated influenza vaccine (LAIV).[13] The formulation of the vaccines must be changed yearly in response to antigenic changes in the influenza virus. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) annually updates its recommendations for the composition of the vaccine. The effectiveness of the influenza vaccine in preventing and lessening the effects of influenza infection depend primarily on the age and immunocompetence of the recipient and the match between the virus strains included in the vaccine and those that circulate during the influenza season. The influenza vaccines are contraindicated in persons with anaphylactic hypersensitivity to eggs or to other components of the vaccine, persons with a history of Guillain-Barré syndrome, and persons with acute febrile illness.[13]

The TIIV, which is administered by injection, has become the mainstay for prevention of influenza. It has proved to be inexpensive and effective in reducing illness caused by influenza. Immunization may be used for any person 6 months of age or older, including those with high-risk conditions. It is recommended for all persons older than 50 years of age, persons with chronic health problems or who have immunodeficiencies (such as HIV infection), residents of nursing homes and other chronic-care facilities, women who are pregnant during the influenza season, health care providers, and household contacts or caregivers of persons who put them at higher risk for severe complications of influenza.[13]

The LAIVs are cold-adapted viruses that replicate efficiently in the 25°C temperatures of the nasopharynx, inducing protective immunity against viruses included in the vaccine, but replicate inefficiently at the 38°C to 39°C temperature of the lower airways. LAIV is an option for vaccination of healthy, nonpregnant persons, 5 to 49 years of age.[13]

Pneumonias

The term *pneumonia* describes inflammation of the parenchymal structures of the lung, such as the alveoli and bronchioles. Although antibiotics have significantly

Pneumonias

- Pneumonias are respiratory disorders involving inflammation of the lung structures, such as the alveoli and bronchioles.
- Pneumonia can be caused by infectious agents such as bacteria and viruses and noninfectious agents such as gastric secretions that are aspirated into the lungs.
- The development of pneumonia is facilitated by an exceedingly virulent organism, large inoculum, and impaired host defenses.
- Pneumonias are commonly classified according to the source of infection (community or hospital acquired), the type of organism (typical or atypical), and location in the lung (lobar or bronchopneumonia).

reduced the mortality rate from pneumonias, these diseases remain a leading cause of morbidity and mortality worldwide, particularly among the elderly and those with debilitating diseases.[17–20] Etiologic agents include both infectious and noninfectious agents.

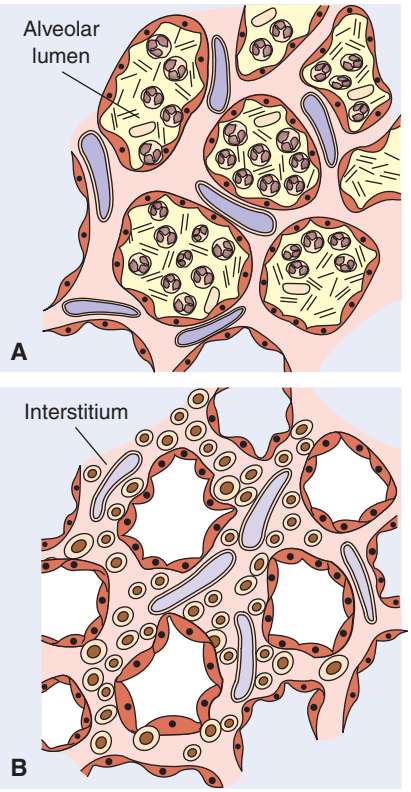


FIGURE 22-3. Location of inflammatory processes in **(A)** typical and **(B)** atypical forms of pneumonia.

Classification

Pneumonias can be commonly classified according the setting (community or hospital) in which they occur, the type of agent (typical or atypical) causing the infection, and distribution of the infection (lobar pneumonia or bronchopneumonia). Because of the overlap in symptomatology and changing spectrum of infectious organisms involved, pneumonias are increasingly being classified as community-acquired and hospital-acquired (nosocomial) pneumonias. Persons with compromised immune function constitute a special concern in both categories.[15,17–20]

Typical pneumonias result from infection by bacteria that multiply extracellularly in the alveoli and cause inflammation and exudation of fluid into the air-filled spaces of the alveoli (Fig. 22-3A). *Atypical pneumonias* are caused by viral and mycoplasma infections that invade the alveolar septum and the interstitium of the lung (Fig. 22-3B). They produce less striking symptoms and physical findings than bacterial pneumonia; there is a lack of alveolar infiltration and purulent sputum, leukocytosis, and lobar consolidation on the radiograph. Acute bacterial pneumonias can be classified as lobar pneumonia or bronchopneumonia, based on their anatomic pattern of distribution. In general, *lobar pneumonia* refers to consolidation of a part or all of a lung lobe, and *bronchopneumonia* signifies a patchy consolidation involving more than one lobe (Fig. 22-4).

Community-Acquired Pneumonia. The term *community-acquired pneumonia* is used to describe infections from organisms found in the community rather than in the hospital or nursing home. It is defined as an infection that begins outside the hospital or is diagnosed within 48 hours after admission to the hospital in a person who has not resided in a long-term care facility for 14 days or more before admission.[18,21] Community-acquired pneumonia may be further categorized according to risk of mortality and need for hospitalization based on age,

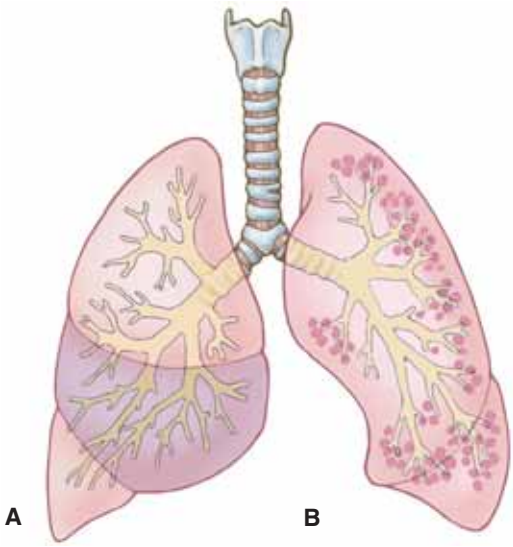


FIGURE 22-4. Distribution of lung involvement in **(A)** lobar pneumonia and **(B)** bronchopneumonia.

presence of coexisting disease, and severity of illness, using physical examination, laboratory, and radiologic findings.

Community-acquired pneumonia may be either bacterial or viral.[15,18,20–23] The most common cause of infection in all categories is *S. pneumoniae*. Other common pathogens include *H. influenzae, S. aureus,* and gram-negative bacilli. Less common agents are *Mycoplasma pneumoniae, Chlamydia* species, and viruses, sometimes called *atypical agents*. Common viral causes of community-acquired pneumonia include the influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza virus.

The methods used in the diagnosis of community-acquired pneumonia depend on age, coexisting health problems, and the severity of illness. In persons younger than 65 years of age and without coexisting disease, the diagnosis usually is based on history and physical examination, chest radiographs, and knowledge of the microorganisms currently causing infections in the community. Sputum specimens may be obtained for staining procedures and culture. Blood cultures may be done for persons requiring hospitalization.

Treatment involves the use of appropriate antibiotic therapy. Empiric antibiotic therapy, based on knowledge regarding an antibiotic's spectrum of action and ability to penetrate bronchopulmonary secretions, often is used for persons with community-acquired pneumonia who do not require hospitalization. Hospitalization and more intensive care may be required depending on the person's age, preexisting health status, and severity of the infection.

Hospital-Acquired Pneumonia. Hospital-acquired, or nosocomial, pneumonia is defined as a lower respiratory tract infection that was not present or incubating on admission to the hospital. Usually, infections occurring 48 hours or more after admission are considered hospital acquired.[15,18,24] Persons requiring intubation and mechanical ventilation are particularly at risk, as are those with compromised immune function, chronic lung disease, and airway instrumentation, such as endotracheal intubation or tracheotomy. Ventilator-associated pneumonia is pneumonia that develops in mechanically ventilated patients more than 48 hours after intubation.[18]

Most hospital-acquired infections are bacterial. The organisms are those present in the hospital environment and include *Pseudomonas aeruginosa, S. aureus, Enterobacter*, *Klebsiella pneumoniae*, and *Escherichia coli*.[15,24] The organisms that are responsible for hospital-acquired pneumonias are different from those responsible for community-acquired pneumonias, and many of them have acquired antibiotic resistance and are more difficult to treat.

Pneumonia in Immunocompromised Persons. Pneumonia in immunocompromised persons remains a major source of morbidity and mortality. The term *immunocompromised host* usually is applied to persons with a variety of underlying defects in host defenses.[15,22] It includes persons with primary and acquired immunodeficiency states, those who have undergone bone marrow or organ transplantation, persons with solid organ or hematologic cancers, and those on corticosteroid and other immunosuppressant drugs.

Although almost all types of microorganisms can cause pulmonary infection in immunocompromised persons, certain types of immunologic defects tend to favor certain types of infections.[15] Defects in humoral immunity predispose to bacterial infections against which antibodies play an important role, whereas defects in cellular immunity predispose to infections caused by viruses, fungi, mycobacteria, and protozoa. Neutropenia and impaired granulocyte function, as occur in persons with leukemia, undergoing chemotherapy, and bone marrow depression, predispose to infections caused by *S. aureus, Aspergillus,* gram-negative bacilli, and *Candida*. The time course of infection often provides a hint to the type of agent involved. A fulminant pneumonia usually is caused by bacterial infection, whereas an insidious onset usually is indicative of a viral, fungal, protozoal, or mycobacterial infection.

Acute Bacterial (Typical) Pneumonia

Bacterial pneumonias remain an important cause of mortality among the elderly and debilitated. The lung below the main bronchi is normally sterile despite frequent entry of microorganisms into the air passages by inhalation during ventilation or aspiration of nasopharyngeal secretions. Most people unknowingly aspirate small amounts of organisms that have colonized their upper airways, particularly during sleep. These organisms do not normally cause infection because of the small numbers that are aspirated and because of the respiratory tract's defense mechanisms that prevent them from entering the distal air passages[15] (Table 22-1). Loss of the cough reflex, damage to the ciliated endothelium that lines the respiratory tract, or impaired immune defenses predispose to colonization and infection of the lower respiratory system. Bacterial adherence also plays a role in colonization of the lower airways. The epithelial cells of critically and chronically ill persons are more receptive to binding microorganisms that cause pneumonia. Other clinical risk factors favoring colonization of the tracheobronchial tree include antibiotic therapy that alters the normal bacterial flora, diabetes, smoking, chronic bronchitis, and viral infection.

Bacterial pneumonias are commonly classified according to etiologic agent. This is because the clinical and morphologic features, and thus the therapeutic implications, often vary with the causative agent. The discussion in this section focuses on two types of bacterial pneumonia: pneumococcal pneumonia and Legionnaire disease.

Pneumococcal Pneumonia. *S. pneumoniae* (pneumococcus) remains the most common cause of bacterial pneumonia.[15,19,25] *S. pneumoniae* is a gram-positive diplococcus, possessing a capsule of polysaccharide. The virulence of the pneumococcus is a function of its capsule, which prevents or delays digestion by phagocytes. The polysaccharide is an antigen that primarily elicits a B-cell response with antibody production. In the absence of antibody, clearance of the pneumococci

TABLE 22-1 Respiratory Defense Mechanisms and Conditions That Impair Their Effectiveness

Defense Mechanism	Function	Factors That Impair Effectiveness
Glottic and cough reflexes	Protect against aspiration into tracheobronchial tree	Loss of cough reflex due to stroke or neural lesion, neuromuscular disease, abdominal or chest surgery, depression of the cough reflex due to sedation or anesthesia, presence of a nasogastric tube (tends to cause adaptation of afferent receptors)
Mucociliary blanket	Removes secretions, microorganisms, and particles from the respiratory tract	Smoking, viral diseases, chilling, inhalation of irritating gases
Phagocytic and bactericidal action of alveolar macrophages	Removes microorganisms and foreign particles from the lung	Tobacco smoke, chilling, alcohol, oxygen intoxication
Immune defenses (IgA and IgG and cell-mediated immunity)	Destroy microorganisms	Congenital and acquired immunodeficiency states

from the body relies on the reticuloendothelial system, with the macrophages in the spleen playing a major role in elimination of the organism.[25] This, along with the spleen's role in antibody generation, increases the risk for pneumococcal bacteremia in persons who are anatomically or functionally asplenic, such as children with sickle cell disease. The initial step in the pathogenesis of pneumococcal infection is the attachment and colonization of the organism to the mucus and cells of the nasopharynx. Colonization does not equate with signs of infection. Perfectly healthy people can be colonized and carry the organism without evidence of infection. The spread of particular strains of pneumococci, particularly antibiotic-resistant strains, is largely by healthy colonized individuals.

The signs and symptoms of pneumococcal pneumonia vary widely, depending on the age and health status of the infected person.[25] In previously healthy persons, the onset usually is sudden and is characterized by malaise; severe, shaking chills; and fever. The temperature may go as high as 106°F (41°C). During the initial or congestive stage, coughing brings up watery sputum and breath sounds are limited, with fine crackles. As the disease progresses, the character of the sputum changes; it may be blood tinged or rust colored to purulent. Pleuritic pain, a sharp pain that is more severe with respiratory movements, is common. With antibiotic therapy, fever usually subsides in approximately 48 to 72 hours, and recovery is uneventful. Elderly persons are less likely to experience marked elevations in temperature; in these persons, the only sign of pneumonia may be a loss of appetite and deterioration in mental status.

Treatment includes the use of antibiotics that are effective against *S. pneumoniae*. In the past, *S. pneumoniae* was uniformly susceptible to penicillin. However, penicillin-resistant and multidrug-resistant strains have been emerging in the United States and other countries.[18]

Pneumococcal pneumonia can be prevented through immunization with the polysaccharide pneumococcal vaccine, composed of antigens from 23 types of *S. pneumoniae* capsular polysaccharides. The vaccine is recommended for persons 65 years of age or older, adult cigarette smokers, adults with chronic illnesses that increase the risk of community-acquired pneumonia, residents in special environments or social settings in which the risk for invasive pneumococcal disease is increased, and residents of nursing homes and long-term care facilities.[26] Immunization also is recommended for immunocompromised persons 2 years of age or older, including those with sickle cell disease, splenectomy, Hodgkin disease, multiple myeloma, renal failure, nephrotic syndrome, organ transplantation, and HIV infection. A single dose of pneumococcal vaccine usually confers some lifetime immunity. Serotype antibody levels decline after 5 to 10 years and decrease more rapidly in some persons than others.[26] Although not currently recommended for immunocompetent people who received the 23-valent vaccine, a second dose of vaccine is recommended for persons older than 65 years of age if 5 years or more have elapsed since the previous vaccine was given. A second dose is also recommended for persons with hematologic cancer, nephrotic syndrome, and chronic kidney diseases, and those with selected immunodeficiency states.[26]

Because of their immature immune system and poor antibody response to pneumococcal capsular polysaccharides, pneumococcal infections are a common cause of community-acquired pneumonia, acute otitis media, and sinusitis in young children. In 2000, a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) became available for use in infants and small children.[27] PCV7 has been succeeded by a 13-valent pneumococcal conjugate vaccine (PCV13), which was licensed by the Food and Drug Administration (FDA) in 2010. In its most recent report, the ACIP recommends routine vaccination of all children aged 2 to 59 months with PCV13, vaccination with PCV13 of children 60 to 71 moths with underlying medical conditions that increase their risk of pneumococcal disease or complications, and PCV13 vaccination of children who received 1 or more doses of PCV7.[27]

Legionnaire Disease. Legionnaire disease is a form of bronchopneumonia caused by a gram-negative rod,

Legionella pneumophila.[15,28] Transmission from person to person has not been documented, and infection normally occurs by acquiring the organism from the environment. Infection typically occurs when water that contains the pathogen is aerosolized into appropriately sized droplets and is inhaled or aspirated by a susceptible host. Although healthy persons can contract the infection, the risk is greater among persons with chronic diseases and those with impaired cell-mediated immunity.

Symptoms of the disease typically begin approximately 2 to 10 days after infection. Onset is usually abrupt, with malaise, weakness, lethargy, fever, and dry cough. Other manifestations include disturbances of central nervous system function, gastrointestinal tract involvement, arthralgias, and elevation in body temperature, sometimes to more than 104°F (40°C).[28] The presence of pneumonia along with diarrhea, hyponatremia, and confusion is characteristic of *Legionella* pneumonia. The disease causes consolidation of lung tissues and impairs gas exchange.

Diagnosis is based on clinical manifestations, radiologic studies, and specialized laboratory tests to detect the presence of the organism. Urine antigen tests and sputum fluorescent antibody tests allow for rapid detection of *L. pneumophila* serotype 1, but are less sensitive than culture for identifying serotypes other than *L. pneumophila* type 1. Treatment consists of administration of antibiotics that are known to be effective against *L. pneumophila*. Delay in instituting antibiotic therapy significantly increases mortality rates; therefore, antibiotics known to be effective against *L. pneumophila* should be included in the treatment regimen for severe community-acquired pneumonia.[28]

Primary Atypical Pneumonia

The atypical pneumonias are characterized by patchy involvement of the lung, largely confined to the alveolar septum and pulmonary interstitium. The term *atypical* denotes a lack of lung consolidation, production of moderate amounts of sputum, moderate elevation of white blood cell count, and lack of alveolar exudate.[15,19] These pneumonias are caused by a variety of agents, the most common being *Mycoplasma pneumoniae*. Mycoplasma infections are particularly common among children and young adults. Other etiologic agents include viruses (e.g., influenza virus, respiratory syncytial virus, adenoviruses, rhinoviruses, rubella [measles] and varicella [chickenpox] viruses) and *Chlamydia pneumoniae*.[15,19] In some cases, the cause is unknown.

The agents that cause atypical pneumonias damage the respiratory tract epithelium and impair respiratory tract defenses, thereby predisposing to secondary bacterial infections. The sporadic form of atypical pneumonia is usually mild with a low mortality rate. It may, however, assume epidemic proportions with intensified severity and greater mortality, as in the influenza pandemics of 1918.

The clinical course among persons with mycoplasma and viral pneumonias varies widely from a mild infection that masquerades as a chest cold to a more serious and even fatal outcome. The symptoms may remain confined to fever, headache, and muscle aches and pains. Cough, when present, is characteristically dry, hacking, and nonproductive. The diagnosis is usually made based on history, physical findings, and chest radiographs.

Tuberculosis

Pulmonary tuberculosis remains one of the deadliest diseases in the world. It is estimated that worldwide nearly 1 billion people will be newly infected with tuberculosis, over 150 million will become clinically ill, and 36 million will die of the disease between now and 2020—if methods to control infection are not strengthened.[29] With the introduction of antibiotics in the 1950s, the United States and other Western countries enjoyed a long decline in the number of infections until the mid-1980s. Since that time, the rate of infection has increased, particularly among HIV-infected people. In the United States, the biggest increase in new cases was from 1985 to 1993, after which the rate of cases reported yearly has again declined.[29] In part, this decline reflects the impact of resources committed to assist state and local control efforts, wider screening and prevention programs, and increased support for prevention programs among HIV-infected persons.

Tuberculosis is more common among foreign-born persons from countries with a high incidence of tuberculosis and among residents of high-risk congregate settings such as correctional facilities, drug treatment facilities, and homeless shelters. Outbreaks of a drug-resistant form of tuberculosis have emerged, complicating the selection of drugs and affecting the duration of treatment.

Etiology

Tuberculosis is an airborne infection caused by the mycobacterium *M. tuberculosis*. The mycobacteria are slender, rod-shaped, aerobic bacilli that do not form spores[2,30,31] (Fig. 22-5). They are similar to other bacteria except for a waxy cell wall that is responsible for many

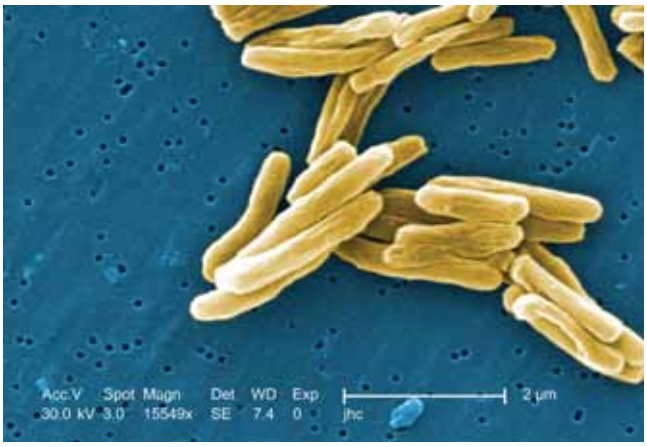


FIGURE 22-5. Scanning electron micrograph (SEM) depicting some of the ultrastructural details seen in the cell wall configuration of a number of gram-positive *Mycobacterium tuberculosis* bacteria. (Courtesy Public Image Library, Centers for Disease Control and Prevention.

Tuberculosis

- Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis,* a rod-shaped, aerobic bacterium that is resistant to destruction and can persist in necrotic and calcified lesions for prolonged periods and remain capable of reinstating growth.
- The organism is spread by inhaling the mycobacterium-containing droplet nuclei that circulate in the air. Overcrowded living conditions increase the risk of tuberculosis spread.
- The tubercle bacillus has no known antigens to stimulate an early immunoglobulin response; instead, the host mounts a delayed-type cell-mediated immune response.
- The cell-mediated response plays a dominant role in walling off the tubercle bacilli and preventing the development of active tuberculosis. People with impaired cell-mediated immunity are more likely to develop active tuberculosis when infected.
- A positive tuberculin skin test results from a cell-mediated immune response and implies that a person has been infected with *M. tuberculosis* and has mounted a cell-mediated immune response. It does not mean that the person has active tuberculosis.

of the characteristics of the bacteria, including its slow growth, antigenicity, and resistance to detergents, disinfectants, and antibacterial antibiotics. It also renders the bacteria resistant to common laboratory stains. Once stained, the dye cannot be discolored with acid solution, hence the name acid-fast bacilli. Although *M. tuberculosis* can infect practically any organ of the body, the lungs are most frequently involved.

Tuberculosis is an airborne infection spread by minute, invisible particles, called *droplet nuclei,* that are harbored in the respiratory secretions of persons with active tuberculosis.[32,33] Coughing, sneezing, and talking all create respiratory droplets; these droplets evaporate, leaving the organisms (droplet nuclei), which remain suspended in the air and are circulated by air currents. Thus, living under crowded and confined conditions increases the risk for spread of the disease.

Pathogenesis

The pathogenesis of tuberculosis in a previously unexposed immunocompetent person is centered on the development of a cell-mediated immune response that confers resistance to the organism and development of tissue hypersensitivity to the tubercular antigens.[2,30,31] The destructive features of the disease, such as caseating necrosis and cavitation, result from a cell-mediated hypersensitivity response (see Chapter 16) rather than the destructive capabilities of the tubercle bacillus.

Macrophages are the primary cell infected with *M. tuberculosis*. Inhaled droplet nuclei pass down the bronchial tree without settling on the epithelium and are deposited in the alveoli. Soon after entering the lung, the bacilli are phagocytosed by alveolar macrophages but resist killing. Although the macrophages that first ingest *M. tuberculosis* cannot kill the organisms, they initiate a cell-mediated immune response that eventually contains the infection. As the tubercle bacilli multiply, the infected macrophages degrade the mycobacteria and present their antigens to helper ($CD4^+$) T lymphocytes. The sensitized helper T cells, in turn, stimulate the macrophages to increase their concentration of lytic enzymes and ability to kill the mycobacteria. When released, these lytic enzymes also damage lung tissue. The development of a population of activated cytotoxic ($CD8^+$) T cells and macrophages capable of ingesting and destroying the bacilli constitutes the cell-mediated immune response, a process that takes about 3 to 6 weeks to become effective.

In persons with intact cell-mediated immunity, the cell-mediated immune response results in the development of a gray-white, circumscribed granulomatous lesion, called a *Ghon focus,* that contains the tubercle bacilli, modified macrophages, and other immune cells.[2,19] It is usually located in the subpleural area of the upper segments of the lower lobes or in the lower segments of the upper lobe. When the number of organisms is high, the hypersensitivity reaction produces significant tissue necrosis, causing the central portion of the Ghon focus to undergo soft, caseous (cheeselike) necrosis. During this same period, tubercle bacilli, free or inside macrophages, drain along the lymph channels to the tracheobronchial lymph nodes of the affected lung and there evoke the formation of caseous granulomas. The combination of the primary lung lesion and lymph node granulomas is called a *Ghon complex* (Fig. 22-6). The Ghon complex eventually heals, undergoing shrinkage, fibrous scarring, and calcification, the latter being visible radiographically. However, small numbers of organisms may remain viable for years. Later, if immune mechanisms decline or fail, latent tuberculosis infection has the potential to develop into secondary tuberculosis.

Primary Tuberculosis

Primary tuberculosis is a form of the disease that develops in previously unexposed, and therefore unsensitized, persons.[2,19] It typically is initiated as a result of inhaling droplet nuclei that contain the tubercle bacillus (Fig. 22-7). Most people with primary tuberculosis are asymptomatic and go on to develop *latent tuberculosis infection* in which T lymphocytes and macrophages surround the organism in granulomas that limit their spread. Individuals with latent tuberculosis do not have active disease and cannot transmit the organism to others.

In approximately 5% of newly infected people, the immune response is inadequate; these people go on to develop progressive primary tuberculosis with continued

FIGURE 22-6. Primary tuberculosis. A healed Ghon complex is represented by a subpleural nodule and involved hilar lymph nodes. (From Beasley M.B., Travis W.D., Rubin E. [2008]. The respiratory system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 496]. Philadelphia: Lippincott Williams & Wilkins.)

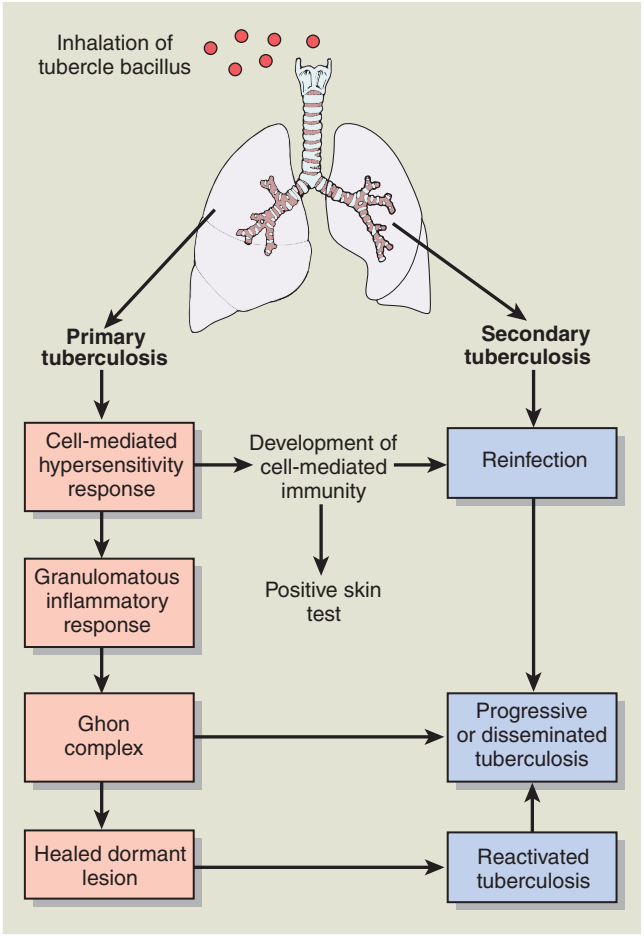


FIGURE 22-7. Pathogenesis of tuberculosis infection.

destruction of pulmonary tissue and spread to multiple sites within the lung.[2] This usually occurs in young children or adults with HIV infection or other immunodeficiency disorders. In those who develop progressive disease, the symptoms are usually insidious and nonspecific, with fever, weight loss, fatigue, and night sweats.[18] Sometimes the onset of symptoms is abrupt, with high fever, pleuritis, and lymphadenitis. As the disease spreads, the organism gains access to the sputum, allowing the person to infect others.

In rare instances, tuberculosis may erode into a blood vessel, giving rise to hematogenic dissemination. *Miliary tuberculosis* describes minute lesions, resembling millet seeds, resulting from this type of dissemination that can involve almost any organ, particularly the brain, meninges, liver, kidney, and bone marrow.

Secondary Tuberculosis

Secondary tuberculosis represents either reinfection from inhaled droplet nuclei or reactivation of a previously healed primary lesion[2,19] (see Fig. 22-7). It often occurs in situations of impaired body defense mechanisms. The partial immunity that follows primary tuberculosis affords protection against reinfection and to some extent aids in localizing the disease should reactivation occur. In secondary tuberculosis, the cell-mediated hypersensitivity reaction can be an aggravating factor, as evidenced by the frequency of cavitation and bronchial dissemination. The cavities may coalesce to a size of up to 10 to 15 cm in diameter (Fig. 22-8). Pleural effusion and tuberculous empyema are common as the disease progresses.

Persons with secondary tuberculosis commonly present with low-grade fevers, night sweats, easy fatigability,

FIGURE 22-8. Cavitary tuberculosis in the apex of the left upper lobe of the lung. (From Beasley M.B., Travis W.D., Rubin E. [2008]. The respiratory system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 496]. Philadelphia: Lippincott Williams & Wilkins.)

anorexia, and weight loss.[2] A cough initially is dry but later becomes productive with purulent and sometimes blood-tinged sputum. Dyspnea and orthopnea develop as the disease advances.

Diagnosis and Treatment

Diagnosis. A definitive diagnosis of active pulmonary tuberculosis requires identification of the organism from cultures or identification of the organism using *M. tuberculosis* nucleic acid (deoxyribonucleic [DNA]) amplification techniques.[18,32–35] Demonstration of acid-fast bacilli in the sputum is not specific for *M. tuberculosis* since nontuberculosis mycobacteria can colonize the airways. Culture specimens may be obtained from early morning sputum specimens, gastric aspirations, or bronchial washings obtained during fiberoptic bronchoscopy. Because most species of mycobacterium grow slowly, cultures on solid media to identify *M. tuberculosis* require up to 12 weeks. The use of liquid media systems may allow for detection of mycobacterial growth in several days, dependent upon the number of organisms in the inoculum. Several test systems based on amplification of microbacterial nucleic acid (nucleic acid amplification [NAA] tests) are available. These systems permit the diagnosis of tuberculosis in as little as several hours. However, their applicability is limited by variable sensitivity and high cost. Culture remains the gold standard for laboratory confirmation of infection and is required for drug sensitivity testing. Chest radiographs are used to determine the extent of lung involvement.

The tuberculin skin test, which measures the delayed hypersensitivity response to an intradermal injection of tuberculin, continues to be used to identify latent tuberculin infections. The test is recommended for targeted testing of high-risk populations including persons who are in close contact with someone who has confirmed active tuberculosis, residents and employees in congregate settings (e.g., corrections facilities, homeless shelters, long-term care facilities), and health care workers with high-risk patients.[32,35] Routine testing of individuals at low risk for infection is not recommended. The tuberculin test cannot distinguish between active and latent infection and is also subject to false-negative and false-positive reactions. Because the hypersensitivity response to the tuberculin test depends on cell-mediated immunity, false-negative test results can occur because of immunodeficiency states that result from HIV infection, immunosuppressive therapy, lymphoreticular malignancies, or aging. This is called *anergy*. In the immunocompromised person, a negative tuberculin test result can mean that the person has a true lack of exposure to tuberculosis or is unable to mount an immune response to the test. False-positive results may be obtained in persons who had a nontuberculosis mycobacteria infection or who have received the bacillus Calmette-Guérin (BCG) vaccine for tuberculosis prevention. Although BCG vaccine is not used in the United States for tuberculosis prevention, many immigrants will have received it.

The use of serial tuberculin skin testing may also create a false impression of test conversion.[18,33] Dormant mycobacterial sensitivity is sometimes restored by antigenic challenge of the initial test. This phenomenon is called *boosting*. A "two-step testing procedure" may be used to reduce the likelihood that a boosted tuberculin response is interpreted as a recent infection. If the first test result of the two-step procedure is negative, a second test is administered 1 week later. If the second test result is negative, the person is considered to be uninfected or anergic. If the second test result is positive, it is assumed to have occurred because of a boosted response. The boosted effect can last for 1 year or longer. The two-step test procedure is often used for initial tuberculin skin testing of individuals, such as health care workers, who will be tested repeatedly.

Antigen-specific interferon (IFN)-γ release assays are available for use in diagnosis of latent tuberculosis infection.[32,35] This test requires overnight incubation of a peripheral blood sample followed by measurement of IFN-γ released by sensitized lymphocytes. Like the tuberculin skin test, IFN-γ release assays are only designed to identify *M. tuberculosis* and, when used alone, cannot distinguish latent infection from active disease, and immunodeficiency states can cause false-negative results. Unlike the tuberculin skin test, they do not produce false-positive results in persons with previous BCG vaccination or most types of nontuberculosis mycobacteria infections.

Genotyping can be done to identify different strains of *M. tuberculosis* in persons who have been diagnosed with active tuberculosis. It can be used to evaluate second episodes of tuberculosis to determine whether the second episode was due to relapse or reinfection. Genotyping also permits the evaluation of isolates with different patterns of drug susceptibility.[36] In addition, genotyping is useful in investigating outbreaks of infection and determining sites and patterns of *M. tuberculosis* transmission in communities.

Treatment. The goals of therapy are to treat infected individuals by eliminating the tubercle bacilli while preventing the spread of infection and development of drug-resistant forms of the disease. The primary drugs used in the treatment of tuberculosis are isoniazid (INH), ethambutol, pyrazinamide, and rifampin. Two groups meet the criteria established for the use of antimycobacterial therapy for tuberculosis: persons with active tuberculosis and those who have had contact with cases of active tuberculosis and who are at risk for development of an active form of the disease.[18,35,37,38] Prophylactic treatment is used for persons who have latent tuberculosis infection but do not have active disease. These persons are considered to harbor a small number of microorganisms and usually are treated with INH.

The tubercle bacillus is an aerobic organism that multiplies slowly and remains relatively dormant in oxygen-poor caseous material. It undergoes a high rate of mutation and tends to acquire resistance to any one drug. For this reason, multidrug regimens are used for treating persons with active tuberculosis. Drug susceptibility tests are used to guide treatment in drug-resistant forms of the disease. Persons with drug-resistant *M. tuberculosis*

infection require careful supervision and more extensive drug regimens. The internationally recommended strategy for tuberculosis control by the World Health Organization is directly observed therapy, short course (DOTS).[29] Tuberculosis in persons with concomitant HIV infection requires management by experts in both tuberculosis and HIV.

New tuberculosis drugs are currently being developed and are in various stages of testing. Of particular interest is the need for drugs that improve current treatment of active tuberculosis by shortening the total duration of treatment or provide more widely spaced intermittent therapy, improving the treatment of drug-resistant tuberculosis and providing more efficient treatment for latent tuberculosis.[39]

Fungal Infections

Although most fungal infections are asymptomatic, they can be severe or even fatal in persons who have experienced a heavy exposure, have underlying immune deficiencies, or develop progressive disease that is not recognized or treated. Immunocompromised persons, particularly those with HIV infection, are particularly prone to development of disseminated infection.

The host's cell-mediated immune response is paramount in controlling such infections. Pathologic fungi generally produce no toxins. In the host, they induce a delayed cell-mediated hypersensitivity response to their chemical constituents (see Chapter 15). Cellular immunity is mediated by antigen-specific T lymphocytes and cytokine-activated macrophages that assume fungicidal properties. The primary pulmonary lesions consist of aggregates of macrophages stuffed with organisms, with similar lesions developing in the lymph nodes that drain the area. These lesions develop into granulomas complete with giant cells and may develop central necrosis and calcification resembling that of primary tuberculosis.

Types of Infections

Fungi are classified as yeasts and molds. Yeasts are round and grow by budding. Molds form tubular structures called *hyphae* and grow by branching and forming spores (see Chapter 14). Some fungi are *dimorphic,* meaning that they grow as yeasts at body temperatures and as molds at room temperatures. A simple classification of mycoses or diseases caused by fungi divides them into superficial, cutaneous, subcutaneous, or deep (systemic) mycoses. The superficial, cutaneous, or subcutaneous mycoses cause disease of the skin, hair, and nails. Deep fungal infections may produce pulmonary and systemic infections and are sometimes fatal. They are caused by virulent fungi that live free in nature or soil or in decaying organic matter and are frequently limited to certain geographic regions. The most common of these are the dimorphic fungi, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*.[40,41] These fungi form infectious spores, which enter the body through the respiratory system. Most people who become infected with these fungi develop only minor symptoms or none at all; only a small minority develop serious disease.

Each of the dimorphic fungi has a typical geographic distribution. *H. capsulatum,* which is the etiologic agent in *histoplasmosis*, is endemic along the major river valleys of the central and eastern United States (i.e., Ohio, Missouri, Mississippi river valleys), eastern Canada, Mexico, Central and South America, Africa, and southeast Asia.[41,42] The organism grows in soil and other areas that have been enriched with bird excreta: old chicken houses, pigeon lofts, barns, and trees where birds roost. The infection is acquired by inhaling the fungal spores that are released when the dirt or dust from the infected areas is disturbed. *C. immitis,* which causes *coccidioidomycosis*, is most prevalent in the southwestern United States, principally in California, Arizona, and Texas; Mexico; and Central and South America.[41,43] Because of its prevalence in the San Joaquin Valley, the disease is sometimes referred to as *San Joaquin fever* or *valley fever. C. immitis* lives in soil and can establish new sites in the soil. Events such as dust storms and digging for construction have been associated with increased incidence of the disease. *B. capsulatum,* the agent causing *blastomycosis*, is most commonly found in south central and northwestern United States and Canada.[41,44]

Clinical Features

The signs and symptoms of the fungal infections of the respiratory tract commonly resemble those of tuberculosis. Depending on the host's resistance and immunocompetence, the diseases usually take one of three forms: (1) an acute primary disease, (2) a chronic (cavitary) pulmonary disease, or (3) a disseminated infection. The primary and secondary lesions of fungal infections consist of epithelioid cell granulomatous containing aggregates of macrophages with engulfed microorganisms. Similar nodules develop in the regional lymph nodes. There is a striking similarity to the primary lesions of tuberculosis. The clinical manifestations often consist of a mild, self-limited flulike syndrome.

In the vulnerable host, chronic cavitary lesions develop, with a predilection for the upper lobe, resembling the secondary form of tuberculosis. The most common manifestations are productive cough, fever, night sweats, and weight loss. Disseminated disease most often develops as an acute and fulminating infection in the very old or the very young or in persons with compromised immune function. Although the macrophages of the reticuloendothelial system can remove the fungi from the bloodstream, they are unable to destroy them. Characteristically, this form of the disease presents with a high fever, generalized lymph node enlargement, hepatosplenomegaly, muscle wasting, anemia, leukopenia, and thrombocytopenia. There may be hoarseness, ulcerations of the mouth and tongue, nausea, vomiting, diarrhea, and abdominal pain. Often, meningitis becomes a dominant feature of the disease. Persons with blastomycosis may experience cutaneous infections that induce pseudoepitheliomatous hyperplasia, which may be mistaken for squamous cell carcinoma.

Diagnosis and Treatment. Skin tests similar to the tuberculin test can be used to detect exposure to *Histoplasma* and *Coccidioides*. There is no reliable skin test for *Blastomyces*. The diagnosis of acute infection is usually made by direct visualization of the organism in tissue sections or sputum culture. Serologic tests that detect antibodies against the specific fungi are available, but lack sensitivity and specificity.

Treatment depends on the severity of infection. Persons without associated risk factors such as HIV infection or without specific evidence of progressive disease usually can be treated without antifungal therapy. The oral or intravenous antifungal drugs are used in the treatment of persons with progressive disease.

In summary, respiratory infections are the most common cause of respiratory illness. They include the common cold, influenza, pneumonias, tuberculosis, and fungal infections. The common cold occurs more frequently than any other respiratory infection. The fingers are the usual source of transmission, and the most common portals of entry are the nasal mucosa and the conjunctiva of the eye. The influenza virus causes three syndromes: an uncomplicated rhinotracheitis, a respiratory viral infection followed by a bacterial infection, and viral pneumonia. The contagiousness of influenza results from the ability of the virus to mutate and form subtypes against which the population is unprotected.

Pneumonia describes an infection of the parenchymal tissues of the lung. Loss of the cough reflex, damage to the ciliated endothelium that lines the respiratory tract, or impaired immune defenses predispose to pneumonia. Pneumonia can be classified according to the type of organism causing the infection (typical or atypical), location of the infection (lobar pneumonia or bronchopneumonia), and setting in which it occurs (community or hospital acquired). Persons with compromised immune function constitute a special concern in both settings. Community-acquired pneumonia involves infections from organisms that are present more often in the community than in the hospital or nursing home. The most common cause of community-acquired pneumonia is *S. pneumoniae.* Hospital-acquired (nosocomial) pneumonia is defined as a lower respiratory tract infection occurring 48 hours or more after admission. Hospital-acquired pneumonia is the second most common cause of hospital-acquired infection. Acute typical pneumonias, including *S. pneumoniae* and *L. pneumophila* pneumonia, are caused by organisms that multiply extracellularly in the alveoli and cause inflammation and transudation of fluid into the air-filled spaces of the alveoli. Atypical pneumonias are caused by a variety of agents, including *M. pneumoniae* and viruses that invade the alveolar septum and interstitium of the lung.

Tuberculosis is a chronic respiratory infection caused by *M. tuberculosis,* which is spread by minute, invisible particles called *droplet nuclei.* Tuberculosis is a particular threat among HIV-infected persons, foreign-born persons from countries with a high incidence of tuberculosis, and residents of high-risk congregate settings such as correctional facilities, drug treatment facilities, and homeless shelters. The tubercle bacillus incites a distinctive chronic inflammatory response referred to as *granulomatous inflammation.* The destructiveness of the disease results from the cell-mediated hypersensitivity response that the bacillus evokes rather than its inherent destructive capabilities. Cell-mediated immunity and hypersensitivity reactions contribute to the evolution of the disease. The treatment of tuberculosis, which focuses on eliminating the tuberculosis bacilli from infected persons and eliminating its spread, has been complicated by outbreaks of drug-resistant forms of the disease.

Infections caused by the fungi *H. capsulatum* (histoplasmosis), *C. immitis* (coccidioidomycosis), and *B. dermatitidis* (blastomycosis) produce pulmonary manifestations that resemble tuberculosis. These infections are common but seldom serious unless they produce progressive destruction of lung tissue or the infection disseminates to organs and tissues outside the lungs.

Cancer of the Lung

Lung cancer is the leading cause of cancer-related death in the United States and worldwide.[15,19,45,46] The incidence of lung cancer is closely linked to cigarette smoking, making it a preventable form of cancer. Because lung cancer often is far advanced before it is discovered, the prognosis is generally poor. The overall 5-year survival rate is 13% to 15%, a dismal statistic that has not changed since the late 1960s.

With regard to carcinogenic influences, there is strong evidence that smoking is to a large extent responsible for the genetic changes that convert normal bronchial cells to cancer cells. Other influences may act in concert with smoking or may by themselves be responsible for some lung cancers. For example, there is increased incidence of lung cancer in asbestos workers and workers exposed to dusts containing arsenic, chromium, nickel, and vinyl chloride.

Types of Lung Cancer

Four histologic types account for most primary lung cancers: adenocarcinoma (males 37%, females 47%), squamous cell lung carcinoma (males 32%, females 25%), small cell carcinoma (males 14%, females 18%), and large cell carcinoma (males18%, females 10%).[15] For therapeutic purposes such as staging and treatment, lung cancers are commonly identified as small cell lung cancer (SCLC) or non–small cell lung cancer (NSCLC). One of the key reasons for this classification is that SCLC has usually metastasized by the time of diagnosis and hence are not amenable to cancer surgery. It is usually best treated with chemotherapy, with or without radiation.

Small Cell Lung Cancer

SCLC is characterized by a distinctive cell type—small round to oval cells that are approximately the size of a lymphocyte.[15,47] The cells grow in clusters that exhibit neither glandular nor squamous organization. Electron microscopic studies demonstrate the presence of neurosecretory granules in some of the tumor cells similar to those found in the bronchial epithelium of the fetus or neonate.[15] The presence of these granules suggests the ability of some of these tumors to secrete polypeptide hormones, and the presence of neuroendocrine markers such as neuron-specific enolase and parathormone-like and other hormonally active products suggests that these tumors may arise from the neuroendocrine cells of the bronchial epithelium. This cell type is associated with several types of paraneoplastic syndrome, including the syndrome of inappropriate antidiuretic hormone secretion (SIADH; see Chapter 8). This type of cancer has the strongest association with cigarette smoking and is rarely observed in someone who has not smoked.[47–49]

SCLC is highly malignant, tends to infiltrate widely, disseminate early, and is rarely resectable. About 70% of the cancers have detectable metastases at the time of diagnosis[48]; the rest are assumed to have micrometastases. Brain metastases are particularly common with SCLC and may provide the first evidence of the tumor. Without treatment, one half of persons with SCLC die within 12 to 15 weeks.

Non–Small Cell Lung Cancers

The NSCLCs include squamous cell carcinomas, adenocarcinomas, and large cell carcinomas. *Squamous cell carcinoma* is found most commonly in men and is closely correlated with a smoking history. Squamous cell carcinoma tends to originate in the central bronchi as an intraluminal growth and is thus more amenable to early detection through cytologic examination of the sputum than other forms of lung cancer. It tends to spread centrally into major bronchi and hilar lymph nodes and disseminates outside the thorax later than other types of bronchogenic cancers. Squamous cell carcinoma is associated with the paraneoplastic syndromes that produce hypercalcemia.

Currently, *adenocarcinoma* is the most common type of lung cancer in North America. Its association with cigarette smoking is weaker than for squamous cell carcinoma. It is the most common type of lung cancer in women and nonsmokers. Adenocarcinomas can have their origin in either the bronchiolar or alveolar tissues of the lung. These tumors tend to be located more peripherally than squamous cell sarcomas and sometimes are associated with areas of scarring (Fig. 22-9). The scars may be due to old infarcts, metallic foreign bodies, wounds, and granulomatous infections such as tuberculosis. In general, adenocarcinomas have a poorer stage-for-stage prognosis than squamous cell carcinomas.

Large cell carcinomas have large, polygonal cells. They constitute a group of neoplasms that are highly anaplastic and difficult to categorize as squamous cell carcinoma or adenocarcinoma. They tend to occur in the periphery of the lung, invading subsegmental bronchi and larger airways. They have a poor prognosis because of their tendency to spread to distant sites early in their course.

FIGURE 22-9. Adenocarcinoma of the lung. A peripheral tumor is located in the upper right lobe of the lung. (From Beasley M.B., Travis W.D., Rubin E. [2008]. The respiratory system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 541]. Philadelphia: Lippincott Williams & Wilkins.)

Clinical Features

Lung cancers are aggressive, locally invasive, and widely metastatic tumors that arise from the epithelial lining of major bronchi. These tumors begin as small mucosal lesions that may follow one of several patterns of growth. They may form intraluminal masses that invade the bronchial mucosa and infiltrate the peribronchial connective tissue, or they may form large, bulky masses that extend into the adjacent lung tissue. Some large tumors undergo central necrosis and acquire local areas of hemorrhage, and some invade the pleural cavity and chest wall and spread to adjacent intrathoracic structures.[15] All types of lung cancer, especially small cell lung carcinoma, have the capacity to synthesize bioactive products and produce paraneoplastic syndromes.

Manifestations

The manifestations of lung cancer are extremely variable, depending on the location of the tumor, the presence of distant metastasis, and the occurrence of paraneoplastic syndromes. Often the malignancy develops insidiously, giving little or no warning of its presence.

The manifestations of lung cancer can be divided into three categories: (1) those due to involvement of the lung and adjacent structures; (2) the effects of local spread and metastasis; and (3) nonmetastatic paraneoplastic manifestations involving endocrine, neurologic, and connective

tissue function. As with other cancers, lung cancer also causes nonspecific symptoms such as anorexia and weight loss. Because its symptoms are similar to those associated with smoking and chronic bronchitis, they often are disregarded. Metastases already exist in many patients presenting with evidence of lung cancer. The most common sites of these metastases are the brain, bone, and liver.

Many of the manifestations of lung cancer result from local irritation and obstruction of the airways and from invasion of the mediastinum and pleural space. The earliest symptoms usually are chronic cough, shortness of breath, and wheezing because of airway irritation and obstruction. Hemoptysis (i.e., blood in the sputum) occurs when the lesion erodes blood vessels. Pain receptors in the chest are limited to the parietal pleura, mediastinum, larger blood vessels, and peribronchial afferent vagal fibers. Dull, intermittent, poorly localized retrosternal pain is common in tumors that involve the mediastinum. Pain becomes persistent, localized, and more severe when the disease invades the pleura.

Tumors that invade the mediastinum may cause hoarseness because of the involvement of the recurrent laryngeal nerve and cause difficulty in swallowing because of compression of the esophagus. An uncommon complication called the *superior vena cava syndrome* occurs in some persons with mediastinal involvement. Interruption of blood flow in this vessel usually results from compression by the tumor or involved lymph nodes. The disorder can interfere with venous drainage from the head, neck, and chest wall. The outcome is determined by the speed with which the disorder develops and the adequacy of the collateral circulation. Tumors adjacent to the visceral pleura often insidiously produce pleural effusion. This effusion can compress the lung and cause atelectasis and dyspnea. It is less likely to cause fever, pleural friction rub, or pain than pleural effusion resulting from other causes.

Paraneoplastic syndromes are those that are unrelated to metastasis (see Chapter 7). These include hypercalcemia from secretion of parathyroid-like peptide, Cushing syndrome from ACTH secretion, SIADH, neuromuscular syndromes (e.g., Eaton-Lambert syndrome), and hematologic disorders (e.g., migratory thrombophlebitis, nonbacterial endocarditis, disseminated intravascular coagulation). Neurologic or muscular symptoms can develop 6 months to 4 years before the lung tumor is detected. One of the more common of these problems is weakness and wasting of the proximal muscles of the pelvic and shoulder girdles, with decreased deep tendon reflexes but without sensory changes. Hypercalcemia is seen most often in persons with squamous cell carcinoma, hematologic syndromes in persons with adenocarcinomas, and the remaining syndromes in persons with small cell neoplasms. Manifestations of the paraneoplastic syndrome may precede the onset of other signs of lung cancer and may lead to discovery of an occult tumor.

Diagnosis and Treatment

The diagnosis of lung cancer is based on a careful history and physical examination and on other tests such as chest radiography, bronchoscopy, cytologic studies (Papanicolaou [Pap] test) of the sputum or bronchial washings, percutaneous needle biopsy of lung tissue, and scalene lymph node biopsy. CT scans, MRI studies, and ultrasonography are used to locate lesions and evaluate the extent of the disease. Positron emission tomography (PET) is a noninvasive alternative for identifying metastatic lesions in the mediastinum or distant sites. Persons with SCLC should also have a CT scan or MRI of the brain for detection of metastasis.

Like other cancers, lung cancer is classified according to extent of disease. NSCLCs are usually classified according to cell type (i.e., squamous cell carcinoma, adenocarcinoma, and large cell carcinoma) and staged according to the tumor, node, metastasis (TNM) international staging system[15] (see Chapter 7). SCLCs are not staged using the TNM system because micrometastases are assumed to be present at the time of diagnosis. Instead, they are usually classified as limited disease, when the tumor is limited to the unilateral hemithorax, or extensive disease, when it extends beyond these boundaries.[15]

Treatment methods for NSCLC include surgery, radiation therapy, and chemotherapy.[50] These treatments may be used singly or in combination. Surgery is used for the removal of small, localized NSCLC tumors. It can involve a lobectomy, pneumonectomy, or segmental resection of the lung. Radiation therapy can be used as a definitive or main treatment modality, as part of a combined treatment plan, or for palliation of symptoms. Because of the frequency of metastases, chemotherapy often is used in treating lung cancer. Combination chemotherapy, which uses a regimen of several drugs, usually is used. New targeted treatments are under development with the goal of increasing survival and ultimately providing a cure for this type of cancer.

Therapy for SCLC is based on chemotherapy and radiation therapy.[50] Advances in the use of combination chemotherapy, along with thoracic irradiation, have improved the outlook for persons with SCLC. Because SCLC may metastasize to the brain, prophylactic cranial irradiation is often indicated. In most persons who achieve a complete remission from SCLC, the brain is the most frequent site of relapse. About half of such persons develop clinical metastasis within 3 years. Newer combination chemotherapy regimens and targeted therapies are being developed in hopes of providing treatment alternatives that increase survival and produce fewer treatment liabilities.

In summary, cancer of the lung is a leading cause of death worldwide. Cigarette smoking is implicated in the majority of cases of lung cancer. The risk for lung cancer among cigarette smokers increases with duration of smoking and the number of cigarettes smoked per day. Industrial hazards, such as exposure to asbestos, increase the risk for development of lung cancer. Because lung cancer develops insidiously, it often is far

advanced before it is diagnosed, a fact that is used to explain the poor 5-year survival rate. Carcinoma, which accounts for most primary lung cancers, can be subdivided into four major categories: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma. For purposes of staging and treatment, lung cancer is divided into small cell lung cancer and non–small cell lung cancer. The main reason for this is that almost all small cell lung cancers have metastasized at the time of diagnosis and are not amenable to surgical resection.

The manifestations of lung cancer can be attributed to the involvement of the lung and adjacent structures, the effects of local spread and metastasis, and paraneoplastic syndromes involving endocrine, neurologic, and hematologic dysfunction. As with other cancers, lung cancer causes nonspecific symptoms such as anorexia and weight loss. Treatment methods for lung cancer include surgery, irradiation, and chemotherapy.

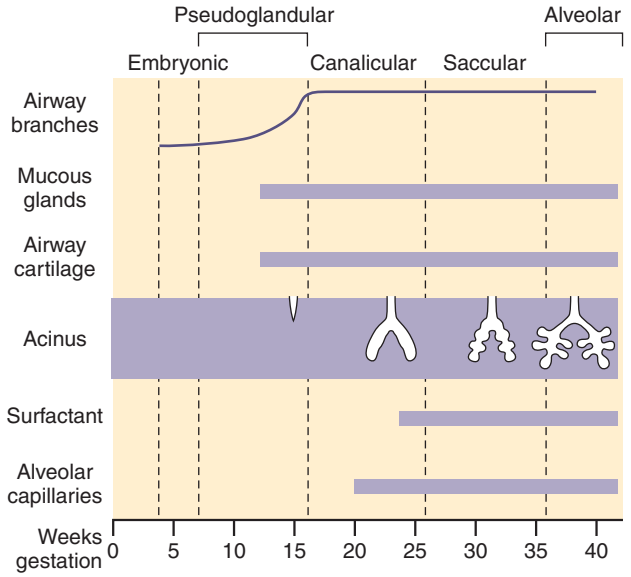


FIGURE 22-10. Development of various respiratory structures during the five stages of lung function. (From Behrman R.E., Kliegman R.M., Jenson H.B. [2004]. *Nelson textbook of pediatrics* [17th ed., p. 1358]. Philadelphia: Elsevier Saunders.)

Respiratory Disorders in Children

Acute respiratory diseases are the most common cause of illness in infancy and childhood. This section focuses on (1) lung development, with an emphasis on the developmental basis for lung disorders in children; (2) respiratory disorders in the neonate; and (3) respiratory infections in children. A discussion of bronchial asthma in children and cystic fibrosis is included in Chapter 23.

Lung Development

Although other body systems are physiologically ready for extrauterine life as early as 25 weeks of gestation, the lungs take much longer to mature. Immaturity of the respiratory system is a major cause of morbidity and mortality in infants born prematurely. Even at birth, the lungs are not fully mature, and additional growth and maturation continue well into childhood.

Lung development may be divided into five stages: embryonic period, pseudoglandular period, canalicular period, terminal saccular period, and alveolar (acinus) period[51,52] (Fig. 22-10). The first three stages are devoted to development of the conducting airways and the last two stages to development of the gas exchange portion of the lung. By the 25th to 28th weeks, sufficient terminal sacs are present to permit survival. Before this time, the premature lungs are incapable of adequate gas exchange. Type II alveolar cells begin to develop at approximately 24 weeks. These cells produce surfactant, a substance capable of lowering the surface tension of the air–alveoli interface (see Chapter 21). By the 26th to 30th weeks, sufficient amounts of surfactant are available to prevent alveolar collapse when breathing begins.

Although transformation of the lungs from glandlike structures to highly vascular, alveoli-like organs occurs during the late fetal period, mature alveoli do not form for some time after birth. The growth of the lung during infancy and early childhood involves an increase in the number rather than the size of the alveoli. Only about one sixth of the adult number of alveoli is present in the lungs of a full-term infant. By the eighth year of life, the adult complement of alveoli is present.[52]

Ventilation in the Neonate

Effective ventilation requires coordinated interaction between the muscles of the upper airways, including those of the pharynx and larynx, the diaphragm, and the intercostal muscles of the chest wall. In the infant, the diaphragm inserts more horizontally than in the adult. As a result, contraction of the diaphragm tends to draw the lower ribs inward, especially if the infant is placed in the horizontal position. The intercostal muscles, which normally lift the ribs during inspiration, are not fully developed in the infant. Instead, they function largely to stabilize the chest. Under circumstances such as crying, the intercostal muscles of the neonate function together with the diaphragm to splint the chest wall and prevent its collapse.

The chest wall of the neonate is highly compliant. A striking characteristic of neonatal breathing is the paradoxical inward movement of the upper chest during inspiration, especially during active sleep. Normally, the infant's lungs also are compliant, which is advantageous to the infant with its compliant chest cage because it takes only small changes in inspiratory pressure to inflate a compliant lung. However, with respiratory disorders that decrease lung compliance, the diaphragm must generate more negative pressure; as a result, the compliant chest wall structures are sucked inward. *Retractions* are abnormal inward movements of the chest wall during

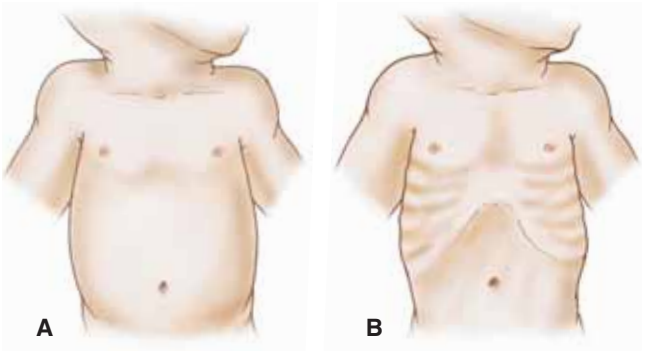


FIGURE 22-11. **(A)** Normal inspiratory appearance of the chest during unobstructed breathing in the neonate. **(B)** Sternal and intercostal retractions during obstructed breathing in the neonate.

inspiration; they may occur intercostally (between the ribs), in the substernal or epigastric area, and in the supraclavicular spaces (Fig. 22-11).

Airway Resistance

Normal lung inflation requires uninterrupted movement of air through the extrathoracic airways (i.e., nose, pharynx, larynx, and upper trachea) and intrathoracic airways (i.e., bronchi and bronchioles). The neonate (0 to 4 weeks of age) breathes predominantly through the nose and does not adapt well to mouth breathing. Any obstruction of the nose or nasopharynx may increase upper airway resistance and increase the work of breathing.

The airways of the infant and small child are much smaller than those of the adult. Because the resistance to airflow is inversely related to the fourth power of the radius (resistance = $1/\text{radius}^4$), relatively small amounts of mucus secretion, edema, or airway constriction can produce marked changes in airway resistance and airflow. Nasal flaring is a method that infants use to take in more air. This method of breathing increases the size of the nares and decreases the resistance of the small airways.

Normally, the extrathoracic airways (i.e., those extending from nose to the thoracic inlet) in the infant narrow during inspiration and widen during expiration, and the intrathoracic airways (i.e., those located within the thorax) widen during inspiration and narrow during expiration.[53] This occurs because the pressure inside the extrathoracic airways reflects the intrapleural pressures that are generated during breathing, whereas the pressure outside the airways is similar to atmospheric pressure. Thus, during inspiration, the pressure inside becomes more negative, causing the airways to narrow, and during expiration it becomes more positive, causing them to widen. In contrast to the extrathoracic airways, the pressure outside the intrathoracic airways is equal to the intrapleural pressure. These airways widen during inspiration as the surrounding intrapleural pressure becomes more negative and pulls them open, and they narrow during expiration as the surrounding pressure becomes more positive.[53] These changes are exaggerated in conditions that cause airway obstruction, particularly in infants with their softer and compliant airways.

Lung Volumes and Gas Exchange

The functional residual capacity, which is the air left in the lungs at the end of normal expiration, plays an important role in the infant's gas exchange. In the infant, the functional residual capacity occurs at a higher lung volume than in the older child or adult.[53] This higher end-expiratory volume results from a more rapid respiratory rate, which leaves less time for expiration. However, the increased residual volume is important to the neonate for several reasons: (1) it holds the airways open throughout all phases of respiration, (2) it favors the reabsorption of intrapulmonary fluids, and (3) it maintains more uniform lung expansion and enhances gas exchange. During active sleep, the tone of the upper airway muscles is reduced, so that the time spent in expiration is shorter and the intercostal activity that stabilizes the chest wall is less. This results in a lower end-expiratory volume and less optimal gas exchange during active sleep.

Control of Ventilation

Fetal arterial oxygen pressures (PO_2) normally range from 25 to 30 mm Hg, and carbon dioxide pressures (PCO_2) range from 45 to 50 mm Hg, independent of any respiratory movements. Any decrease in oxygen levels induces quiet sleep in the fetus with subsequent cessation of breathing movements, both of which lead to a decrease in oxygen consumption. Switching to oxygen derived from the aerated lung at birth causes an immediate increase in arterial PO_2 to approximately 50 mm Hg; within a few hours, it increases to approximately 70 mm Hg.[53] These levels, which greatly exceed fetal levels, cause the chemoreceptors that sense arterial PO_2 levels to become silent for several days. Although the infant's arterial PO_2 may fluctuate during this critical time, the chemoreceptors do not respond appropriately. It is not until several days after birth that the chemoreceptors "reset" their PO_2 threshold; only then do they become the major controller of breathing. However, the response seems to be biphasic, with an initial hyperventilation followed by a decreased respiratory rate and even apnea. In normal infants, especially those that are born prematurely, breathing patterns and respiratory reflexes depend on the arousal state.[54] Periodic breathing and apnea are characteristic of premature infants and reflect patterns of fetal breathing. The fact that they occur with sleep and disappear during wakefulness underscores the importance of arousal.

Alterations in Breathing Patterns

Most respiratory disorders in the infant or small child produce a decrease in lung compliance or an increase in airway resistance manifested by changes in breathing patterns, rib cage distortion (retractions), audible sounds, and use of accessory muscles.[53]

Children with restrictive lung disorders, such as pulmonary edema or respiratory distress syndrome, breathe at faster rates, and their respiratory excursions are shallow.

Grunting is an audible noise emitted during expiration. An expiratory grunt is common as the child tries to raise the end-expiratory pressure to maintain airway patency and prolong the period of oxygen and carbon dioxide exchange across the alveolar–capillary membrane.

Increased airway resistance can occur in either the extrathoracic or intrathoracic airways. When the obstruction is in the extrathoracic airways, inspiration is more prolonged than expiration. *Nasal flaring* (enlargement of the nares) helps reduce the nasal resistance and maintain airway patency. It can be a sign of increased work of breathing and is a significant finding in an infant. *Inspiratory retractions*, or pulling in of the soft tissue surrounding the cartilaginous and bony thorax, are often observed with airway obstruction in infants and small children (see Fig. 22-11). In conditions such as croup, the pressures distal to the point of obstruction must become more negative to overcome the resistance; this causes collapse of the distal airways, and the increased turbulence of air moving through the obstructed airways produces an audible crowing sound called a *stridor* during inspiration.

When the obstruction is in the intrathoracic airways, as occurs with bronchiolitis and bronchial asthma, expiration is prolonged and the child makes use of the accessory expiratory muscles (abdominals). Rib cage retractions may also be present. Intrapleural pressure becomes more positive during expiration because of air trapping; this causes collapse of intrathoracic airways and produces an audible wheezing or whistling sound during expiration.

Respiratory Disorders in the Neonate

The neonatal period is one of transition from placental dependency to air breathing. This transition requires functioning of the surfactant system, conditioning of the respiratory muscles, and establishment of parallel pulmonary and systemic circulations. Respiratory disorders develop in infants who are born prematurely or who have other problems that impair this transition. Among the respiratory disorders of the neonate are the respiratory distress syndrome, bronchopulmonary dysplasia, and persistent fetal circulation (i.e., delayed closure of the ductus arteriosus and foramen ovale; see Chapter 19).

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), also known as *hyaline membrane disease*, is one of the most common causes of respiratory disease in premature infants.[55,56] In these infants, pulmonary immaturity, together with surfactant deficiency, leads to alveolar collapse (see Chapter 21). The type II alveolar cells that produce surfactant do not begin to mature until approximately the 25th to 28th weeks of gestation; consequently, many premature infants are born with poorly functioning type II alveolar cells and have difficulty producing sufficient amounts of surfactant. The incidence of RDS is higher among preterm male infants, white infants, infants of diabetic mothers, and those subjected to asphyxia, cold stress,

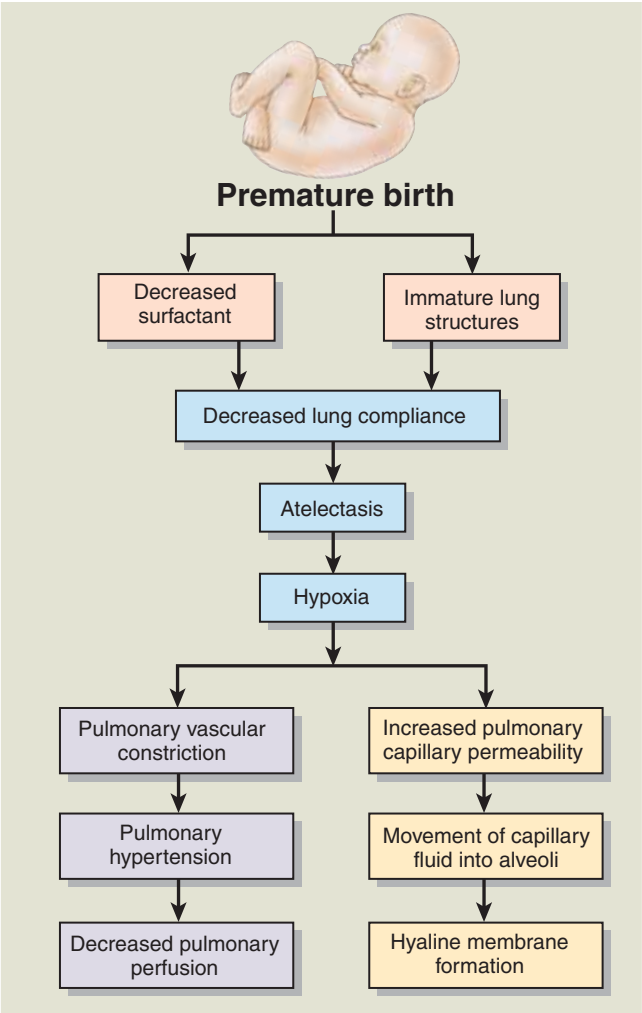


FIGURE 22-12. Pathogenesis of respiratory distress syndrome (RDS) in the infant.

precipitous deliveries, and delivery by cesarean section (when performed before the 38th week of gestation).

Surfactant synthesis is influenced by several hormones, including insulin and cortisol. Insulin tends to inhibit surfactant production; this explains why infants of insulin-dependent diabetic mothers are at increased risk for development of RDS. Cortisol can accelerate maturation of type II cells and formation of surfactant. The reason that premature infants born by cesarean section presumably are at greater risk for development of RDS is that they are not subjected to the stress of vaginal delivery, which is thought to increase the infants' cortisol levels. These observations have led to administration of corticosteroid drugs before delivery to mothers with infants at high risk for development of RDS.[55]

Surfactant reduces the surface tension in the alveoli, thereby equalizing the retractive forces in the large and small alveoli and reducing the amount of pressure needed to inflate and hold the alveoli open. Without surfactant, the large alveoli remain inflated, whereas the small alveoli become difficult to inflate. At birth, the first breath requires high inspiratory pressures to expand the lungs.

With normal levels of surfactant, the lungs retain up to 40% of the residual volume after the first breath, and subsequent breaths require far lower inspiratory pressures. With a surfactant deficiency, the lungs collapse between breaths, making the infant work as hard with each successive breath as with the first breath. The airless portions of the lungs become stiff and noncompliant. A hyaline membrane forms inside the alveoli as protein- and fibrin-rich fluids are pulled into the alveolar spaces. The fibrin–hyaline membrane constitutes a barrier to gas exchange, leading to hypoxemia and carbon dioxide retention, a condition that further impairs surfactant production.

Infants with RDS present with multiple signs of respiratory distress, usually within the first 24 hours of birth. Central cyanosis is a prominent sign. Breathing becomes more difficult, and retractions occur as the infant's soft chest wall is pulled in as the diaphragm descends. Grunting sounds accompany expiration. As the tidal volume drops because of atelectasis, the respiration rate increases (usually to 60 to 120 breaths per minute) in an effort to maintain normal minute ventilation. Fatigue may develop rapidly because of the increased work of breathing. The stiff lungs of infants with RDS also increase the resistance to blood flow in the pulmonary circulation. As a result, a hemodynamically significant patent ductus arteriosus may develop in infants with RDS (see Chapter 19).

The basic principles of treatment for infants with suspected RDS focus on the provision of supportive care, including gentle handling and minimal disturbance.[55] An incubator or radiant warmer is used to prevent hypothermia and increased oxygen consumption. Continuous cardiorespiratory monitoring is needed. Monitoring of blood glucose and prevention of hypoglycemia are also recommended. Oxygen levels can be assessed through an arterial (umbilical) line or by a transcutaneous oxygen sensor. Treatment includes administration of supplemental oxygen, continuous positive airway pressure through nasal prongs, and often assisted mechanical ventilation.

Exogenous surfactant therapy is used to prevent and treat RDS. The surfactants are suspended in saline and administered into the airways, usually through an endotracheal tube. The treatment often is initiated soon after birth in infants who are at high risk for RDS.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that occurs in infants, usually preterm infants treated with mechanical ventilation or prolonged oxygen supplementation.[55,57] BPD is primarily a disease of infants weighing less than 1000 g born at less than 28 weeks' gestation, many of whom have little or no lung disease at birth but develop progressive respiratory failure over the first few weeks of life. Although the disorder is most often associated with preterm birth, it can occur in term infants who require aggressive ventilator therapy for severe, acute lung disease.

Morphologic features of BPD include alveolar hypoplasia, variable alveolar wall fibrosis, and minimal airway disease.[55] The histopathology of BPD indicates interference with normal lung maturation, which may prevent subsequent lung growth and development. This pathogenesis is thought to be multifactorial and affect both the lungs and the heart. Mechanical ventilation and oxygen produce lung injury through their effect on alveolar and vascular development. Oxygen induces injury by producing free radicals that cannot be metabolized by the immature antioxidant systems of the preterm infant. Several clinical features, including immaturity, acquired infections, malnutrition, and symptomatic patent ductus arteriosus, may contribute to the development of BPD.[55]

BPD is characterized by chronic respiratory distress, persistent hypoxemia when breathing room air, reduced lung compliance, increased airway resistance, and severe expiratory flow limitation. There is a mismatching of ventilation and perfusion with development of hypoxemia and hypercapnia. Acute lung injury also impairs growth, structure, and function of the developing pulmonary circulation after premature birth. Pulmonary vascular resistance may be increased and pulmonary hypertension and cor pulmonale (i.e., right heart failure associated with lung disease) may develop. The infant with BPD often demonstrates tachycardia, rapid and shallow breathing, chest retractions, cough, and poor weight gain. Clubbing of the fingers occurs in children with severe disease. Hepatomegaly and periorbital edema may develop in infants with right heart failure.

The treatment of BPD includes nutritional support, maintenance of adequate oxygenation, and prompt treatment of infections. Severe BPD requires mechanical ventilation and administration of supplemental oxygen. Weaning from ventilation is accomplished gradually, and some infants may require ventilation at home. Rapid lung growth occurs during the first year of life, and lung function usually improves. Adequate nutrition is essential for recovery of infants with BPD. There has been an interest in the protective effect of polyunsaturated fatty acids, vitamin A, and other nutrients such as inositol (a sulfur-containing amino acid) and selenium in preventing lung injury in high-risk premature infants.[57]

Most adolescents and young adults who had severe BPD during infancy have some degree of pulmonary dysfunction, consisting of airway obstruction, airway hyperreactivity, or hyperinflation.

Respiratory Infections in Children

In children, respiratory tract infections are common, and although they are troublesome, they usually are not serious. Frequent infections occur because the immune system of infants and small children has not been exposed to many common pathogens; consequently, they tend to contract infections with each new exposure. Although most of these infections are not serious, the small size of an infant's or child's airways tends to foster impaired airflow and obstruction. For example, an infection that causes only sore throat and hoarseness in an adult may result in serious airway obstruction in a small child.

TABLE 22-2 Characteristics of Epiglottitis, Croup, and Bronchiolitis in Small Children

Characteristics	Epiglottitis	Croup	Bronchiolitis
Common causative agent	*Haemophilus influenzae* type B bacterium	Mainly parainfluenza virus	Respiratory syncytial virus
Most commonly affected age group	2–7 years (peak 3–5 years)	3 months to 5 years	Less than 2 years (most severe in infants younger than 6 months)
Onset and preceding history	Sudden onset	Usually follows symptoms of a cold	Preceded by stuffy nose and other signs
Prominent features	Child appears very sick and toxic Sits with mouth open and chin thrust forward Low-pitched stridor, difficulty swallowing, fever, drooling, anxiety *Danger of airway obstruction and asphyxia*	Stridor and a wet, barking cough Usually occurs at night Relieved by exposure to cold or moist air	Breathlessness; rapid, shallow breathing; wheezing; cough; and retractions of lower ribs and sternum during inspiration
Usual treatment	Hospitalization Intubation or tracheotomy Treatment with appropriate antibiotic	Mist tent or vaporizer Administration of oxygen	Supportive treatment, administration of oxygen and hydration

Upper Airway Infections

Acute upper airway infections are important in infants and small children. They include croup (laryngotracheobronchitis) and epiglottitis.[58–60] Croup is the more common and usually is benign and self-limited. Epiglottitis is a rapidly progressive and life-threatening condition. The site of involvement is illustrated in Figure 22-13, and the characteristics of both infections are described in Table 22-2.

Obstruction of the upper airways because of infection tends to exert its greatest effect during the inspiratory phase of respiration. Movement of air through an obstructed upper airway, particularly the vocal cords in the larynx, causes stridor. Impairment of the expiratory phase of respiration also can occur, causing wheezing. With mild to moderate obstruction, inspiratory stridor is more prominent than expiratory wheezing because the airways tend to dilate with expiration. When the swelling and obstruction become severe, the airways no longer can dilate during expiration, and both stridor and wheezing occur.

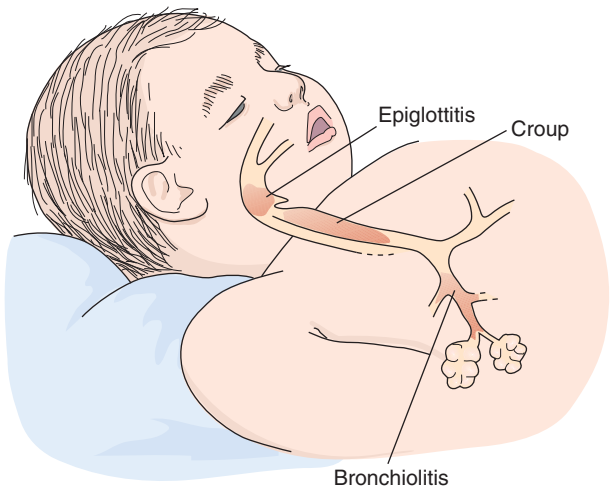


FIGURE 22-13. Location of airway obstruction in epiglottitis, acute laryngotracheobronchitis (croup), and bronchiolitis. (Courtesy of Carole Russell Hilmer, C.M.)

Cartilaginous support of the trachea and the larynx is poorly developed in infants and small children. These structures are soft and tend to collapse when the airway is obstructed and the child cries, causing the inspiratory pressures to become more negative. When this happens, the stridor and inspiratory effort are increased. The phenomenon of airway collapse in the small child is analogous to what happens when a thick beverage, such as a milkshake, is drunk through a soft paper or plastic straw. The straw collapses when the negative pressure produced by the sucking effort exceeds the flow of liquid through the straw.

Viral Croup. Croup is characterized by inspiratory stridor, hoarseness, and a barking cough. The British use the term *croup* to describe the cry of the crow or raven, and this is undoubtedly how the term originated.

Viral croup, more appropriately called *acute laryngotracheobronchitis,* is a viral infection that affects the larynx, trachea, and bronchi. The parainfluenza viruses account for approximately 75% all cases; the remaining 25% are caused by adenoviruses, respiratory syncytial virus, influenza A and B viruses, and measles virus.[60,61] Viral croup usually is seen in children 3 months to 5 years of age. The condition may affect the entire laryngotracheal tree, but because the subglottic area is the narrowest part of the respiratory tree in this age group, the obstruction usually is greatest in this area.

Although the respiratory manifestations of croup often appear suddenly, they usually are preceded by upper respiratory infections that cause rhinorrhea (i.e., runny nose), coryza (i.e., common cold), hoarseness, and a low-grade fever. In most children, the manifestation of croup advances only to stridor and slight dyspnea before they begin to recover. The symptoms usually subside when the child is exposed to moist air. For example, letting the bathroom shower run and then taking the child into the bathroom often brings prompt and dramatic relief of symptoms. Exposure to cold air also seems to relieve the airway spasm; often, the severe symptoms are relieved simply because the child is exposed to cold air on the way to the hospital emergency department. Viral croup does not respond to antibiotics; expectorants, bronchodilating agents, and antihistamines are not helpful. The child should be disturbed as little as possible and carefully monitored for signs of respiratory distress.

Airway obstruction may progress in some children. As obstruction increases, the stridor becomes continuous and is associated with nasal flaring with substernal and intercostal retractions. Agitation and crying aggravate the signs and symptoms, and the child prefers to sit up or be held upright. In the cyanotic, pale, or obstructed child, any manipulation of the pharynx, including use of a tongue depressor, can cause cardiorespiratory arrest and should be done only in a medical setting that has the facilities for emergency airway management. Other treatments may be required when a humidifier or mist tent is ineffective. One method is to administer a racemic mixture of epinephrine (L-epinephrine and D-epinephrine) by positive-pressure breathing through a face mask.[58] Establishment of an artificial airway may become necessary in severe airway obstruction.

Spasmodic Croup. Spasmodic croup manifests with symptoms similar to those of acute viral croup. Because the child is afebrile and lacks other manifestations of the viral prodrome, it is thought that it may have an allergic origin. Spasmodic croup characteristically occurs at night and tends to recur with respiratory tract infections. The episode usually lasts several hours and may recur several nights in a row.[60]

Most children with spasmodic croup can be effectively managed at home. An environment of high humidification (i.e., cold-water room humidifier or taking the child into a bathroom with a warm, running shower) lessens irritation and prevents drying of secretions.

Epiglottitis. Acute epiglottitis is a dramatic, potentially fatal condition characterized by inflammatory edema of the supraglottic area, including the epiglottis and pharyngeal structures (see Fig. 22-13), that comes on suddenly, bringing danger of airway obstruction and asphyxia.[60] In the past, the *H. influenzae* type B bacterium was the most commonly identified etiologic agent. It is seen less commonly since the widespread use of immunization against *H. influenzae* type B. Therefore, other agents such as *Streptococcus pyogenes, S. pneumoniae,* and *S. aureus* now represent the most common causes of pediatric epiglottitis.

The child appears pale, toxic, and lethargic and assumes a distinctive position—sitting up with the mouth open and the chin thrust forward. The child has difficulty in swallowing, a muffled voice, drooling, fever, and extreme anxiety. Moderate to severe respiratory distress is evident. There is inspiratory and sometimes expiratory stridor, flaring of the nares, and inspiratory retractions of the suprasternal notch and supraclavicular and intercostal spaces. Within a matter of hours, epiglottitis may progress to complete obstruction of the airway and death unless adequate treatment is instituted. Epiglottitis is a medical emergency and immediate establishment of an airway by endotracheal tube or tracheostomy usually is needed. If epiglottitis is suspected, the child should never be forced to lie down because this causes the epiglottis to fall backward and may lead to complete airway obstruction. Examination of the throat with a tongue blade or other instrument may cause airway spasm and cardiopulmonary arrest and should be done only by medical personnel experienced in intubation of small children. It also is unwise to attempt any procedure, such as drawing blood, that would heighten the child's anxiety because this also could precipitate airway spasm and cause death. Recovery from epiglottitis usually is rapid and uneventful after an adequate airway has been established and appropriate antibiotic therapy initiated.

Lower Airway Infections

Lower airway infections produce air trapping with prolonged expiration. Wheezing results from bronchospasm, mucosal inflammation, and edema. The child presents with increased expiratory effort, increased respiratory rate, and wheezing. If the infection is severe, there also are marked intercostal retractions and signs of impending respiratory failure.

Acute bronchiolitis is a viral infection of the lower airways, most commonly caused by the respiratory syncytial virus.[62–64] Other viruses, such as parainfluenza-3 virus and some adenoviruses, as well as mycoplasmas, also are causative. The infection produces inflammatory obstruction of the small airways and necrosis of the cells lining the lower airways. It usually occurs during the first 2 years of life, with a peak incidence between 3 and 6 months of age. The source of infection usually is a family member with a minor respiratory illness. Older children and adults tolerate bronchiolar edema much better than infants and do not manifest the clinical picture of bronchiolitis. Because the resistance to airflow in a tube is inversely related to the fourth power of the radius, even minor swelling of bronchioles in an infant can produce profound changes in airflow.

Most affected infants in whom bronchiolitis develops have a history of a mild upper respiratory tract infection. These symptoms usually last several days and may be accompanied by fever and diminished appetite. There is then a gradual development of respiratory distress, characterized by a wheezy cough, dyspnea, and irritability. The infant usually is able to take in sufficient air but has trouble exhaling it. Air becomes trapped in the lung distal to the site of obstruction and interferes with gas

exchange. Hypoxemia and, in severe cases, hypercapnia may develop. Airway obstruction may produce air trapping and hyperinflation of the lungs or collapse of the alveoli. Infants with acute bronchiolitis have a typical appearance, marked by breathlessness with rapid respirations, a distressing cough, and retractions of the lower ribs and sternum. Crying and feeding exaggerate these signs. Wheezing and crackles may or may not be present, depending on the degree of airway obstruction. In infants with severe airway obstruction, wheezing decreases as the airflow diminishes. Usually, the most critical phase of the disease is the first 48 to 72 hours. Cyanosis, pallor, listlessness, and sudden diminution in or absence of breath sounds indicates impending respiratory failure. The characteristics of bronchiolitis are described in Table 22-2.

Infants with respiratory distress usually are hospitalized. Treatment is supportive and includes administration of supplemental oxygen if the oxygen saturation consistently falls below 90%.[64] Elevation of the head facilitates respiratory movements and avoids airway compression. Handling is kept at a minimum to avoid tiring. Because the infection is viral, antibiotics are not effective and are given only for a secondary bacterial infection. Dehydration may occur as the result of increased insensible water losses because of the rapid respiratory rate and feeding difficulties, and measures to ensure adequate hydration are needed. If the child is in respiratory distress and adequate hydration cannot be achieved, the child should receive intravenous fluids.[64] Recovery usually begins after the first 48 to 72 hours and usually is rapid and complete. Adequate hand washing is essential to prevent the nosocomial spread of respiratory syncytial virus.

Signs of Impending Respiratory Failure

Respiratory problems of infants and small children often originate suddenly, and recovery usually is rapid and complete. Children are at risk for the development of airway obstruction and respiratory failure resulting from obstructive disorders or lung infection. The child with epiglottitis is at risk for airway obstruction. The child with bronchiolitis is at risk for respiratory failure resulting from impaired gas exchange. Children with impending respiratory failure due to airway or lung disease have rapid breathing; exaggerated use of the accessory muscles; retractions, which are more pronounced in the child than in the adult because of more compliant chest; nasal flaring; and grunting during expiration.[65] The signs and symptoms of impending respiratory failure are listed in Chart 22-1.

CHART 22-1 Signs of Respiratory Distress and Impending Respiratory Failure in the Infant and Small Child

- Severe increase in respiratory effort, including severe retractions or grunting, decreased chest movement
- Cyanosis that is not relieved by administration of oxygen (40%)
- Heart rate of 150 per minute or greater and increasing bradycardia
- Very rapid breathing (rate 60 per minute in the newborn to 6 months or above 30 per minute in children 6 months to 2 years)
- Very depressed breathing (rate 20 per minute or below)
- Retractions of the supraclavicular area, sternum, epigastrium, and intercostal spaces
- Extreme anxiety and agitation
- Fatigue
- Decreased level of consciousness

In summary, acute respiratory disease is the most common cause of illness in infancy and childhood, accounting for 50% of illnesses in children younger than 5 years of age and 30% of illnesses in children between 5 and 12 years of age. Although other body systems are physiologically ready for extrauterine life as early as 25 weeks of gestation, the lungs take longer. Immaturity of the respiratory system is a major cause of morbidity and mortality in premature infants.

Lung development may be divided into five stages: embryonic period, pseudoglandular period, canalicular period, saccular period, and alveolar period. By the 25th to 28th weeks of gestation, sufficient terminal air sacs are present to permit survival. It is also during this period that type II alveolar cells, which produce surfactant, begin to function. Lung development is incomplete at birth; an infant is born with only one-eighth to one-sixth the adult number of alveoli. Alveoli continue to be formed during early childhood, reaching the adult number of 300 million alveoli by 8 years of age.

Most respiratory disorders in infants and children involve a loss of lung compliance that results in shallow respirations. An expiratory grunt is common as the child tries to raise the functional residual capacity by closing the glottis at the end of expiration. Obstruction of the extrathoracic airways often produces turbulence of airflow and an audible inspiratory crowing sound called *stridor,* and obstruction of the intrathoracic airways produces an audible expiratory wheezing or whistling sound. Respiratory distress syndrome is one of the most common causes of respiratory disease in premature infants. In these infants, pulmonary immaturity, together with surfactant deficiency, leads to alveolar collapse. Bronchopulmonary dysplasia is a chronic pulmonary disease that develops in premature infants who were treated with mechanical ventilation.

Because of the small size of the airway of infants and children, respiratory tract infections in these groups often are more serious. Infections that may cause only a sore throat and hoarseness in the adult may produce serious obstruction in the child. Among the respiratory tract infections that affect small children are croup, epiglottitis, and bronchiolitis. Epiglottitis is a life-threatening supraglottic infection that may cause airway obstruction and asphyxia.

REVIEW EXERCISES

1. It is flu season, and although you had a flu shot last year, you have not had one this year. Imagine yourself experiencing an abrupt onset of fever, chills, malaise, muscle aching, and nasal stuffiness.

A. Which of these symptoms would lead you to believe you are coming down with the flu?
B. Because you hate to miss classes, you decide to go to the student health center to get an antibiotic. After being seen by a health professional, you are told that antibiotics are ineffective against the flu virus, and you are instructed not to attend classes but instead to go home, take acetaminophen for your fever, go to bed and stay warm, and drink a lot of fluids. Explain the rationale for each of these recommendations.
C. Explain why last year's flu shot did not protect you during this year's flu season.
D. There is current concern about the possibility of an influenza pandemic such as the one that occurred during the 1917–1918 season. What is the rationale for this concern?

2. Bacterial (e.g., *S. pneumoniae*) pneumonia is commonly manifested by a cough productive of sputum, whereas with atypical (e.g., *M. pneumoniae*) pneumonia, the cough is usually nonproductive or absent.

A. Explain.

3. A 4-month-old infant is admitted to the pediatric intensive care unit with a diagnosis of bronchiolitis. The infant is tachypneic, with wheezing, nasal flaring, and retractions of the lower sternum and intercostal spaces during inspiration.

A. What is the usual pathogen in bronchiolitis? Would this infection be treated with an antibiotic?
B. Explain the physiologic mechanism involved in the retraction of the lower sternum and intercostal spaces during inspiration.
C. What would be the signs of impending respiratory failure in this infant?

REFERENCES

1. American Lung Association. (2007). *Pneumonia fact sheet.* [Online] Available: http://www.lungusa.org. Accessed May 22, 2009.
2. McAdams A.J., Sharpe A.H. (2010). Infectious Diseases. In Kumar V., Abbas A.K., Fausto N., Aster J.C. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 366–372). Philadelphia: Saunders Elsevier.
3. Covington T.R., Henkin R., Miller S., et al. (2004). Treating the common cold. *American Journal of Nurse Practitioners* 8(11), 77–88.
4. Heikkinen T., Järvinsen A. (2003). The common cold. *Lancet* 361, 51–59.
5. Goldman D.A. (2000). Transmission of viral respiratory tract infections in the home. *Pediatric Infectious Disease Journal* 19, S97–S107.
6. Simasek M., Blandino D.A. (2007). Treatment of the common cold. *American Family Physician* 75, 512–522.
7. Winstead W. (2003). Rhinosinusitis. *Primary Care Clinics in Office Practice* 30, 137–154.
8. Brook I. (2007). Acute and chronic bacterial sinusitis. *Infectious Disease Clinics of North America* 21, 427–446.
9. Scheid D.C., Hamm R.M. (2004). Acute bacterial rhinosinusitis in adults: Part I. Evaluation; Part II. Treatment. *American Family Physician* 70, 1685–1692, 1697–1704.
10. Leung R.S., Katial R. (2007). The diagnosis and management of acute and chronic sinusitis. *Primary Care: Clinics in Office Practice* 35, 11–24.
11. Slavin R.G., Spector S.L., Bernstein I.L., Chief editors, American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. (2005). The diagnosis and management of sinusitis: A practice parameter update. *Journal of Allergy and Clinical Immunology* 116(Suppl 6), S13–S17.
12. Piccirillo J.F. (2004). Acute bacterial sinusitis. *New England Journal of Medicine* 351, 902–910.
13. Advisory Committee on Immunization Practices. (2007). Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 56(RR-6), 1–54.
14. Cunha B.A. (2004). Influenza: Historical aspects of epidemics and panepidemics. *Infectious Disease Clinics of North America* 18, 141–155.
15. Husain A.N. (2010). The Lung. In Kumar V., Abbas A.K., Fausto N., Aster J.C. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 710–731). Philadelphia: Saunders Elsevier.
16. Beigel J.H. (2008). Influenza. *Critical Care Medicine* 36(9), 2660–2666.
17. Waite S., Jeudy J., White C.S. (2006). Acute lung infections in normal and immunocompromised hosts. *Radiologic Clinics of North America* 44, 295–315.
18. Chestnut M.S., Murray J.A., Prendergast T.J. (2009). Pulmonary disorders. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 237–255). New York: McGraw-Hill.
19. Beasley M.B., Travis W.D., Rubin E. (2008). The respiratory system. In Rubin R., Strayer D. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 491–503). Philadelphia: Lippincott Williams & Wilkins.
20. Moran G.J., Talan D.A., Abrahamian F.M. (2008). Diagnosis and management of pneumonia in the emergency department. *Infectious Disease Clinics of North America* 22, 53–72.
21. Halm E.A., Teirstein A.S. (2002). Management of community-acquired pneumonia. *New England Journal of Medicine* 347, 2039–2045.
22. Apisarnthanarak A., Mundy L.M. (2005). Etiology of community-acquired pneumonia. *Clinics in Chest Medicine* 26, 47–55.
23. Lutfiyya N.N., Henley E., Chang L.F. (2006). Diagnosis and treatment of community-acquired pneumonia. *American Family Physician* 73, 442–450.
24. Kieninger A.N., Lipsett P.A. (2009). Hospital-acquired pneumonia: Pathophysiology, diagnosis, and treatment. *Surgical Clinics of North America* 89, 439–461.
25. Catterall J.R. (1999). *Streptococcus pneumoniae. Thorax* 54, 929–937.
26. Centers for Disease Control and Prevention. (2010). Recommended adult immunization schedule. *Morbidity and Mortality Weekly Report* 59(01), 1–4.
27. Centers for Disease Control and Prevention. (2010). Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and

recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010. *Morbidity and Mortality Weekly Report* 59(08), 258–261.
28. Stout J.E., Yu V.C. (1997). Legionellosis. *New England Journal of Medicine* 337, 682–688.
29. American Lung Association. (2008). *Tuberculosis* [Online] Available: http://www.lungusa.org. Accessed May 25, 2009.
30. Schwartz D.A., Genta R.M., Bennett D.P., et al. (2008). Infectious and parasitic diseases. In Rubin R., Strayer D. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 341–344). Philadelphia: Lippincott Williams & Wilkins.
31. Murray P.R., Rosenthal K.S., Kobayaski G.S., et al. (2002). *Medical microbiology* (4th ed., pp. 366–377). St. Louis: Mosby.
32. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. (2005). Controlling tuberculosis in the United States. *American Journal of Respiratory Critical Care Medicine* 172, 1169–1227.
33. Goldberg S. (2004). Tuberculosis. *Clinics in Family Practice* 6, 175–197.
34. Brodie D., Schluger N.W. (2005). The diagnosis of tuberculosis. *Clinics in Chest Medicine* 26, 247–271.
35. Nahid P., Pal M., Hopewell P.C. (2006). Advances in the diagnosis and treatment of tuberculosis. *Proceedings of the American Thoracic Society* 3, 103–110.
36. Barnes P.F., Cave M.D. (2003). Molecular epidemiology of tuberculosis. *New England Journal of Medicine* 349(12), 1149–1156.
37. Ingle L.D., Wilson J.W. (2008). Update on the treatment of tuberculosis. *American Family Physician* 78(4), 457–465, 469–470.
38. Potter B., Rindfleisch K. (2005). Management of active tuberculosis. *American Family Physician* 72, 2225–2232.
39. O'Brien R.J., Spigelman M. (2005). New drugs for tuberculosis: Current status and future prospects. *Clinics in Chest Medicine* 26, 327–340.
40. Shelburne S.A., Hamill R.J. (2009). Mycotic infections. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 1358–1366). New York: McGraw-Hill.
41. Kauffman C.A. (2006). Endemic mycoses: Blastomycosis, histoplasmosis, and sporotrichosis. *Infectious Disease Clinics of North America* 20, 645–662.
42. Wheat L.J., Kauffman C.A. (2003). Histoplasmosis. *Infectious Disease Clinics of North America* 17, 1–19.
43. Anstead G.M., Grayhill J.R. (2006). Coccidioidomycosis. *Infectious Disease Clinics of North America* 20, 621–643.
44. Bradsher R.W., Chapman S.W., Pappas P.G. (2003). Blastomycosis. *Infectious Disease Clinics of North America* 17, 21–40.
45. Herbst R.S., Heymach J.V., Lippman S.M. (2008). Lung cancer. *New England Journal of Medicine* 359(73), 1367–1380.
46. Ginsberg M.S., Grewal R.K., Heelan R.T. (2007). Lung cancer. *Radiologic Clinics of North America* 45, 21–43.
47. Oklund S.H., Jett J.R. (2002). Small cell lung cancer: Current therapy and promising new regimens. *Oncologist* 7, 563–568.
48. Walker S. (2003). Updates in small cell lung cancer treatment. *Clinical Journal of Oncology Nursing* 7, 563–568.
49. Simson G.R. (2003). Small cell lung cancer. *Chest* 123(Suppl), 259S–268S.
50. Spira A., Ettinger D.S. (2004). Multidisciplinary management of lung cancer. *New England Journal of Medicine* 350, 379–392.
51. Haddad G.G., Fontán J.J.P. (2004). Development of the respiratory system. In Behrman R.E., Kliegman R.M., Jenson H.L. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 1362–1370). Philadelphia: W.B. Saunders.
52. Moore K., Persaud T.V.N. (2003). *The developing human* (6th ed., pp. 242–253). Philadelphia: W.B. Saunders.
53. Sarnaik A.P., Heidemann S.M. (2007). Respiratory pathophysiology and regulation. In Behrman R.E., Kliegman R.M., Jensen H.L., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1719–1731). Philadelphia: Saunders Elsevier.
54. Crocetti M., Barone M.A. (Eds.). (2004). *Oski's essential pediatrics* (2nd ed., pp. 44–52, 374–388). Philadelphia: Lippincott Williams & Wilkins.
55. Dudell G.G., Stoll B.J. (2007). Respiratory tract disorders. In Behrman R.E., Kliegman R.M., Jensen H.L., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 731–741). Philadelphia: Saunders Elsevier.
56. Rodriguez R.J. (2003). Management of respiratory distress syndrome. *Respiratory Care* 48, 279–286.
57. Kinsella J.P., Greenough A., Abman S.H. (2006). Bronchopulmonary dysplasia. *Lancet* 367, 1421–1430.
58. Roosevelt G.E. (2007). Acute inflammatory upper airway obstruction. In Behrman R.E., Kliegman R.M., Jenson H.L., et. al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1762–1766). Philadelphia: Saunders Elsevier.
59. Shah S., Sharieff G.Q. (2007). Pediatric respiratory infections. *Emergency Clinics of North America* 25, 961–979.
60. Sobol S.E., Zapata S. (2008). Epiglottitis and croup. *Otolaryngologic Clinics of North America* 41, 551–566.
61. Knutson D., Arling A. (2004). Viral croup. *American Family Physician* 69, 535–542.
62. Smyth R.L., Openshaw P.J.M. (2006). Bronchiolitis. *Lancet* 368, 312–322.
63. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. (2006). Diagnosis and management of bronchiolitis. *Pediatrics* 118, 1774–1793.
64. Coffin S.E. (2005). Bronchiolitis: In-patient focus. *Pediatrics* 52, 1047–1057.
65. Frankel L.R. (2007). Respiratory distress and failure. In Behrman R.E., Kliegman R.M., Jenson H.L., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 421–424). Philadelphia: Saunders Elsevier.

Physiologic Effects of Ventilation and Diffusion Disorders
Hypoxemia
Hypercapnia
Disorders of Lung Inflation
Disorders of the Pleura
Pleuritis
Pleural Effusion
Pneumothorax
Atelectasis
Obstructive Airway Disorders
Physiology of Airway Disease
Bronchial Asthma
Etiology and Pathogenesis
Clinical Features
Severe Asthma
Bronchial Asthma in Children
Chronic Obstructive Pulmonary Disease
Emphysema
Chronic Bronchitis
Clinical Features
Bronchiectasis
Etiology and Pathogenesis
Clinical Features
Cystic Fibrosis
Etiology and Pathogenesis
Clinical Features
Interstitial Lung Diseases
Pathogenesis
Clinical Features
Idiopathic Pulmonary Fibrosis
Sarcoidosis
Disorders of the Pulmonary Circulation
Pulmonary Embolism
Clinical Features
Pulmonary Hypertension
Secondary Pulmonary Hypertension
Primary Pulmonary Arterial Hypertension
Cor Pulmonale
Acute Respiratory Disorders
Acute Lung Injury/Acute Respiratory Distress Syndrome
Etiology and Pathogenesis
Clinical Features
Acute Respiratory Failure
Hypoxemic Respiratory Failure
Hypercapnic/Hypoxemic Respiratory Failure
Clinical Features

Chapter 23

Disorders of Ventilation and Gas Exchange

The major function of the lungs is to oxygenate the blood and remove carbon dioxide as a means of supporting the metabolic functions of the body's tissues. Many types of disease are capable of disrupting the normal gas exchange function of the lungs. In some cases the disruption is temporary and in other cases it is marked and disabling. This chapter focuses on disorders that disrupt ventilation and pulmonary gas exchange. It is divided into six sections: the physiologic effects of altered ventilation and gas exchange, disorders of lung inflation, obstructive airway disorders, chronic interstitial lung disorders, disorders of the pulmonary circulation, and acute respiratory disorders.

Physiologic Effects of Ventilation and Diffusion Disorders

The primary function of the respiratory system is gas exchange between the atmospheric air in the alveoli and the blood in the pulmonary circulation.[1–3] In the process, oxygen (O_2) from air in the alveoli diffuses into the blood in the pulmonary capillaries and carbon dioxide (CO_2) moves in the opposite direction, from the blood in pulmonary capillaries into the alveoli (discussed in Chapter 21). This section of the chapter provides a brief overview of the causes and manifestations of hypoxemia and hypercapnia (hypercarbia) that develop as the result of impaired ventilation and gas exchange that occur with many of the disorders discussed in the chapter.

Respiration can be divided into three parts: ventilation, perfusion, and diffusion. *Ventilation* involves the movement of air into the lungs. However, not all inspired air reaches the alveoli where gas exchange takes place. Of each 500 mL of air, which is the typical volume in the air that is inhaled in the average-sized adult, about 150 mL remains behind in the airways, with the remainder (350 mL) moving into the alveoli. This is called *alveolar ventilation* and is of key importance because it represents the amount of air that is available for gas exchange. The actual movement or *diffusion* of O_2 and CO_2 takes place

in the lung driven by the partial pressure (P) of the gases. Thus, oxygen moves from alveoli, where the partial pressure of oxygen (PO_2) averages 104 mm Hg when breathing room air, to the blood in the pulmonary capillaries, where the average PO_2 is only 40 mm Hg.[1] Carbon dioxide moves in the opposite direction, from the blood in the pulmonary capillaries, where the average PCO_2 is 45 mm Hg, to the alveolar air, where the PCO_2 is 40 mm Hg.[1] These values vary with tissue metabolism and the oxygen content of the inspired air.

Perfusion involves circulation of blood through the pulmonary circulation, including the pulmonary capillaries, where gas exchange takes place. Adequate oxygenation of the blood and removal of CO_2 depend on perfusion of blood through the pulmonary blood vessels and appropriate contact between ventilated alveoli and perfused capillaries of the pulmonary circulation (ventilation and perfusion matching).

Hypoxemia

Hypoxemia refers to a reduction in PO_2 of the arterial blood. Hypoxemia can result from an inadequate amount of O_2 in the air, disease of the respiratory system, dysfunction of the neurologic system, or alterations in circulatory function. The mechanisms whereby respiratory disorders lead to a significant reduction in PO_2 are hypoventilation, impaired diffusion of gases, inadequate circulation of blood through the pulmonary capillaries, and mismatching of ventilation and perfusion[2] (see Chapter 21). Often, more than one mechanism contributes to hypoxemia in persons with a respiratory or cardiac disease.

Hypoxemia produces its effects through tissue hypoxia and the compensatory mechanisms that the body uses to adapt to the lowered oxygen level. Body tissues vary considerably in their vulnerability to hypoxia; those with the greatest need are the brain and heart. If the PO_2 of the tissues falls below a critical level, aerobic metabolism ceases and anaerobic metabolism takes over, with formation and release of lactic acid. This results in increased serum lactate levels and metabolic acidosis (see Chapter 8).

Mild hypoxemia or reduction in the PO_2 of arterial blood produces few manifestations. Recruitment of sympathetic nervous system compensatory mechanisms produces an increase in heart rate, peripheral vasoconstriction, diaphoresis, and a mild increase in blood pressure. There may be slight impairment of mental performance, a decrease in visual acuity, and sometimes hyperventilation. This is because hemoglobin saturation still is approximately 90% when the PO_2 is only 60 mm Hg (see Chapter 21, Fig. 21-22). More pronounced hypoxemia may produce personality changes, restlessness, agitated or combative behavior, uncoordinated muscle movements, euphoria, impaired judgment, delirium, and, eventually, stupor and coma.

Cyanosis refers to the bluish discoloration of the skin and mucous membranes that results from an excessive concentration of reduced or deoxygenated hemoglobin in the small blood vessels. It usually is most marked in the lips, nail beds, ears, and cheeks. The degree of cyanosis is modified by the amount of cutaneous pigment, skin thickness, and the state of the cutaneous capillaries. Cyanosis is more difficult to distinguish in persons with dark skin and in areas of the body with increased skin thickness. Although cyanosis may be evident in persons with respiratory failure, it often is a late sign. A concentration of approximately 5 g/dL of deoxygenated hemoglobin is required in the circulating blood for cyanosis to occur.[1] The absolute quantity of reduced hemoglobin, rather than the relative quantity, is important in producing cyanosis. Persons with anemia and low hemoglobin levels are less likely to exhibit cyanosis (because they have less hemoglobin to deoxygenate), even though they may be relatively hypoxic because of their decreased ability to transport oxygen, than persons who have high hemoglobin concentrations. A person with a high hemoglobin level because of polycythemia may be cyanotic without being hypoxic.

Cyanosis can be divided into two types: central and peripheral. *Central cyanosis* is evident in the tongue and lips. It is caused by an increased amount of deoxygenated hemoglobin in the arterial blood. *Peripheral cyanosis* occurs in the extremities and on the tip of the nose or ears. It is caused by slowing of blood flow to an area of the body, with increased extraction of oxygen from the blood. It results from vasoconstriction and diminished peripheral blood flow, as occurs with cold exposure, shock, heart failure, or peripheral vascular disease.

The manifestations of chronic hypoxemia may be insidious in onset and attributed to other causes, particularly in persons with chronic lung disease. The body compensates for chronic hypoxemia by increased ventilation, pulmonary vasoconstriction, and increased production of red blood cells. Pulmonary vasoconstriction occurs as a local response to alveolar hypoxia; it increases pulmonary arterial pressure and improves the matching of ventilation and blood flow. Increased production of red blood cells results from the release of erythropoietin from the kidneys in response to hypoxia (see Chapter 13). Polycythemia increases the red blood cell concentration and the oxygen-carrying capacity of the blood. Other adaptive mechanisms include a shift to the right in the oxygen dissociation curve, which increases O_2 release to the tissues (see Chapter 21).

Diagnosis of hypoxemia is based on clinical observation and diagnostic tests that measure PO_2 levels. The analysis of arterial blood gases provides a direct measure of the O_2 content of the blood and is the best indicator of the ability of the lungs to oxygenate the blood. Mixed venous oxygen saturation (SvO_2; i.e., hemoglobin saturation) reflects the body's extraction at the tissue levels. Venous blood samples can be obtained either through a pulmonary artery catheter or central line. The latter is less accurate because the blood has not yet been mixed in the right ventricle.

Noninvasive measurements of arterial O_2 saturation of hemoglobin can be obtained using an instrument called the *pulse oximeter.* The pulse oximeter uses light-emitting diodes and combines plethysmography (i.e., changes in light absorbance and vasodilation) with spectrophotometry.[4] Spectrophotometry uses a red-wavelength

light that passes through oxygenated hemoglobin and is absorbed by deoxygenated hemoglobin, and an infrared-wavelength light that is absorbed by oxygenated hemoglobin and passes through deoxygenated hemoglobin. Sensors that can be placed on the finger, toe, ear, or forehead are available. The pulse oximeter cannot distinguish between oxygen-carrying hemoglobin and carbon monoxide–carrying hemoglobin. In addition, the pulse oximeter cannot detect elevated levels of methemoglobin. Although pulse oximetry is not as accurate as arterial blood gas measurements, it provides the means for noninvasive and continuous monitoring of O_2 saturation, which is a useful indicator of respiratory and circulatory status.

Treatment of hypoxemia is directed toward correcting the cause of the disorder and increasing the gradient for diffusion through the administration of supplemental oxygen. Oxygen may be delivered by nasal cannula or mask or administered directly into an endotracheal or tracheostomy tube in persons who are mechanically ventilated. A high-flow administration system is one in which the flow rate and reserve capacity are sufficient to provide all the inspired air.[5] A low-flow administration system delivers less than the total inspired air. The concentration of O_2 being administered (usually determined by the flow rate) is based on the PO_2. A high flow rate must be carefully monitored in persons with chronic lung disease because increases in PO_2 above 60 mm Hg may depress the ventilatory drive. Although oxygen is necessary and vital to life, there also is the danger of oxygen toxicity with high concentrations of oxygen. Continuous breathing of oxygen at high concentrations can lead to diffuse parenchymal lung injury. Persons with healthy lungs begin to experience respiratory symptoms such as cough, sore throat, substernal distress, nasal congestion, and painful inspiration after breathing pure oxygen for 24 hours.[2]

Hypercapnia

Hypercapnia refers to an increase in the carbon dioxide content of the arterial blood.[3,6] The carbon dioxide level in the arterial blood, or PCO_2, is proportional to carbon dioxide production and inversely related to alveolar ventilation. The diagnosis of hypercapnia is based on physiologic manifestations, arterial pH, and arterial blood gas levels.

Hypercapnia can occur in a number of disorders that cause hypoventilation or mismatching of ventilation and perfusion.[3,6] The diffusing capacity of carbon dioxide is 20 times that of oxygen; therefore, hypercapnia without hypoxemia is usually observed only in situations of hypoventilation.[2] In cases of ventilation–perfusion mismatching, hypercapnia is usually accompanied by a decrease in arterial PO_2 levels. Conditions that increase carbon dioxide production, such as an increase in metabolic rate or a high-carbohydrate diet, can contribute to the degree of hypercapnia that occurs in persons with impaired respiratory function. Changes in the metabolic rate resulting from an increase in activity, fever, or disease can have profound effects on carbon dioxide production. Alveolar ventilation usually rises proportionally with these changes, and hypercapnia occurs only when this increase is inappropriate.

Hypercapnia affects a number of body functions, including acid-base balance and kidney, nervous system, and cardiovascular function. Elevated levels of PCO_2 produce a decrease in pH and respiratory acidosis (see Chapter 8). The body normally compensates for an increase in PCO_2 by increasing renal bicarbonate (HCO_3^-) retention, which results in an increase in serum HCO_3^- and pH levels. As long as the pH is within normal range, the main complications of hypercapnia are those resulting from the accompanying hypoxia. Because the body adapts to chronic increases in blood levels of carbon dioxide, persons with chronic hypercapnia may not have symptoms until the PCO_2 becomes markedly elevated.

The treatment of hypercapnia is directed at decreasing the work of breathing and improving the ventilation–perfusion balance. The use of intermittent rest therapy, such as nocturnal negative-pressure ventilation, in persons with chronic obstructive disease or chest wall disease may be effective in increasing the strength and endurance of the respiratory muscles and improving the PCO_2. Respiratory muscle retraining aimed at improving the respiratory muscles, their endurance, or both has been used to improve exercise tolerance and diminish the likelihood of respiratory fatigue. Mechanical ventilation may become necessary in situations of acute hypercapnia.

In summary, the primary function of the respiratory system is to remove appropriate amounts of CO_2 from the blood entering the pulmonary circulation and provide adequate O_2 to blood leaving the pulmonary circulation. This is accomplished through the process of ventilation, in which air moves into and out of the lungs, and diffusion, in which gases move between the alveoli and the pulmonary capillaries. Although both diffusion and ventilation affect gas exchange, oxygenation of the blood largely depends on diffusion, and removal of carbon dioxide depends on ventilation.

Hypoxemia refers to a decrease in arterial blood oxygen levels that results in a decrease in tissue oxygenation. Hypoxemia can occur as the result of hypoventilation, diffusion impairment, shunt, and ventilation–perfusion impairment. Acute hypoxemia is manifested by increased respiratory effort (increased respiratory and heart rates), cyanosis, and impaired sensory and neurologic function. The body compensates for chronic hypoxemia by increased ventilation, pulmonary vasoconstriction, and increased production of red blood cells.

Hypercapnia refers to an increase in carbon dioxide levels. The manifestations of hypercapnia consist of those associated with a decrease in pH (respiratory acidosis); vasodilation of blood vessels, including those in the brain; and depression of central nervous system function.

Disorders of Lung Inflation

Air entering through the airways inflates the lung, and the negative pressure in the pleural cavity keeps the lung from collapsing. Disorders of lung inflation are caused by conditions that obstruct the airways, cause lung compression, or produce lung collapse. There can be compression of the lung by an accumulation of fluid in the intrapleural space; complete collapse of an entire lung, as in pneumothorax; or collapse of a segment of the lung due to airway obstruction, as in atelectasis.

Disorders of the Pleura

The pleura is a thin, double-layered serous membrane that encases the lungs. The outer *parietal layer* lines the thoracic wall and superior aspect of the diaphragm. It continues around the heart and between the lungs, forming the lateral walls of the mediastinum. The inner *visceral layer* covers the lung and is adherent to all its surfaces. The pleural cavity or space between the two layers contains a thin layer of serous fluid that lubricates the pleural surfaces and allows the parietal and visceral pleurae to slide smoothly over each other during breathing movements. The pressure in the pleural cavity, which is negative in relation to atmospheric pressure, holds the lungs against the chest wall and keeps them from collapsing. Disorders of the pleura include pleural inflammation, pleural effusion, hemothorax, and pneumothorax.

Pleuritis

Pleuritis (also called *pleurisy*) refers to inflammation of the parietal pleura that typically results in characteristic pleural pain.[7] Since the visceral pleura does not contain pain receptors, pleural pain results from somatic pain fibers that innervate the parietal pleura. The pain is usually unilateral and abrupt in onset, and is usually made worse by chest movements such as deep breathing and coughing that exaggerate pressure changes in the pleural cavity and increase movement of the inflamed or injured pleural surfaces. Because deep breathing is painful, tidal volumes usually are kept small, and breathing becomes more rapid to maintain the minute volume. Reflex splinting of the chest muscles may occur, causing a lesser respiratory expansion on the affected side. There are numerous causes of pleuritis and pleuritic pain. The setting in which it occurs provides useful diagnostic information. In young healthy individuals, it is commonly caused by viral infections or pneumonia. The presence of pleural effusion or air in the pleural cavity requires further diagnostic information.

It is important to differentiate pleural pain from pain produced by other conditions, such as musculoskeletal strain of chest muscles, bronchial irritation, and myocardial disease. Musculoskeletal pain may occur as the result of frequent, forceful coughing. This type of pain usually is bilateral and located in the inferior portions of the rib cage, where the abdominal muscles insert into the anterior rib cage. It is made worse by movements associated with contraction of the abdominal muscles. The pain associated with irritation of the bronchi usually is substernal and dull in character rather than sharp. It is made worse with coughing but is not affected by deep breathing. Myocardial pain, which is discussed in Chapter 19, usually is located in the substernal area and is not affected by respiratory movements.

Treatment of pleuritis consists of treating the underlying disease and inflammation. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., indomethacin) may be used for pleural pain. Although these agents reduce inflammation, they may not entirely relieve the discomfort associated with deep breathing and coughing.

Pleural Effusion

Pleural effusion refers to an abnormal collection of fluid in the pleural cavity.[8,9] Like fluid developing in other transcellular spaces in the body, pleural effusion occurs when the rate of fluid formation exceeds the rate of its removal (see Chapter 8). Normally, fluid enters the pleural space from capillaries in the parietal pleura and is removed by the lymphatics situated in the parietal pleura. Fluid can also enter from the interstitial spaces of the lung through the visceral pleura or from small holes in the diaphragm. The lymphatics have the capacity to reabsorb about 20 times the fluid that is formed.[9] Accordingly, fluid may accumulate when there is excess fluid formation (from the interstitium of the lung, the parietal pleura, or the peritoneal cavity) or when there is decreased removal by the lymphatics.

The fluid that accumulates in a pleural effusion may be a transudate or exudate, purulent (containing pus), chyle, or sanguineous (bloody). The accumulation of a serous transudate (clear fluid) in the pleural cavity often is referred to as *hydrothorax*. The condition may be unilateral or bilateral. The most common cause of hydrothorax is congestive heart failure.[9] Other causes are renal failure, nephrosis, liver failure, and malignancy. An *exudate* is a pleural fluid that has a specific gravity greater than 1.020 and often contains inflammatory cells.

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid.[9] LDH is an enzyme that is released from inflamed and injured pleural tissue. Exudative pleural effusions are characterized by the presence of proteins and/or elevated LDH levels in the pleural fluid, whereas transudates have none of these features. Because measurements of LDH are easily obtained from a sample of pleural fluid, it is a useful marker for diagnosis of exudative pleural disorders. Conditions that produce exudative pleural effusions are bacterial pneumonia, viral infection, pulmonary infarction, and malignancies.

Empyema refers to an infection in the pleural cavity that results in exudate containing glucose, proteins, leukocytes, and debris from dead cells and tissue.[9] It is caused by an adjacent bacterial pneumonia, rupture of a lung abscess into the pleural space, invasion from a subdiaphragmatic infection, or infection associated with trauma.

Chylothorax is the effusion of lymph in the thoracic cavity.[10] Chyle, a milky fluid containing chylomicrons, is found in the lymph fluid originating in the gastrointestinal tract. The thoracic duct transports chyle to the central circulation. Chylothorax also results from trauma, inflammation, or malignant infiltration obstructing chyle transport from the thoracic duct into the central circulation. It is the most common cause of pleural effusion in the fetus and neonate, resulting from congenital malformation of the thoracic duct or lymph channels. Chylothorax also can occur as a complication of intrathoracic surgical procedures and use of the great veins for total parenteral nutrition and hemodynamic monitoring.

Hemothorax is the presence of blood in the pleural cavity. Bleeding may arise from chest injury, a complication of chest surgery, malignancies, or rupture of a great vessel such as an aortic aneurysm. It is usually diagnosed by the presence of blood in the pleural fluid. Hemothorax usually requires drainage, and if the bleeding continues, surgery to control the bleeding may be required.

The manifestations of pleural effusion vary with the cause. Empyema may be accompanied by fever, increased white blood cell count, and other signs of inflammation. Fluid in the pleural cavity acts as a space-occupying mass; it causes a decrease in lung expansion on the affected side that is proportional to the amount of fluid collected. Characteristic signs of pleural effusion are dullness or flatness to percussion and diminished breath sounds. Hypoxemia may occur due to the decreased surface area and usually is corrected with supplemental oxygen. Dyspnea, the most common symptom, occurs when fluid in the pleural cavity compresses the lung, resulting in increased effort or rate of breathing. Pleuritic pain usually occurs only when inflammation is present, although constant discomfort may be felt with large effusions.

Diagnosis of pleural effusion is based on chest radiographs, chest ultrasonography, and computed tomography (CT). Thoracentesis (aspiration of fluid from the pleural space) can be used to obtain a sample of pleural fluid for diagnosis. The treatment of pleural effusion is directed at the cause of the disorder. With large effusions, thoracentesis may be used to remove fluid from the intrapleural space and allow for reexpansion of the lung. A palliative method used for treatment of pleural effusions caused by a malignancy is the injection of a sclerosing agent into the pleural cavity. This method of treatment causes obliteration of the pleural space and prevents the reaccumulation of fluid. Chest tube drainage may be necessary in cases of continued effusion.

Pneumothorax

Pneumothorax refers to the presence of air in the pleural space. Pneumothorax causes partial or complete collapse of the affected lung. Pneumothorax can occur without an obvious cause or injury (i.e., spontaneous pneumothorax) or as a result of direct injury to the chest or major airways (i.e., traumatic pneumothorax). Tension pneumothorax describes a life-threatening condition in which increased pressure within the pleural cavity impairs both respiratory and cardiac function.

Spontaneous Pneumothorax. Spontaneous pneumothorax is hypothesized to occur due to the rupture of an air-filled bleb, or blister, on the surface of the lung. Rupture of these blebs allows atmospheric air from the airways to enter the pleural cavity (Fig. 23-1). Because alveolar pressure normally is greater than pleural pressure, air flows from the alveoli into the pleural space, causing the involved portion of the lung to collapse as a result of its own recoil. Air continues to flow into the pleural space until a pressure gradient no longer exists or until the decline in lung size causes the leak to seal. Spontaneous pneumothoraces can be divided into primary and secondary pneumothoraces. Primary pneumothorax occurs in otherwise healthy persons, whereas secondary pneumothorax occurs in persons with underlying lung disease.

In primary spontaneous pneumothorax, the blebs usually are located at the top of the lungs.[11] The condition is seen in persons who are taller and thinner when compared with reference averages for height and weight.[12] It has been suggested that the difference in pleural pressure from the top to the bottom of the lung is greater in tall persons and that this difference in pressure may contribute to the development of blebs. Smoking is another factor that has been associated with primary spontaneous pneumothorax. Inflammation of the small airways related to smoking probably contributes to the condition, and cessation of smoking may reduce the recurrence.[13]

Secondary spontaneous pneumothoraces usually are more serious because they occur in persons with lung disease. They are associated with many different types of lung conditions that cause trapping of gases and destruction of lung tissue, including asthma, tuberculosis, cystic fibrosis, sarcoidosis, bronchogenic carcinoma, and metastatic pleural diseases. The most common cause of secondary spontaneous pneumothorax is emphysema. Secondary spontaneous pneumothorax may be life-threatening

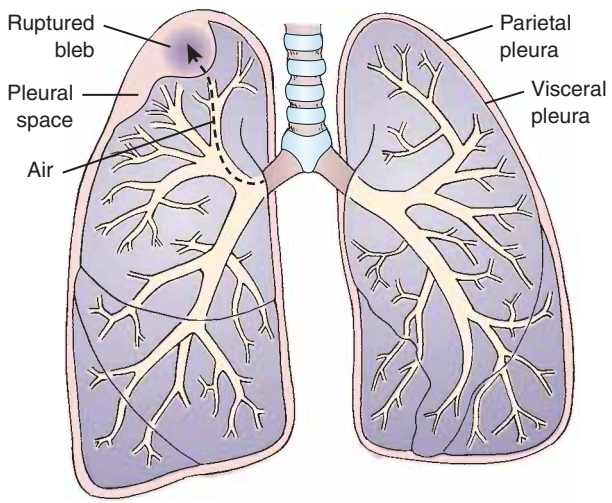


FIGURE 23-1. Mechanism for development of spontaneous pneumothorax, in which an air-filled bleb on the surface of the lung ruptures, allowing atmospheric air from the airways to enter the pleural space.

because of the underlying lung injury and poor compensatory reserves.

Traumatic Pneumothorax. Traumatic pneumothorax may be caused by penetrating or nonpenetrating chest injuries. Fractured or dislocated ribs that penetrate the pleura are the most common cause of pneumothorax from nonpenetrating chest injuries. Hemothorax may accompany these injuries. Pneumothorax also may accompany fracture of the trachea or major bronchus or rupture of the esophagus. Persons with pneumothorax due to chest trauma frequently have other complications and may require chest surgery. Medical procedures such as transthoracic needle aspirations, central line insertion, intubation, and positive-pressure ventilation occasionally may cause pneumothorax. Traumatic pneumothorax also can occur as a complication of cardiopulmonary resuscitation.

Tension Pneumothorax. Tension pneumothorax occurs when the intrapleural pressure exceeds atmospheric pressure. It is a life-threatening condition and occurs when injury to the chest or respiratory structures allows air to enter but not leave the pleural space (Fig. 23-2). This results in a rapid increase in pressure within the chest that causes compression atelectasis of the unaffected lung, a shift in the mediastinum to the opposite side of the chest, and compression of the vena cava, which results in a decrease in venous return to the heart and reduced cardiac output.[9] Although tension pneumothorax can develop in persons with spontaneous pneumothoraces, it is seen most often in persons with traumatic pneumothoraces. It also may result from mechanical ventilation.

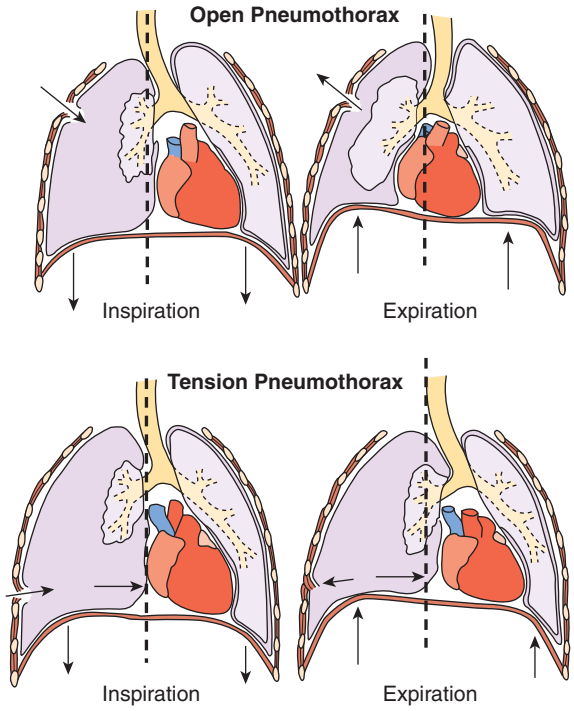


FIGURE 23-2. Open or communicating pneumothorax (*top*) and tension pneumothorax (*bottom*). In an open pneumothorax, air enters the chest during inspiration and exits during expiration. There may be slight inflation of the affected lung because of a decrease in pressure as air moves out of the chest. In tension pneumothorax, air can enter but not leave the chest. As the pressure in the chest increases, the heart and great vessels are compressed and the mediastinal structures are shifted toward the opposite side of the chest. The trachea is pushed from its normal midline position toward the opposite side of the chest, and the unaffected lung is compressed.

Clinical Features. The manifestations of pneumothorax depend on its size and the integrity of the underlying lung. In spontaneous pneumothorax, manifestations of the disorder include development of ipsilateral chest pain. There is an almost immediate increase in respiratory rate, often accompanied by dyspnea that occurs as a result of the activation of receptors that monitor lung volume. Asymmetry of the chest may occur because of the air trapped in the pleural cavity on the affected side. This asymmetry may be evidenced during inspiration as a lag in the movement of the affected side, with inspiration delayed until the unaffected lung reaches the same level of pressure as the lung with the air trapped in the pleural space. Percussion of the chest produces a more hyperresonant sound, and breath sounds are decreased or absent over the area of the pneumothorax.

With tension pneumothorax, the structures in the mediastinal space shift toward the opposite side of the chest (see Fig. 23-2). When this occurs, the position of the trachea, normally located in the midline of the neck, deviates with the mediastinum. The position of the trachea can be used as a means of assessing for a mediastinal shift. Because of the increase in intrathoracic pressure, stroke volume or the amount of blood that the heart ejects with each beat is reduced to such an extent that cardiac output is decreased despite an increase in heart rate. There may be distention of the neck veins, subcutaneous emphysema (i.e., presence of air in the subcutaneous tissues of the chest and neck), and clinical signs of shock due to impaired cardiac function.

Hypoxemia usually develops immediately after a large pneumothorax, followed by vasoconstriction of the blood vessels in the affected lung, causing the blood flow to shift to the unaffected lung. In persons with primary spontaneous pneumothorax, this mechanism usually returns oxygen saturation to normal within 24 hours. Hypoxemia usually is more serious in persons with underlying lung disease in whom secondary spontaneous pneumothorax develops or in persons with underlying heart disease who are unable to compensate with an increase in heart rate and stroke volumes. Regardless of etiology, the hypoxemia caused by the partial or total loss of lung function can be life-threatening. Without immediate intervention, the increased thoracic pressure will further impair both cardiac and pulmonary function, resulting in severe hypoxemia and hypotension.

Diagnosis of pneumothorax can be confirmed by chest radiograph or CT scan. Pulse oximetry and blood gas analysis may be done to determine the effect on blood oxygen levels. Treatment of pneumothorax varies with the cause and extent of the disorder. In small spontaneous

pneumothoraces, the air usually reabsorbs spontaneously, and only observation and follow-up chest radiographs are required.[14] Supplemental oxygen may be used to correct the hypoxemia until the air is reabsorbed. In larger pneumothoraces, the air is removed by needle aspiration or a closed drainage system used with or without suction. This type of drainage system uses a one-way valve or a water-seal chamber to allow air to exit the pleural space and prevent it from reentering the chest.

Emergency treatment of tension pneumothorax involves the prompt insertion of a large-bore needle or chest tube into the affected side of the chest along with one-way valve drainage or continuous chest suction to aid in lung reexpansion.[9] Sucking chest wounds, which allow air to pass in and out of the chest cavity, should be treated by promptly covering the area with an airtight covering. Chest tubes are inserted as soon as possible.

Atelectasis

Atelectasis refers to an incomplete expansion of a lung or portion of a lung. It can be caused by airway obstruction, lung compression such as occurs in pneumothorax or pleural effusion, or increased recoil of the lung due to loss of pulmonary surfactant (see Chapter 21). The disorder may be present at birth (i.e., primary atelectasis) or develop during the neonatal period or later in life (i.e., acquired or secondary atelectasis).

Primary atelectasis of the newborn implies that the lung has never been inflated. It is seen most frequently in premature and high-risk infants. A secondary form of atelectasis can occur in infants who established respiration and subsequently experienced impairment of lung expansion. Among the causes of secondary atelectasis in the newborn is the respiratory distress syndrome associated with lack of surfactant and airway obstruction due to aspiration of amniotic fluid or blood.

Acquired atelectasis occurs mainly in adults. It is caused most commonly by airway obstruction and lung compression (Fig. 23-3). Obstruction can be caused by a mucous plug in the airway or by external compression by fluid, tumor mass, exudate, or other matter in the area surrounding the airway. Portions of alveoli, a small segment of lung, or an entire lung lobe may be involved in obstructive atelectasis. Complete obstruction of an airway is followed by the absorption of air from the dependent alveoli and collapse of that portion of the lung. Breathing high concentrations of oxygen increases the rate at which gases are absorbed from the alveoli and predisposes to atelectasis. The danger of obstructive atelectasis increases after surgery.[15] Anesthesia, pain, administration of narcotics, and immobility tend to promote retention of viscid bronchial secretions and hence airway obstruction. The encouragement of coughing and deep breathing, frequent change of position, adequate hydration, and early ambulation decrease the likelihood of atelectasis developing.

Another cause of atelectasis is compression of lung tissue. It occurs when the pleural cavity is partially or completely filled with fluid, exudate, blood, a tumor mass, or air. It is observed most commonly in persons with pleural effusion from congestive heart failure or cancer.

The clinical manifestations of atelectasis include tachypnea, tachycardia, dyspnea, cyanosis, signs of hypoxemia, diminished chest expansion, absence of breath sounds, and intercostal retractions. Both chest expansion and breath sounds are decreased on the affected side. There may be intercostal retraction (pulling in of the intercostal spaces) over the involved area during inspiration. Signs of respiratory distress are proportional to the extent of lung collapse. If the collapsed area is large, the mediastinum and trachea shift to the affected side. In compression atelectasis, the mediastinum shifts away from the affected lung.

The diagnosis of atelectasis is based on signs and symptoms. Chest radiographs are used to confirm the diagnosis. CT scans may be used to show the exact location of the obstruction. Treatment depends on the cause and extent of lung involvement. It is directed at reducing the airway obstruction or lung compression and at reinflation of the collapsed area of the lung. Ambulation, deep breathing, and body positions that favor increased lung expansion are used when appropriate. Administration of oxygen may be needed to correct the hypoxemia. Bronchoscopy may be used as both a diagnostic and treatment method.

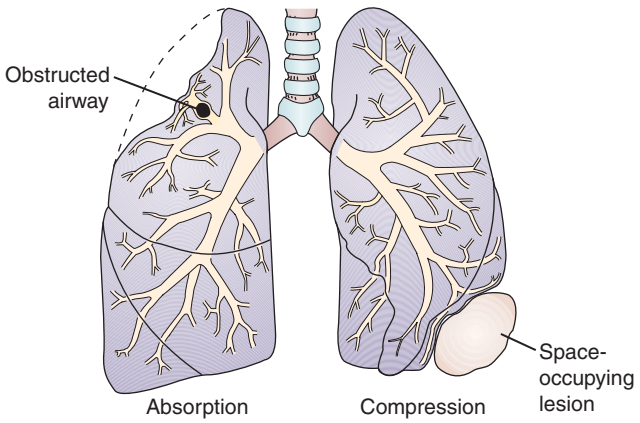


FIGURE 23-3. Atelectasis caused by airway obstruction and absorption of air from the involved lung area (*left*) and by compression of lung tissue (*right*).

In summary, disorders of the pleura include pleuritis, pleural effusion, hemothorax, and pneumothorax. Pain is a common symptom of conditions that produce pleuritis or inflammation of the pleura. Characteristically, the pain is unilateral, abrupt in onset, and exaggerated by respiratory movements. Pleural effusion refers to the abnormal accumulation of fluid in the pleural cavity. The fluid may be a transudate (i.e., hydrothorax), exudate (i.e., empyema), or chyle (i.e., chylothorax). Hemothorax refers to the presence of blood in the pleural cavity. Pneumothorax refers to an accumulation of air in the pleural cavity that causes partial or complete collapse of the lung. Pneumothorax can result from rupture of an

air-filled bleb on the lung surface or from penetrating or nonpenetrating injuries. A tension pneumothorax is a life-threatening event in which air progressively accumulates in the thorax, collapsing the lung on the injured side and progressively shifting the mediastinum to the opposite side of the thorax, producing severe cardiac and respiratory impairment.

Atelectasis refers to an incomplete expansion of the lung. Primary atelectasis occurs most often in premature and high-risk infants. Acquired atelectasis occurs mainly in adults and is caused most commonly by a mucous plug in the airway or by external compression by fluid, tumor mass, exudate, or other matter in the area surrounding the airway.

Airway Disorders

- Airway disorders affect airway patency and movement of atmospheric air into and out of the gas exchange portion of the lung.
- Changes in airway patency involve changes in airway diameter due to bronchial smooth muscle hyperreactivity or changes in bronchial wall structure, injury to the mucosal lining of the airways, or excess respiratory tract secretions.
- Bronchial asthma is a chronic disorder of the airways that causes episodes of airway obstruction due to bronchial smooth muscle hyperreactivity and airway inflammation. The episodes usually are reversible.
- Chronic obstructive pulmonary disease represents a group of disorders that cause chronic and recurrent obstruction of the pulmonary airways. These disorders can affect patency of the bronchial structures (chronic bronchitis), the gas-diffusing air spaces distal to the terminal bronchioles (emphysema), or a combination of both.

Obstructive Airway Disorders

Obstructive airway disorders are caused by conditions that limit expiratory airflow. Bronchial asthma represents an acute and reversible form of airway disease caused by narrowing of airways due to bronchospasm, inflammation, and increased airway secretions. Chronic obstructive disorders include a variety of airway diseases, such as bronchial asthma, chronic obstructive pulmonary disease, bronchiectasis, and cystic fibrosis.

Physiology of Airway Disease

Air moves through the upper airways (i.e., trachea and major bronchi) into the lower or pulmonary airways (i.e., bronchi and alveoli), which are located in the lung. In the pulmonary airways, the cartilaginous layer that provides support for the trachea and major bronchi gradually disappears and is replaced with crisscrossing strips of smooth muscle (see Chapter 21). The contraction and relaxation of the smooth muscle layer, which is innervated by the autonomic nervous system, controls the diameter of the bronchial airways and consequent resistance to airflow. Parasympathetic stimulation, through the vagus nerve and cholinergic receptors, produces bronchoconstriction, whereas sympathetic stimulation, through β_2-adrenergic receptors, produces bronchodilation. At rest, a slight vagal-mediated bronchoconstrictor tone predominates. When there is need for increased airflow, as during exercise, the bronchodilator effects of the sympathetic nervous system are stimulated and the bronchoconstrictor effects of the parasympathetic nervous system are inhibited. Bronchial smooth muscle also responds to inflammatory mediators, such as histamine, that act directly on bronchial smooth muscle cells to produce bronchoconstriction.

Bronchial Asthma

Bronchial asthma is a common obstructive airway disease affecting approximately 5% of the population.[15] According to 2006 data, an estimated 22.2 million Americans (4.1 million children younger than 18 years of age) had an asthma attack.[16] Although the prevalence rates for asthma have increased over the past several decades, hospitalizations and the mortality rate due to asthma have stabilized, indicating a higher level of disease management.[16]

Asthma is a chronic inflammatory disease of the airways characterized by variable recurring symptoms, airflow obstruction, and bronchial hyperresponsiveness.[15–17] Airway obstruction is characterized by episodic wheezing, difficulty breathing, chest tightness, and a cough that often is worse at night and in the early morning. These episodes, which usually are reversible either spontaneously or with treatment, also cause an associated increase in bronchial responsiveness to a variety of stimuli.

In susceptible persons, an asthma attack can be triggered by a variety of stimuli that do not normally cause symptoms. Asthma is commonly categorized into two types: *extrinsic*, initiated by a type I hypersensitivity (atopic) response to an extrinsic antigen; and *intrinsic*, initiated by diverse nonimmune mechanisms, including respiratory tract infections, exercise, ingestion of aspirin, emotional upset, and exposure to bronchial irritants such as cigarette smoke.[17,18] Although this distinction is useful from the perspective of pathophysiology, it is less useful clinically because many persons with asthma manifest overlapping characteristics of both extrinsic and intrinsic asthma.

Etiology and Pathogenesis

The common denominator underlying all forms of asthma is an exaggerated hypersensitivity response to a

variety of stimuli. Most current information suggests that the presence of inflammatory cells (neutrophils, eosinophils, lymphocytes, and mast cells) and damage to the bronchial epithelium contributes to the pathogenesis of the disease. In some persons, persistent changes in airway structures occur, including mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and blood vessel proliferation. Genetic and environmental interactions play an important role in the pathogenesis of the disease.

Recent research has focused on the role of T lymphocytes in the pathogenesis of bronchial asthma. It is now known that there are two subsets of T-helper cells (T_H1 and T_H2) that develop from the same precursor $CD4^+$ T lymphocyte (see Chapter 15).[17–20] T_H1 cells differentiate in response to microbes and stimulate the differentiation of B cells into immunoglobulin (Ig) M– and IgG-producing plasma cells. T_H2 cells, on the other hand, respond to allergens by stimulating B cells to differentiate into IgE-producing plasma cells that bind to mast mucosal mast cells. Subsequent IgE-mediated reactions to inhaled allergens elicit the immediate early-phase and late-phase responses (see Chapter 16, Fig. 16-1). In persons with allergic asthma, T-cell differentiation appears to be skewed toward T_H2 cells. Although the molecular basis for this preferential differentiation is unclear, it seems likely that both genetic and environmental factors play a role.

Extrinsic (Atopic) Asthma. Extrinsic or atopic asthma is typically initiated by a type I hypersensitivity reaction induced by exposure to an extrinsic antigen or allergen.[18,20,21] It usually has its onset in childhood or adolescence and is seen in persons with a family history of atopic allergy (see Chapter 16).

Persons with atopic asthma often have other allergic disorders, such as hay fever, urticaria, and eczema. Attacks are related to exposure to specific allergens. Among air-borne allergens implicated in perennial (year-round) asthma are house dust mite allergens, cockroach allergens, animal danders, and *Alternaria* (a fungus).

The mechanisms of response to antigens in atopic asthma can be described in terms of the early- or acute-phase and the late-phase responses[18,19] (Fig. 23-4). The symptoms of the *acute-phase response,* which usually develop within 10 to 20 minutes, are caused by the release of chemical mediators from presensitized IgE-coated mast cells. In the case of air-borne antigens, the reaction occurs when antigen binds to previously sensitized mast cells on the mucosal surface of the airways (Fig. 23-5A). Mediator release results in the infiltration of inflammatory cells, opening of the mucosal intercellular junctions, and increased access of antigen to the more prevalent submucosal mast cells. In addition, there is bronchospasm caused by stimulation of parasympathetic receptors, mucosal edema caused by increased vascular permeability, and increased mucus secretions. The

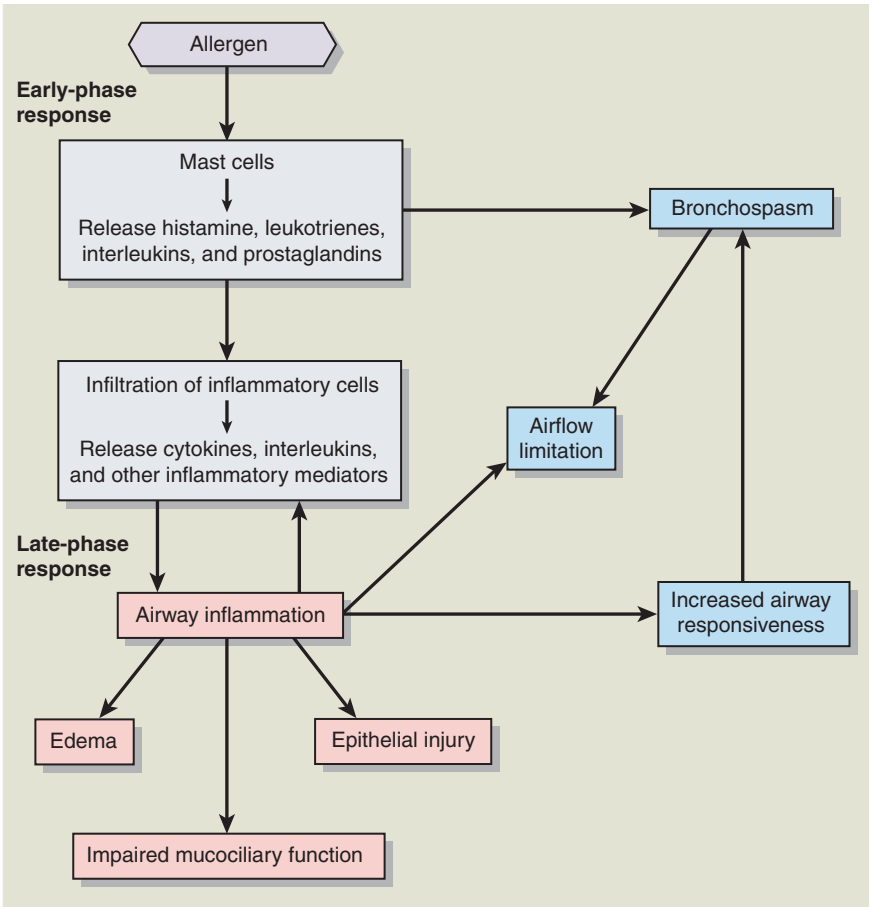


FIGURE 23-4. Mechanisms of early- and late-phase IgE-mediated bronchospasm.

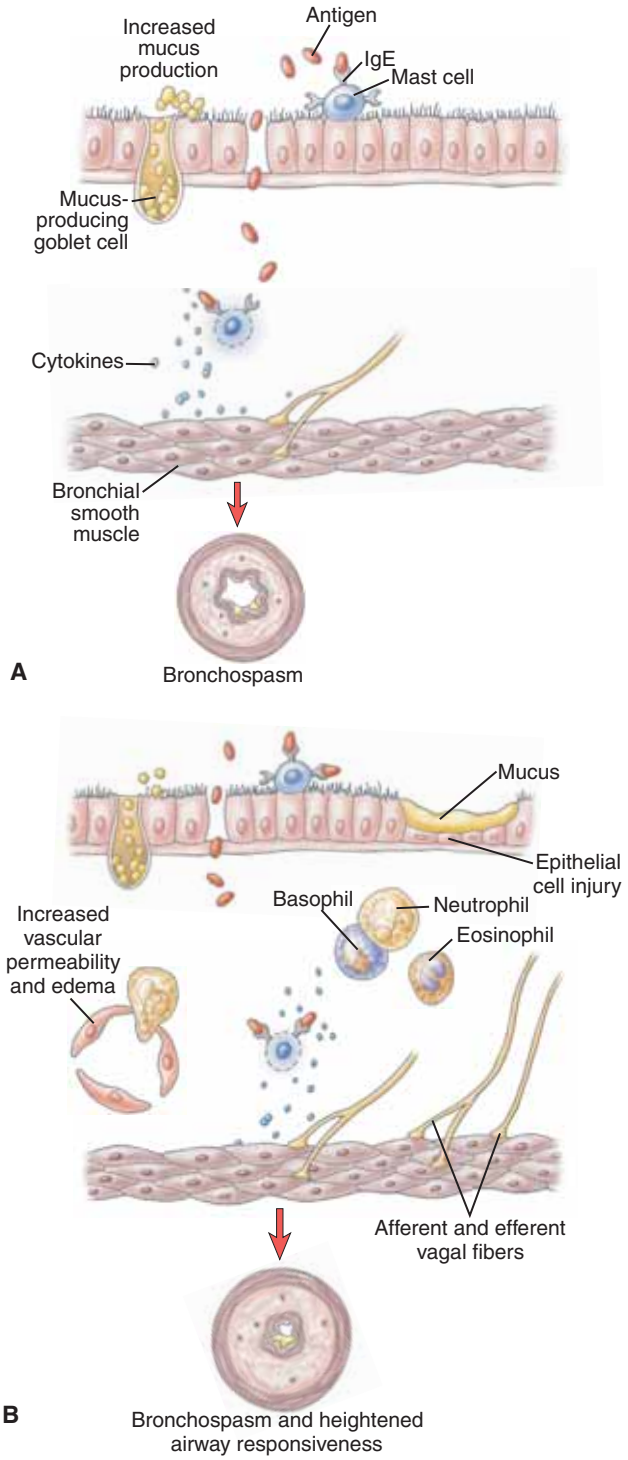


FIGURE 23-5. Pathogenesis of bronchial asthma. **(A)** The immediate or early-phase response triggered by an IgE-mediated release of mediators from sensitized mast cells. The release of chemical mediators results in increased mucus production, opening of mucosal intercellular junctions with exposure of submucosal mast cells to antigen, and bronchospasm. **(B)** The late-phase response involves epithelial cell injury with decreased mucociliary function and accumulation of mucus; release of inflammatory mediators with recruitment of neutrophils, eosinophils, and basophils; increased vascular permeability and edema; and increased airway responsiveness and bronchospasm.

acute response usually can be inhibited or reversed by bronchodilators, such as β_2-agonists, but not by the anti-inflammatory actions of the corticosteroids.

The *late-phase response,* which develops 4 to 8 hours after exposure to an asthmatic trigger, involves inflammation and increased airway responsiveness that prolong the asthma attack and set into motion a vicious cycle of exacerbations.[18] Typically, the response reaches a maximum within a few hours and may persist for 12 to 24 hours or longer. An initial trigger in the late-phase response causes the release of inflammatory mediators from mast cells, macrophages, and epithelial cells. These substances induce the migration and activation of other inflammatory cells (e.g., basophils, eosinophils, neutrophils), which then produce epithelial injury and edema, changes in mucociliary function, reduced clearance of respiratory tract secretions, and increased airway responsiveness (see Fig. 23-5B). Chronic inflammation can lead to airway remodeling, in which case airflow limitations may be only partially reversible.[19]

Intrinsic (Nonatopic) Asthma. Intrinsic or nonatopic asthma triggers include respiratory tract infections, exercise, hyperventilation, cold air, drugs and chemicals, hormonal changes and emotional upsets, air-borne pollutants, and gastroesophageal reflux. Respiratory tract infections, especially those caused by viruses, may produce their effects by causing epithelial damage and stimulating the production of IgE antibodies directed toward the viral antigens. In addition to precipitating an asthmatic attack, viral respiratory infections increase airway responsiveness to other asthma triggers that may persist for weeks beyond the original infection.

Exercise-induced asthma occurs in a number of persons with bronchial asthma. Although the cause of exercise-induced asthma is unclear, hyperventilation and corresponding changes in airway physiology may play a role. It has been suggested that the increased ventilatory rate required to meet the higher oxygen demands during exercise challenges the ability of the airways to condition the inhaled air to the correct moist and heat levels before the air reaches the alveoli.[22] Vigorous exercise results in the inhalation of increased volumes of relatively cold and dry air and loss of body heat from the respiratory mucosa, which in turn induces mast cells and epithelial cells to release proinflammatory mediators such as histamine and leukotrienes. The response commonly is exaggerated when the person exercises in a cold environment. Wearing a mask over the nose and mouth often minimizes the attack or prevents it. In addition to inflammatory cytokines, airway cooling stimulates cholinergic receptors in the airways, with a resultant increase in airway tone. A warm-up period alleviates the symptoms for some persons.

Inhaled irritants, such as tobacco smoke and strong odors, are thought to induce bronchospasm by way of irritant receptors and a vagal reflex. Exposure to parental smoking has been reported to increase asthma severity in children.[23] High doses of irritant gases such as sulfur dioxide, nitrogen dioxide, and ozone may induce inflammatory exacerbations of airway responsiveness (e.g.,

smog-related asthma). Occupational asthma is stimulated by fumes and gases (e.g., epoxy resins, plastics, toluene), organic and chemical dusts (e.g., wood, cotton, platinum), and other chemicals (e.g., formaldehyde) in the workplace.[24] A group of chemicals that can provoke an asthmatic attack are the sulfites used in food processing and as preservatives added to beer, wine, and fresh vegetables.

There is a small group of persons in whom aspirin and other NSAIDs evoke the clinical triad of nasal polyps, chronic rhinosinusitis, and bronchial asthma.[17,18,25] The mechanism of the hypersensitivity reaction is complex and not fully understood, but most evidence points toward an abnormality in arachidonic acid (AA) metabolism in which aspirin inhibits the bronchodilating cyclooxygenase pathway without affecting the lipoxygenase pathway, thereby shifting the balance toward the bronchoconstrictor leukotrienes (see Chapter 3, Fig. 3-4). Avoidance of aspirin and all NSAIDs is a necessary part of the treatment program.

Both emotional factors and changes in hormone levels are thought to contribute to an increase in asthma symptoms. Emotional factors produce bronchospasm by way of vagal pathways. They can act as a bronchospastic trigger, or they can increase airway responsiveness to other triggers through noninflammatory mechanisms. The role of sex hormones in asthma is unclear, although there is much circumstantial evidence to suggest that they may be important. Up to 40% of women with asthma report a premenstrual increase in asthma symptoms.[26] Female sex hormones have a regulatory role on β_2-adrenergic function, and it has been suggested that abnormal regulation may be a possible mechanism for premenstrual asthma.

Symptoms of gastroesophageal reflux are common in both adults and children with asthma, suggesting that reflux of gastric secretions may act as a bronchospastic trigger. Reflux during sleep can contribute to nocturnal asthma.[17]

Clinical Features

Persons with asthma exhibit a wide range of signs and symptoms ranging from episodes of wheezing and feelings of chest tightness to acute immobilizing attacks. The attacks differ from person to person, and between attacks, many persons are symptom free. Attacks may occur spontaneously or in response to various triggers, respiratory infections, emotional stress, or weather changes. Asthma is often worse at night, referred to as *nocturnal asthma*. Studies of nocturnal asthma suggest that there is a circadian and sleep-related variation in hormones and respiratory function.[27] The greatest decrease in respiratory function occurs at about 4:00 AM, at which time cortisol levels are low, melatonin levels high, and eosinophil activity increased.[28]

During an asthmatic attack, the airways narrow because of bronchospasm, edema of the bronchial mucosa, and mucus plugging. Expiration becomes prolonged because of progressive airway obstruction. The amount of air that can be forcibly expired in 1 second (forced expiratory volume in 1 second [$FEV_{1.0}$]) and the peak expiratory flow rate (PEF), measured in liters per second, are decreased.

During a prolonged attack, air becomes trapped behind the occluded and narrowed airways, causing hyperinflation of the lungs. This produces an increase in the residual volume (RV) along with a decrease in the inspiratory reserve capacity (tidal volume + inspiratory reserve volume [IRC]) and forced vital capacity (FVC), such that the person breathes close to his or her functional residual capacity (residual volume + expiratory reserve volume; see Chapter 21, Fig. 21-17). As a result, more energy is needed to overcome the tension already present in the lungs, and the accessory muscles (e.g., sternocleidomastoid muscles) are required to maintain ventilation and gas exchange. This increased work of breathing further increases oxygen demands and causes dyspnea and fatigue. Because air is trapped in the alveoli and inspiration is occurring at higher residual lung volumes, the cough becomes less effective. As the condition progresses, the effectiveness of alveolar ventilation declines, and mismatching of ventilation and perfusion occurs, causing hypoxemia and hypercapnia. Pulmonary vascular resistance may increase as a result of the hypoxemia and hyperinflation, leading to a rise in pulmonary arterial pressure and increased work demands on the right heart.

Manifestations. The physical signs of bronchial asthma vary with the severity of the attack. A mild attack may produce a feeling of chest tightness, a slight increase in respiratory rate with prolonged expiration, and mild wheezing. A cough may accompany the wheezing. More severe attacks are accompanied by use of the accessory muscles, distant breath sounds due to air trapping, and loud wheezing. As the condition progresses, fatigue develops, the skin becomes moist, and anxiety and apprehension are obvious. Sensations of shortness of breath may be severe, and often the person is able to speak only one or two words before taking a breath. At the point at which airflow is markedly decreased, breath sounds become inaudible, wheezing diminishes, and the cough becomes ineffective despite being repetitive and hacking.[17] This point often marks the onset of respiratory failure.

Diagnosis and Treatment. The diagnosis of asthma is based on a careful history and physical examination, laboratory findings, and pulmonary function studies (see Chapter 21). Spirometry provides a means for measuring FVC, $FEV_{1.0}$, PEF, tidal volume, expiratory reserve volume, and inspiratory reserve volume. The $FEV_{1.0}$/FVC ratio can then be calculated. The level of airway responsiveness can be measured by inhalation challenge tests using methacholine (a cholinergic agonist), histamine, or exposure to a nonpharmacologic agent such as cold air. The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) has developed classification systems intended for use in directing asthma treatment and identifying persons at high risk for development of life-threatening asthma attacks[17] (Table 23-1). Based on these classifications systems, the panel recommends two categories for management and treatment of asthma:

TABLE 23-1 Classification of Asthma Severity

Asthma Severity	Symptoms, Interference with Normal Activities, and Frequency of Short-Acting β_2-Agonist Use	Nighttime Awakenings	Lung Function
Mild intermittent	Symptoms ≤2 days a week No interference with normal activity Short-acting β_2-agonist use <2 days a week	<2 times a month	Normal $FEV_{1.0}$ between exacerbations $FEV_{1.0}$ >80% predicted $FEV_{1.0}$/FVC normal
Mild persistent	Symptoms 2 days a week but not daily Minor limitation in normal activity Short-acting β_2-agonist use ≥2 days a week but not daily	3–4 times a month	$FEV_{1.0}$ >80% predicted $FEV_{1.0}$/FVC normal
Moderate persistent	Symptoms daily Some limitation in normal activity Short-acting β_2-agonist daily	>1 time a week but not nightly	$FEV_{1.0}$ >60% normal but <80% predicted $FEV_{1.0}$/FVC reduced 5%
Severe persistent	Symptoms throughout the day Extreme limitation in normal activity Short-acting β_2-agonist several times a day	Often 7 times a week	$FEV_{1.0}$ <60% normal $FEV_{1.0}$/FVC reduced >5%

$FEV_{1.0}$, forced expiratory volume in 1 second; FVC, forced vital capacity.

Adapted from National Lung, Heart, and Blood Institute National Asthma Education and Prevention Program (2007). *Expert panel report 3: Guidelines for diagnosis and management of asthma.* Bethesda MD: National Institutes of Health.

measures to control factors contributing to asthma severity and pharmacologic treatment.[1]

Small, inexpensive, portable meters that measure PEF are available. Although not intended for use in the diagnosis of asthma, they can be used in clinics and physicians' offices and by patients in their home to provide frequent measures of flow rates. Day–night (circadian) variations in asthma symptoms and PEF variability can be used to indicate the severity of bronchial hyperresponsiveness. The person's best performance is established from readings taken over several weeks. This often is referred to as the individual's *personal best* and is used as a reference to indicate changes in respiratory function.[17] A PEF below 50% of the predicted value during an acute asthmatic attack indicates a severe exacerbation and the need for immediate intervention.[17]

The treatment of bronchial asthma focuses on control of factors contributing to asthma severity and pharmacologic treatment. Measures to control factors contributing to asthma severity are aimed at prevention of exposure to irritants and factors that increase asthma symptoms and precipitate asthma exacerbations. They include education of the patient and family regarding measures used in avoiding exposure to irritants and allergens that are known to induce or trigger an attack. A careful history often is needed to identify all the contributory factors. Factors such as nasal polyps, a history of aspirin sensitivity, and gastroesophageal reflux should be considered. Annual influenza vaccination is recommended for persons with persistent asthma.

A program of desensitization may be undertaken in persons with persistent asthma who react to allergens, such as house dust mites, that cannot be avoided. This involves the injection of selected antigens (based on skin tests) to stimulate the production of IgG antibodies that block the IgE response. A course of allergen immunotherapy is typically of 3 to 5 years' duration.[17]

Traditionally, drugs used to treat asthma were categorized according to their predominant mechanism of action—relaxation of bronchial smooth muscle (bronchodilator) and suppression of airway inflammation (anti-inflammatory drugs).[29] A more recent classification divides asthma medications into two general categories according to their roles in the overall management of asthma symptoms (quick-relief or long-term medications).

The *quick-relief medications* include the short-acting β_2-agonists, anticholinergic agents, and systemic corticosteroids.[17] The short-acting β_2-agonists relax bronchial smooth muscle and provide prompt relief of symptoms, usually within 30 minutes. They are administered by inhalation (i.e., metered-dose inhaler [MDI] or nebulizer). The anticholinergic medications block cholinergic receptors and reduce intrinsic vagal tone that causes bronchoconstriction. These medications, which are administered by inhalation, produce bronchodilation by direct action on the large airways but do not change the composition or viscosity of the bronchial mucus. It is thought that they may provide some additive benefit for treatment of asthma exacerbations when administered with inhaled β_2-agonists. A short course of systemic corticosteroids, administered orally or parenterally, may be used for treating the inflammatory reaction associated with the late-phase response. Although their onset of action is slow (>4 hours), systemic corticosteroids may be used in the treatment of moderate to severe exacerbations because of their action in preventing the progression of the exacerbation, speeding recovery, and preventing early relapses.

The *long-term medications* are taken on a daily basis to achieve and maintain control of persistent asthma symptoms. They include inhaled corticosteroids, long-acting bronchodilators, cromolyn and nedocromil, leukotriene pathway inhibitors, and theophylline.[17] The corticosteroids are considered the most

effective anti-inflammatory agents for use in long-term treatment of asthma. Inhaled corticosteroids administered by MDI usually are preferred because of minimal systemic absorption and degree of disruption in hypothalamic-pituitary-adrenal function. The long-acting β_2-agonists, available for administration by the inhaled or oral routes, act by relaxing bronchial smooth muscle. They are used as an adjunct to anti-inflammatory medications for providing long-term control of symptoms, especially nocturnal symptoms, and for preventing exercise-induced bronchospasm. The long-acting β_2-agonists have durations of action of at least 12 hours and should not be used to treat acute symptoms or exacerbations.[17] Cromolyn sodium and nedocromil are long-term medications that act by stabilizing mast cells and inhibiting chloride channel function, thereby preventing release of the inflammatory mediators that cause an asthmatic attack. They are administered by MDI or nebulization as a preventative treatment prior to exercise or unavoidable exposure to known antigens. A group of medications called the *leukotriene pathway inhibitors* are available for use in the treatment of asthma.[29] Leukotrienes are potent biochemical mediators released from mast cells that cause bronchoconstriction, increased mucus secretion, and attraction and activation of inflammatory cells in the airways. A particular advantage of the leukotriene pathway inhibitors is that they are taken orally.

Theophylline, a phosphodiesterase inhibitor, is a bronchodilator that acts by relaxing bronchial smooth muscle. The sustained-release form of the drug is used as an adjuvant therapy and is particularly useful in relieving nighttime symptoms. It may be used as an alternative, but not preferred, medication in long-term preventative therapy when there are issues concerning adherence with regimens using inhaled medications or when cost is a factor. Because elimination of the drug varies widely among persons, blood levels are required to ensure that the therapeutic, but not toxic, dose is achieved.[17]

The anti-IgE monoclonal antibody omalizumab is the first biologic immunoregulatory agent available to treat asthma.[29] It binds to the portion of the IgE that recognizes its receptor on the surface of mast cells and basophils. Omalizumab, which is indicated for treatment of moderate and severe persistent asthma, is administered subcutaneously every 2 to 4 weeks, depending on the dose. The drug has been approved for adults and children 12 years of age and older.

Severe Asthma

Severe or refractory asthma represents a subgroup (probably <10%) of persons with asthma who have more troublesome disease as evidenced by high medication requirements to maintain good symptom control or who continue to have persistent symptoms despite high medication use.[30,31] Severe or refractory asthma has been described as persistent asthma that required continuous high-dose inhaled or oral corticosteroids for more than 50% of the previous year and the need for additional daily treatment with controller medications, exhibited evidence of disease exacerbations or instability, and required hospitalizations or emergency room visits.[17,30,31] These persons are at increased risk for a fatal or near-fatal asthmatic attack. It has been suggested that an underestimation of the severity of the attack may be a contributing factor.[32] Deterioration often occurs rapidly during an acute attack, and underestimation of its severity may lead to a life-threatening delay in seeking medical attention.

Little is known about the causes of severe asthma. Among the proposed risk factors are genetic predisposition, continued allergen or tobacco exposure, infection, intercurrent sinusitis or gastroesophageal reflux disease, and lack of compliance or adherence with treatment measures.[31] It has been proposed that because asthma is a disease involving multiple genes, mutations in genes regulating cytokines (e.g., IL-4), growth factors, or receptors for medications used in treatment of asthma (β_2-adrenergic agonist or glucocorticoid) could be involved. Environmental factors include both allergen and tobacco exposure, with the strongest reaction occurring in response to house dust mite antigens, cockroach allergen, and *Alternaria* exposure.

Bronchial Asthma in Children

Asthma is a common chronic illness in children. In the United States, asthma is the most common cause of childhood emergency department visits, hospitalizations, and missed school days.[33] Although childhood asthma may have its onset at any age, up to 80% of children who develop asthma are symptomatic before 6 years of age.[34] Asthma is more prevalent among black than white children.[33,34] Worldwide, childhood asthma appears to be increasing in prevalence.[34] It is particularly common in children living in modern metropolitan locales, as compared to rural areas of developing countries.

As with adults, asthma in children commonly is associated with an IgE-related reaction. It has been suggested that IgE directed against respiratory viruses in particular may be important in the pathogenesis of wheezing illnesses in infants (i.e., bronchiolitis), which often precede the onset of asthma. Previous severe infections with the respiratory syncytial virus (RSV) are a risk factor in the development of asthma.[35] Other contributing factors include exposure to environmental allergens such as pet dander, dust mite antigens, and cockroach allergens. Exposure to environmental tobacco smoke also contributes to asthma in children.[35,36]

The signs and symptoms of asthma in infants and small children vary with the stage and severity of an attack. Because airway patency decreases at night, many children have acute signs of asthma at this time. Often, previously well infants and children develop what may seem to be a cold with rhinorrhea, rapidly followed by irritability, a tight and nonproductive cough, wheezing, tachypnea, dyspnea with prolonged expiration, and use of accessory muscles of respiration. Cyanosis, hyperinflation of the chest, and tachycardia indicate increasing severity of the attack. Wheezing may

be absent in children with extreme respiratory distress. The symptoms may progress rapidly and require a trip to the emergency department or hospitalization.

As with adults and older children, the Expert Panel of the NAEPP recommends a stepwise approach to diagnosing and managing childhood asthma.[17] Treatment involves not only pharmacologic agents but also recognition and modification of potential environmental triggers, such as tobacco smoke, and allergens, such as dust mites and pet dander. Inhaled corticosteroids are the preferred first-line controller therapy for treatment of persistent asthma in all age groups. Alternative or supplemental medications include long-acting β-agonists and leukotriene pathway inhibitors. Short-acting β-agonists may be used to relieve acute symptoms. Systemic corticosteroids may be required during an episode of severe disease. The systemic side effects of inhaled corticosteroids are usually limited to children receiving very high doses and are similar to the side effects seen with systemic corticosteroids: adrenal suppression, growth suppression, decreased bone density, myopathy, and weight gain. Despite the low risk of side effects, growth velocity should be monitored in children and adolescents receiving long-term corticosteroid therapy.[17]

Special delivery systems for administration of inhalation medications are available for infants and small children, including nebulizers with face masks and spacers or holding chambers for use with an MDI. For children younger than 2 years of age, nebulizer therapy usually is preferred. Children between 3 and 5 years of age may begin using an MDI with a spacer and holding chamber. The child's caregiver should be carefully instructed in the appropriate use of these devices. The Expert Panel recommends that adolescents (and younger children when appropriate) be directly involved in developing their asthma management plans.[17] Active participation in physical activities, exercise, and sports should be encouraged.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) denotes a group of respiratory disorders characterized by chronic and recurrent obstruction of airflow in the pulmonary airways.[15,37–40] The airflow obstruction is usually progressive, may be accompanied by airway hyperreactivity, and may be partially reversible. COPD remains a leading cause of morbidity and mortality worldwide. It is the fourth leading cause of death in the United States, and is projected to rank fifth in the burden of disease worldwide.[39]

The most common cause of COPD is smoking, as evidenced by the fact that 80% to 85% of persons with COPD have a history of smoking.[15,37] Other predisposing factors include exposure to occupational dusts and chemicals, airway infections, and asthma or airway hyperresponsiveness. Unfortunately, clinical findings are almost always absent during the early stages of COPD, and as many as 50% of smokers may have undiagnosed COPD.[41] By the time symptoms appear or are recognized, the disease is usually far advanced. For smokers with early signs of airway disease, there is hope that early recognition, combined with appropriate treatment and smoking cessation, may prevent or delay the usually relentless progression of the disease.

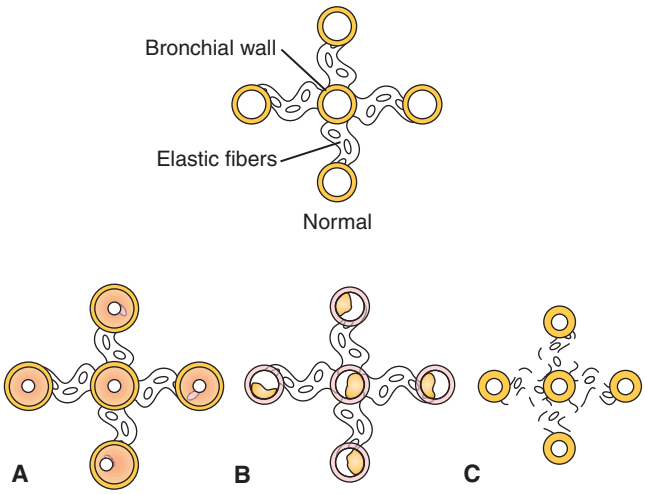


FIGURE 23-6. Mechanisms of airflow obstruction in chronic obstructive lung disease. (*Top*) Normal bronchial airway with elastic fibers that provide traction and hold the airway open. (*Bottom*) Obstruction of the airway caused by **(A)** inflammation and fibrosis of the bronchial wall, **(B)** hypersecretion of mucus, and **(C)** destruction of the elastic fibers that hold the airway open.

The term *chronic obstructive pulmonary disease* encompasses two types of obstructive airway disease: *emphysema,* with enlargement of air spaces and destruction of lung tissue, and *chronic obstructive bronchitis,* with increased mucus production, obstruction of small airways, and a chronic productive cough. Persons with COPD often have overlapping features of both emphysema and chronic bronchitis.

The mechanisms involved in the pathogenesis of COPD usually are multiple and include inflammation and fibrosis of the bronchial wall, hypertrophy of the submucosal glands and hypersecretion of mucus, and loss of elastic lung fibers and alveolar tissue (Fig. 23-6). Inflammation and fibrosis of the bronchial wall, along with excess mucus secretion and destruction of elastic fibers, cause mismatching of ventilation and perfusion. Destruction of alveolar tissue decreases the surface area for gas exchange, and loss of elastic fibers, which normally provide traction and hold the airways open, impairs the expiratory flow rate, increases air trapping, and predisposes to airway collapse.

Emphysema

Emphysema is characterized by a loss of lung elasticity and abnormal enlargement of the air spaces distal to the terminal bronchioles, with destruction of the alveolar walls and capillary beds (Fig. 23-7). Enlargement of the air spaces leads to hyperinflation of the lungs and produces an increase in total lung capacity (TLC). Two of the recognized causes of emphysema are smoking, which incites lung injury, and an inherited deficiency of

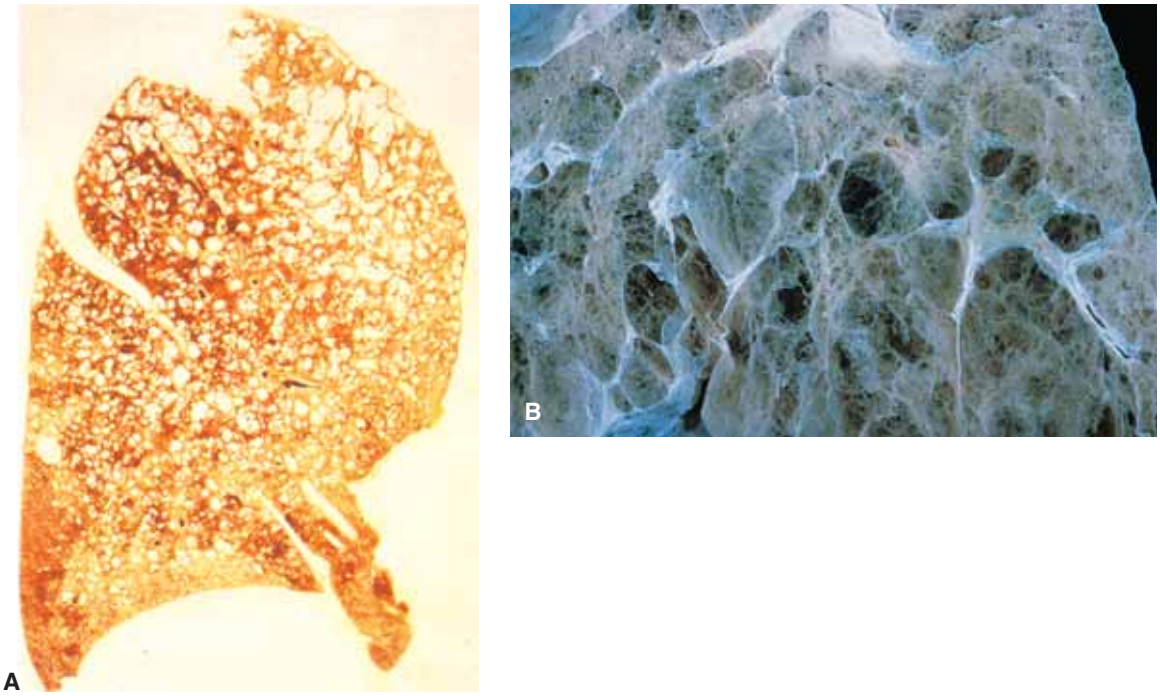


FIGURE 23-7. Panacinar emphysema. **(A)** A whole mount of the left lung from a patient with severe emphysema reveals widespread destruction of pulmonary parenchyma that in some areas leaves behind a lacy network of supporting tissue. **(B)** The lung from a patient with α_1-antitrypsin deficiency shows a panacinar pattern of emphysema. The loss of alveolar walls has resulted in markedly enlarged air spaces. (From Bearsley M.B., Travis W.D., Rubin E. [2008]. The respiratory system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 515]. Philadelphia: Lippincott Williams & Wilkins.)

α_1-antitrypsin, an antiprotease enzyme that protects the lung from injury. Genetic factors other than an inherited α_1-antitrypsin deficiency also may play a role in smokers who develop COPD at an early age.[41]

Emphysema is thought to result from the breakdown of elastin and other alveolar wall components by enzymes, called *proteases,* that digest proteins. The proteases, particularly elastase, which is an enzyme that digests elastin, are released from polymorphonuclear leukocytes (i.e., neutrophils), alveolar macrophages, and other inflammatory cells.[37] Normally, the lung is protected by antiprotease enzymes including α_1-antitrypsin. Cigarette smoke and other irritants stimulate the movement of inflammatory cells into the lungs, resulting in increased release of elastase and other proteases. In smokers in whom COPD develops, antiprotease production and release may be inadequate to neutralize the excess protease production such that the process of elastic tissue destruction goes unchecked (Fig. 23-8).

A hereditary deficiency in α_1-antitrypsin accounts for approximately 1% of all cases of COPD and is more common in young persons with emphysema.[37] The type and amount of α_1-antitrypsin that a person has are determined by a pair of codominant genes referred to as *protein inhibitor* (PI) genes. An α_1-antitrypsin deficiency is inherited as an autosomal recessive disorder. It is most common in persons of Scandinavian descent and is rare

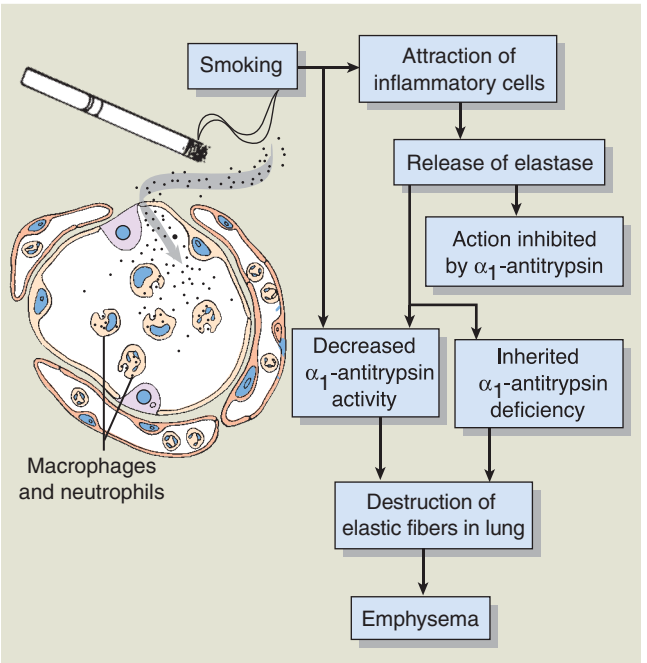


FIGURE 23-8. Protease (elastase)–antiprotease (antitrypsin) mechanisms of emphysema. The effects of smoking and an inherited α_1-antitrypsin deficiency on the destruction of elastic fibers in the lung and development of emphysema are shown.

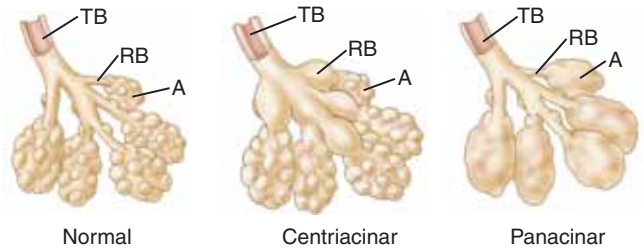


FIGURE 23-9. Centriacinar and panacinar emphysema. In centriacinar emphysema, the destruction is confined to the terminal (TB) and respiratory bronchioles (RB). In panacinar emphysema, the peripheral alveoli (A) are also involved. (Adapted from West J.B. [2008]. *Pulmonary pathophysiology: The essentials* [7th ed., p. 56]. Philadelphia: Wolters Kluwer/ Lippincott Williams & Wilkins.)

in Jews, blacks, and the Japanese.[41] Homozygotes who carry two defective PI genes have only about 15% to 20% of the normal plasma concentration of α_1-antitrypsin.[41] Most persons with clinically diagnosed emphysema before the age of 40 years have an α_1-antitrypsin deficiency. Smoking and repeated respiratory tract infections, which also decrease α_1-antitrypsin levels, contribute to the risk for emphysema in persons with α_1-antitrypsin deficiency. Laboratory methods are available for measuring α_1-antitrypsin levels. Human α_1-antitrypsin is available for replacement therapy in persons with a hereditary deficiency of the enzyme.

There are two commonly recognized types of emphysema: centriacinar or centrilobular, and panacinar (Fig. 23-9). The centriacinar type affects the bronchioles in the central part of the respiratory lobule, with initial preservation of the alveolar ducts and sacs.[41] It is the most common type of emphysema and is seen predominantly in male smokers. The panacinar type produces initial involvement of the peripheral alveoli and later extends to involve the more central bronchioles. This type of emphysema is more common in persons with α_1-antitrypsin deficiency. It also is found in smokers in association with centriacinar emphysema. In such cases, the panacinar pattern tends to occur in the lower parts of the lung and centriacinar emphysema is seen in the upper parts of the lung.

Chronic Bronchitis

Chronic bronchitis represents airway obstruction of the major and small airways.[18,41] The condition is seen most commonly in middle-aged men and is associated with chronic irritation from smoking and recurrent infections. A clinical diagnosis of chronic bronchitis requires a history of a chronic productive cough that has persisted for at least 3 consecutive months in at least 2 consecutive years.[38] Typically, the cough has been present for many years, with a gradual increase in acute exacerbations that produce frankly purulent sputum.

The earliest feature of chronic bronchitis is hypersecretion of mucus in the large airways, associated with hypertrophy of the submucosal glands in the trachea and bronchi.[18,41] Although mucus hypersecretion in the large airways is the cause of sputum overproduction, the accompanying changes in the small airways (small bronchi and bronchioles) are now thought to be important in the airway obstruction that develops.[18] Histologically, these changes include a marked increase in goblet cells and excess mucus production with plugging of the airway lumen, inflammatory infiltration, and fibrosis of the bronchiolar wall. It is thought that both the submucosal hypertrophy in the larger airways and the increase in goblet cells in the smaller airways are a protective reaction against tobacco smoke and other pollutants. Viral and bacterial infections are common in persons with chronic bronchitis and are thought to be a result rather than a cause of the problem. While infections are not responsible for initiating the problem, they are probably important in maintaining it and may be critical in producing acute exacerbations.

Clinical Features

The clinical manifestations of COPD usually have an insidious onset and patients characteristically seek medical attention in the fifth or sixth decade of life, with manifestations such as fatigue, exercise intolerance, cough, sputum production, or shortness of breath. The productive cough usually occurs in the morning and the dyspnea becomes more severe as the disease progresses. Frequent exacerbations of infection and respiratory insufficiency are common, causing absence from work and eventual disability. The late stages of COPD are characterized by recurrent respiratory infections and chronic respiratory failure. Death usually occurs during an exacerbation of illness associated with infection and respiratory failure.

Manifestations. The mnemonics "pink puffer" and "blue bloater" have been used to differentiate the clinical manifestations of emphysema and chronic obstructive bronchitis.[15,18,42] Persons with predominant emphysema are classically referred to as *pink puffers,* a reference to the lack of cyanosis, the use of accessory muscles, and pursed-lip ("puffer") breathing. With loss of lung elasticity and hyperinflation of the lungs, the airways often collapse during expiration because pressure in surrounding lung tissues exceeds airway pressure. Air becomes trapped in the alveoli and lungs, producing an increase in the anteroposterior dimensions of the chest, the so-called *barrel chest* that is typical of persons with emphysema (Fig. 23-10). Such persons have a dramatic decrease in breath sounds throughout the chest. Because the diaphragm may be functioning near its maximum ability, the person is vulnerable to diaphragmatic fatigue and acute respiratory failure. Persons with a clinical syndrome of chronic bronchitis are classically labeled *blue bloaters,* a reference to cyanosis and fluid retention associated with right-sided heart failure. In practice, differentiation between the two types of COPD is often difficult. This is because persons with COPD often have some degree of both emphysema and chronic bronchitis.

The manifestations of COPD represent a progressive change in respiratory function. There is moderate to

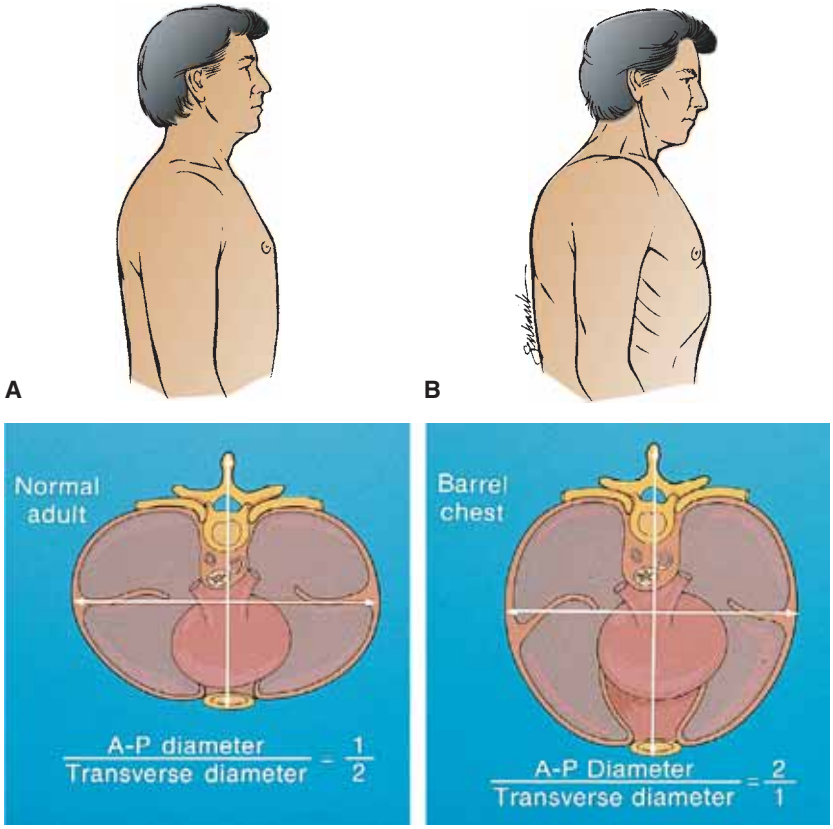


FIGURE 23-10. Characteristics of normal chest wall and chest wall in emphysema. The normal chest wall and its cross-section are illustrated on the left **(A)**. The barrel-shaped chest of emphysema and its cross-section are illustrated on the right **(B)**. (From Smeltzer S.C., Bare B.G. [2004]. *Medical-surgical nursing* [10th ed., p. 572]. Philadelphia: Lippincott Williams & Wilkins.)

severe respiratory impairment due to obstruction of airflow, which is greater on expiration than inspiration, resulting in increased work of breathing but decreased effectiveness. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious. Activities involving significant arm work, particularly above the shoulders, are usually difficult for persons with COPD. As the disease progresses, breathing becomes increasingly more labored, even at rest. The expiratory phase of respiration is prolonged, and expiratory wheezes and crackles can be heard on auscultation. Persons with severe airflow obstruction may also exhibit use of the accessory muscles, often sitting in the characteristic "tripod" position in which the arms are braced to facilitate use of the sternocleidomastoid, scalene, and intercostal muscles.[41] Pursed-lip breathing enhances airflow because it increases the resistance to the outflow of air and helps to prevent airway collapse by increasing airway pressure. Eventually, persons with COPD are unable to maintain normal blood gases by increasing their breathing effort. Hypoxemia, hypercapnia, and cyanosis develop, reflecting an imbalance between ventilation and perfusion.

Severe hypoxemia, in which arterial PO_2 levels fall below 55 mm Hg, causes reflex vasoconstriction of the pulmonary vessels and further impairment of gas exchange in the lung. It is more common in persons with the chronic bronchitis form of COPD. Hypoxemia also stimulates red blood cell production, causing polycythemia. The increase in pulmonary vasoconstriction and subsequent elevation in pulmonary artery pressure further increase the work of the right ventricle. As a result, persons with COPD may develop right-sided heart failure with peripheral edema (i.e., cor pulmonale). However, signs of overt right-sided heart failure are seen less frequently since the advent of supplemental oxygen therapy.

Diagnosis and Treatment. The diagnosis of COPD is based on a careful history and physical examination, pulmonary function studies, chest radiographs, and laboratory tests.[41] Airway obstruction prolongs the expiratory phase of respiration and affords the potential for impaired gas exchange because of mismatching of ventilation and perfusion. The FVC is the amount of air that can be forcibly exhaled after maximal inspiration. In patients with chronic lung disease, the FVC is decreased, the $FEV_{1.0}$ is decreased, and the ratio of $FEV_{1.0}$ to FVC is decreased. Lung volume measurements reveal a marked increase in RV, an increase in TLC, and elevation of the RV-to-TLC ratio. These and other measurements of expiratory flow are determined by spirometry and are used in the diagnosis of COPD (see Chapter 21, Fig. 21-15). Other diagnostic measures become important as the disease advances. Measures of exercise tolerance, nutritional status, hemoglobin saturation, and arterial blood gases can be used to assess the overall impact of COPD on health status and to direct treatment.

The treatment of COPD depends on the stage of the disease and often requires an interdisciplinary approach.

Smoking cessation is the only measure that slows the progression of the disease. Maintaining and improving physical and psychosocial functioning is an important part of the treatment program for persons with COPD. A long-term pulmonary rehabilitation program can significantly reduce hospitalizations and increase a person's ability to manage and cope with his or her impairment in a positive way. This program includes breathing exercises that focus on restoring the function of the diaphragm, reducing the work of breathing, and improving gas exchange. Physical conditioning with appropriate exercise training increases maximal oxygen consumption and reduces ventilatory effort and heart rate for a given workload. Work simplification and energy conservation strategies may be needed when impairment is severe.

Respiratory tract infections can prove life-threatening to persons with severe COPD. A person with COPD should avoid exposure to others with known respiratory tract infections and should avoid attending large gatherings during periods of the year when influenza or respiratory tract infections are prevalent. Immunization for influenza and pneumococcal infections decreases the likelihood of their occurrence. Although antibiotics are used to treat acute exacerbations of COPD due to bacterial infection, there is no evidence that the prophylactic use of antibiotics prevents acute exacerbations.[38]

The pharmacologic treatment of COPD includes the use of bronchodilators, including inhaled adrenergic and anticholinergic agents.[37,38,42] Inhaled β_2-agonists have been the mainstay of treatment of COPD for many years. It has been suggested that long-acting inhaled β_2-agonists may be even more effective than the short-acting forms of the drug. The anticholinergic drugs, which are administered by inhalation, produce bronchodilation by blocking parasympathetic cholinergic receptors that produce contraction of bronchial smooth muscle. They also reduce the volume of sputum without altering its viscosity. Because these drugs have a slower onset and longer duration of action, they typically are used on a regular basis rather than on an as-needed basis. Inhalers that combine an anticholinergic drug with a β_2-adrenergic agonist are available. Oral theophylline may be used in treatment of persons who fail to respond to inhaled bronchodilators. The long-acting theophylline preparations may be used to reduce overnight declines in respiratory function. When theophylline is prescribed, blood levels are used as a guide in arriving at an effective dose schedule.

Although inhaled corticosteroids often are used in treatment of COPD, there is controversy regarding their usefulness. There is evidence that inflammation in COPD is not suppressed by inhaled or oral corticosteroids.[40] Because corticosteroids are useful in relieving asthma symptoms, they may benefit persons with asthma concomitant with COPD. Inhaled corticosteroids also may be beneficial in treating acute exacerbations of COPD, minimizing the undesirable effects that often accompany systemic use.

Oxygen therapy is prescribed for selected persons with significant hypoxemia (arterial PO_2 <55 mm Hg). Administration of continuous low-flow (1 to 2 L/minute) oxygen to maintain arterial PO_2 levels between 55 and 65 mm Hg decreases dyspnea and pulmonary hypertension and improves neuropsychological function and activity tolerance. The overall goal of oxygen therapy is to maintain a hemoglobin oxygen saturation of at least 90%.[37] Portable oxygen administration units, which allow mobility and the performance of activities of daily living, usually are used. Because the ventilatory drive associated with hypoxic stimulation of the peripheral chemoreceptors does not occur until the arterial PO_2 has been reduced to about 60 mm Hg or less, increasing the arterial PO_2 above 60 mm Hg tends to depress the hypoxic stimulus for ventilation and often leads to hypoventilation and carbon dioxide retention.

Bronchiectasis

Bronchiectasis is an uncommon type of COPD characterized by a permanent dilation of the bronchi and bronchioles caused by destruction of the muscle and elastic supporting tissue as the result of a vicious cycle of infection and inflammation[43] (Fig. 23-11). It is not a primary disease but occurs secondary to persistent infection or obstruction.[18] In the past, bronchiectasis often followed

FIGURE 23-11. Bronchiectasis. The resected upper lobe shows widely dilated bronchi, with thickening of the bronchial walls and collapse and fibrosis of the pulmonary parenchyma. (From Bearsley M.B., Travis W.D., Rubin E. [2008]. The respiratory system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 490]. Philadelphia: Lippincott Williams & Wilkins.)

a necrotizing bacterial pneumonia that frequently complicated measles, pertussis (whooping cough), or influenza. Tuberculosis was also commonly associated with bronchiectasis. Thus, with the advent of antibiotics that more effectively treat respiratory infections such as tuberculosis, and with immunization against pertussis and measles, there has been a marked decrease in the prevalence of bronchiectasis.

Etiology and Pathogenesis

Two processes are critical to the pathogenesis of bronchiectasis: obstruction and chronic persistent infection.[18] Regardless of which may come first, both cause damage to the bronchial walls, leading to weakening and dilation. On gross examination, bronchial dilation is classified as saccular, cylindrical, or varicose. Saccular bronchiectasis involves the proximal third to fourth generation of bronchi[18,41] (see Chapter 21, Fig. 21-4). These bronchi become severely dilated and end blindly in dilated sacs, with collapse and fibrosis of more distal lung tissue. Cylindrical bronchiectasis involves uniform and moderate dilation of the sixth to eighth generations of airways. It is a milder form of disease than saccular bronchiectasis and leads to fewer symptoms. Varicose bronchiectasis involves the second through eighth branchings of bronchi and results in bronchi that resemble varicose veins. Bronchiolar obliteration is not as severe and symptoms are variable.

Bronchiectasis can present in either of two forms: a local obstructive process involving a lobe or segment of a lung or a diffuse process involving much of both lungs.[41] *Localized bronchiectasis* is most commonly caused by conditions such as tumors, foreign bodies, and mucous plugs that produce atelectasis and infection due to obstructed drainage of bronchial secretions. It can affect any area of the lung, the area being determined by the site of obstruction or infection. *Generalized bronchiectasis* usually is bilateral and most commonly affects the lower lobes. It is due largely to inherited impairments of host mechanisms or acquired disorders that permit introduction of infectious organisms into the airways. They include inherited conditions such as cystic fibrosis, in which airway obstruction is caused by impairment of normal mucociliary function; congenital and acquired immunodeficiency states, which predispose to respiratory tract infections; lung infection (e.g., tuberculosis, fungal infections, lung abscess); and exposure to toxic gases that cause airway obstruction.

Clinical Features

Bronchiectasis is associated with a number of abnormalities that profoundly affect respiratory function, including atelectasis, obstruction of the smaller airways, and diffuse bronchitis. Affected persons have recurrent bronchopulmonary infection; coughing; production of copious amounts of foul-smelling, purulent sputum; and hemoptysis. Weight loss and anemia are common.

Manifestations. The manifestations of bronchiectasis are similar to those seen in chronic bronchitis and emphysema. As in the latter two conditions, chronic bronchial obstruction leads to marked dyspnea and cyanosis. Clubbing of the fingers, which is not usually seen in other types of obstructive lung diseases, is more common in moderate to advanced bronchiectasis.

Diagnosis and Treatment. Diagnosis is based on history and imaging studies. The condition often is evident on chest radiographs. High-resolution CT scanning of the chest allows for definitive diagnosis. Accuracy of diagnosis is important because interventional bronchoscopy or surgery may be palliative or curative in some types of obstructive disease.

Treatment consists of early recognition and treatment of infection along with regular postural drainage and chest physical therapy. Persons with this disorder benefit from many of the rehabilitation and treatment measures used for chronic bronchitis and emphysema.

Cystic Fibrosis

Cystic fibrosis (CF), which is a major cause of severe chronic respiratory disease in children and young adults, is an inherited disorder involving fluid secretion by the exocrine glands in the epithelial lining of the respiratory, gastrointestinal, and reproductive tracts.[44–46] In addition to chronic respiratory disease, CF is manifested by pancreatic exocrine deficiency and elevation of sodium chloride in the sweat. Nasal polyps, sinus infections, pancreatitis, and cholelithiasis also are common. Excessive loss of sodium in the sweat predisposes young children to salt depletion episodes. Most boys with CF have congenital bilateral absence of the vas deferens with azoospermia.

CF is inherited as an autosomal recessive trait. Homozygotes (i.e., persons with two defective genes) have all or substantially all of the clinical symptoms of the disease, compared with heterozygotes, who are carriers of the disease but have no recognizable symptoms. Cystic fibrosis occurs most frequently in white populations of northern Europe, North America, and Australia/New Zealand.[46] The disease is rare in African blacks and Asians.

Etiology and Pathogenesis

Cystic fibrosis is caused by mutations in a single gene on the long arm of chromosome 7 that encodes for the cystic fibrosis transmembrane regulator (CFTR), which functions as a chloride channel in epithelial cell membranes.[44] Mutations in the *CFTR* gene render the epithelial membrane relatively impermeable to the chloride (Cl^-) ion (Fig. 23-12).

The impact on impaired Cl^- transport is relatively tissue specific. In the sweat glands, the concentration of sodium (Na^+) and Cl^- secreted into the lumen of the gland remains unaffected, whereas the reabsorption of Cl^- through the CFTR and accompanying reabsorption of Na^+ in the ducts of the gland fail to occur. This defect accounts for the high concentration of NaCl in the sweat of persons with CF.[45,46] In the normal airway epithelium, Cl^- is secreted into airway lumen through the CFTR. The

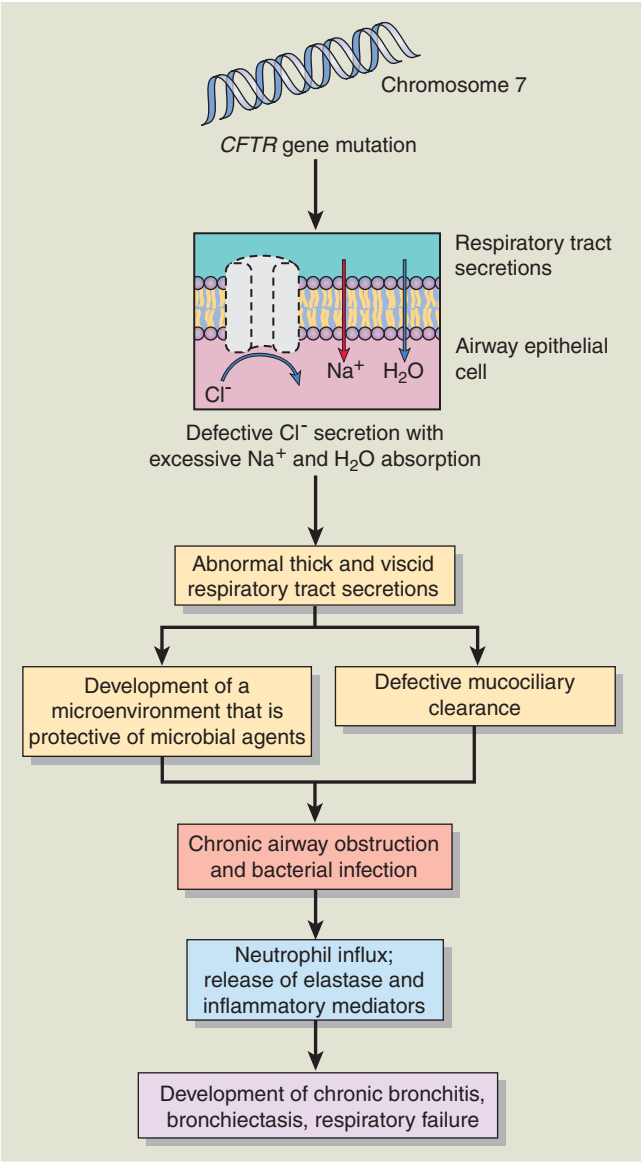


FIGURE 23-12. Pathogenesis of cystic fibrosis.

impaired transport of Cl^- ultimately leads to a series of secondary events, including increased absorption of Na^+ and water from the airways into the blood. This lowers the water content of the mucociliary blanket coating the respiratory epithelium, causing it to become more viscid. The resulting dehydration of the mucous layer leads to defective mucociliary function and accumulation of viscid secretions that obstruct the airways and predispose to recurrent pulmonary infections. Similar transport abnormalities and pathophysiologic events take place in the pancreatic and biliary ducts and in the vas deferens in boys.

Clinical Features

Respiratory manifestations of CF are caused by an accumulation of viscid mucus in the bronchi, impaired mucociliary clearance, and lung infections. Chronic bronchiolitis and bronchitis are the initial lung manifestations, but after months and years, structural changes in the bronchial wall lead to bronchiectasis. In addition to airway obstruction, the basic genetic defect that occurs with CF predisposes to chronic infection with a surprisingly limited number of organisms, the most common being *Pseudomonas aeruginosa, Burkholderia cepacia, Staphylococcus aureus,* and *Haemophilus influenzae.*[44,47] Soon after birth, initial infection with bacterial pathogens occurs and is associated with an excessive neutrophilic inflammatory response that appears to be independent of the infection itself. There is evidence that the airway secretions in persons with CF provide a favorable environment for harboring these organisms. *P. aeruginosa,* in particular, has a propensity to undergo mucoid transformation in this environment.[47] The complex polysaccharide produced by these organisms provides a hypoxic environment and generates a biofilm that protects *Pseudomonas* against antimicrobial agents. Pulmonary inflammation is another cause of decline in respiratory function in persons with CF and may precede the onset of chronic infection.

Pancreatic function is abnormal in approximately 80% to 90% of affected persons.[46] Steatorrhea, diarrhea, and abdominal pain are common. In the newborn, meconium ileus may cause intestinal obstruction, a fatal condition if left untreated. The degree of pancreatic involvement is highly variable. In some children, the defect is relatively mild, and in others, the involvement is severe and impairs intestinal absorption. In addition to exocrine pancreatic insufficiency, hyperglycemia may occur, especially after 10 years of age, when approximately 8% of persons with CF develop diabetes mellitus.[46]

Diagnosis and Treatment. Early diagnosis and treatment are important in delaying the onset and severity of chronic illness in children with CF. Diagnosis is based on the presence of respiratory and gastrointestinal manifestations typical of CF, a history of CF in a sibling, or a positive newborn screening test result. Confirmatory laboratory tests include the sweat test, assessment of bioelectrical properties of respiratory epithelia by measurement of transepithelial potential differences in the nasal membrane, and genetic tests for *CFTR* gene mutations.[46] The *sweat test,* using pilocarpine iontophoresis to collect the sweat followed by chemical analysis of its chloride content, remains the standard approach to diagnosis. Newborns with CF have elevated blood levels of immunoreactive trypsinogen, presumably because of secretory obstruction in the pancreas. *Newborn screening* consists of a test for determination of immunoreactive trypsinogen. The test can be done on blood spots collected for routine newborn screening tests.

At present, there are no approved treatments for correcting the genetic defects in CF or to reverse the ion transport abnormalities associated with the dysfunctional CFTR. Thus, treatment measures are directed toward slowing the progression of secondary organ dysfunction and sequelae such as chronic lung infection and pancreatic insufficiency.[46] They include the use of antibiotics to prevent and manage infections, the use of chest physical therapy (chest percussion and postural drainage)

and mucolytic agents to prevent airway obstruction, and pancreatic enzyme replacement and nutritional therapy. Routine laboratory evaluations are key to assessing pulmonary function and response to therapeutic interventions. These studies include radiologic examinations, pulmonary function testing, and microbiologic cultures of respiratory secretions.

Appropriate antibiotic therapy directed against bacterial pathogens isolated from the respiratory tract is an essential component in the management of CF lung disease. Antibiotics are initially used to prevent colonization with *P. aeruginosa;* they are used as maintenance therapy once the airways are colonized with *P. aeruginosa* and other organisms such as *S. aureus;* and they are administered as aggressive treatment during acute exacerbations of pulmonary symptoms caused by infections.[47] To avoid adverse effects and to obtain high airway concentrations, the inhalation route is often used. Indications for oral antibiotics include the presence of respiratory tract symptoms and identification of pathogenic organisms in respiratory tract cultures. Intravenous antibiotics are used for progressive and unrelenting symptoms.

The abnormal viscosity of airway secretions is attributed largely to the presence of polymorphonuclear white blood cells and their degradation products. A purified recombinant human deoxyribonuclease (rhDNase), an enzyme that breaks down these products, has been developed.[45] Clinical trials have shown that the drug, which is administered by inhalation, can improve pulmonary symptoms and reduce the frequency of respiratory exacerbations. Although many persons benefit from the therapy, the drug is costly, and recommendations for its use are evolving.

Up to 90% of patients with CF have complete loss of exocrine pancreas function and inadequate digestion of fats and proteins. They require diet adjustment, pancreatic enzyme replacement, and supplemental vitamins and minerals. Pancreatic enzyme dosage and product type are individualized for each patient. Enteric-coated, pH-sensitive enzyme microspheres are available.[46] A low-fat, high-protein, high-calorie diet was generally recommended in the past. With the advent of improved pancreatic enzyme products, however, normal amounts of fat in the diet are usually tolerated and preferred.

Progress of the disease is variable. Improved medical management has led to longer survival. Today, many people with the disease can expect to live into their 30s, 40s, and beyond.[47] Lung transplantation is being used as a treatment for persons with end-stage lung disease. Current hopes reside in research that would make gene therapy a feasible alternative for persons with the disease.

In summary, obstructive ventilatory disorders are characterized by airway obstruction and limitation in expiratory airflow. Bronchial asthma is a chronic inflammatory disorder of the airways characterized by airway hyperreactivity and episodic attacks of airway narrowing. An asthmatic attack can be triggered by a variety of stimuli. Based on their mechanism of response, these triggers can be divided into two types: extrinsic (atopic) and intrinsic (nonatopic). Atopic asthma is typically initiated by a type I hypersensitivity reaction triggered by an extrinsic antigen or allergen, whereas intrinsic asthma has triggers such as respiratory tract infections, exercise, drugs and chemicals, air-borne pollutants, and gastroesophageal reflux. There are two types of responses in persons with asthma: the acute- or early-phase response and the late-phase response. The acute-phase response results in immediate bronchoconstriction on exposure to an inhaled antigen and usually subsides within 90 minutes. The late-phase response usually develops 4 to 8 hours after exposure to an asthmatic trigger; it involves inflammation and increased airway responsiveness that prolong the attack and cause a vicious cycle of exacerbations.

Chronic obstructive pulmonary disease (COPD) describes a group of conditions characterized by obstruction to airflow in the lungs. Among the conditions associated with COPD are emphysema, chronic bronchitis, and bronchiectasis. Emphysema is characterized by a loss of lung elasticity; abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles; and hyperinflation of the lungs. Chronic bronchitis is caused by inflammation of major and small airways and is characterized by edema and hyperplasia of submucosal glands and excess mucus secretion into the bronchial tree. A history of a chronic productive cough that has persisted for at least 3 months in at least 2 consecutive years in the absence of other disease is necessary for the diagnosis of chronic bronchitis. Emphysema and chronic bronchitis are manifested by eventual mismatching of ventilation and perfusion. As the condition advances, signs of respiratory distress and impaired gas exchange become evident, with development of hypercapnia and hypoxemia. Bronchiectasis is a less common form of COPD that is characterized by an abnormal dilation of the large bronchi associated with infection and destruction of the bronchial walls.

Cystic fibrosis (CF) is an autosomal recessive genetic disorder manifested by chronic lung disease, pancreatic exocrine deficiency, and elevation of sodium chloride in the sweat. The disorder is caused by a mutation of a single gene on the long arm of chromosome 7 that codes for the cystic fibrosis transmembrane regulator (CFTR), which functions in the transepithelial transport of the chloride ion. The defect causes exocrine gland secretions to become exceedingly viscid, and it promotes colonization of the respiratory tract with *P. aeruginosa* and other organisms such as *S. aureus*. Accumulation of viscid mucus in the bronchi, impaired mucociliary function, and infection contribute to the development of chronic lung disease and a decreased life expectancy.

Interstitial Lung Diseases

The diffuse interstitial diseases, also called *diffuse parenchymal lung diseases*, are a diverse group of lung disorders that produce similar inflammatory and fibrotic

changes in the interstitium or interalveolar septa of the lung.[18,41,48,49] Because the interstitial lung diseases result in a stiff and noncompliant lung, they are commonly classified as *restrictive lung disorders*.

In contrast to the obstructive lung diseases, which primarily involve the airways of the lung, the interstitial lung disorders exert their effects on the collagen and elastic connective tissue found in the delicate interstitium of the alveolar walls. Many of these diseases also involve the airways, arteries, and veins. The clinical hallmark of these widespread lung changes is diminished lung compliance, which presents as restrictive lung disease. The lungs are stiff and difficult to inflate. More pressure is needed to expand the lungs, which in turn necessitates more effort in breathing. Damage to alveolar epithelium and interstitial vasculature produces impaired gas exchange and hypoxemia. With progression, persons develop respiratory failure, often in association with pulmonary hypertension and cor pulmonale.

The interstitial lung diseases may be acute or insidious in onset; they may be rapidly progressive, slowly progressive, or static in their course. Over 100 distinct entities of interstitial lung diseases have been recognized including hypersensitivity pneumonitis (discussed in Chapter 16); lung diseases caused by drugs (e.g., the cancer drug bleomycin the and antiarrhythmic drug amiodarone) and radiation therapy; the occupational lung diseases, including the pneumoconioses that are caused by the inhalation of inorganic dusts such as silica, coal dust, and asbestos; immunologic lung disorders, such as those that accompany rheumatoid arthritis and scleroderma; and granulomatous diseases such as sarcoidosis.[18,41,49] Examples of interstitial lung diseases and their causes are listed in Chart 23-1. The discussion in this chapter focuses on idiopathic pulmonary fibrosis and sarcoidosis, two of the most common types of interstitial lung diseases seen in the clinical setting.[49]

CHART 23-1 Causes of Interstitial Lung Disease*

Occupational and Environmental Inhalants
Pneumoconioses (coal miner's pneumoconiosis, silicosis, asbestosis)
Hypersensitivity pneumonitis (farmer's lung, bird breeder's lung)
Talcosis (talc inhalation in injection drug users)
Smoking related

Drugs and Therapeutic Agents
Cancer drugs (e.g., bleomycin, busulfan, cyclophosphamide, methotrexate)
Antiarrhythmic drugs (amiodarone)
Ionizing radiation (i.e., radiation therapy)

Granulomatous Disorders
Sarcoidosis

Immunologic Disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma

Unknown Causes
Idiopathic pulmonary fibrosis

*This list is not intended to be inclusive.

Pathogenesis

Current theory suggests that most interstitial lung diseases, regardless of their cause, have a common pathogenesis.[15,18,48] It is thought that these disorders are initiated by some type of injury to the alveolar epithelium, followed by an inflammatory process that involves the alveoli and interstitium of the lung. If the injury is mild and self-limited, resolution with restoration of normal lung structures follows. However, with persistence of the injurious agent, an accumulation of inflammatory and immune cells causes continued damage to lung tissue and replacement of normally functioning lung tissue with fibrous scar tissue. Alveolar macrophages secrete a host of fibrogenic factors, including fibroblast growth factor, transforming growth factor-β (TGF-β), and platelet-derived growth factor, which can attract fibroblasts as well as stimulate their proliferation. Alveolar cells also appear to play a role in the process. Destruction of type I alveolar cells is often accompanied by proliferation of type II alveolar cells (see Chapter 21). These cells secrete chemotactic factors that attract additional macrophages, growth factors, and cytokines such as TGF-β that contribute to fibrotic changes.

Clinical Features

In general, the interstitial lung diseases are characterized by clinical changes consistent with restrictive rather than obstructive changes in the lung. Persons with interstitial lung diseases have dyspnea, tachypnea, and eventual cyanosis, without evidence of wheezing or signs of airway obstruction. Usually, there is an insidious onset of

Interstitial or Restrictive Lung Diseases

- Interstitial lung diseases result from inflammatory conditions that affect the interalveolar structures of the lung and produce lung fibrosis and a stiff lung.
- A stiff and noncompliant lung is difficult to inflate, increasing the work of breathing and causing decreased exercise tolerance due to hypoxemia.
- Because of the increased effort needed for lung expansion, persons with interstitial lung disease tend to take small but more frequent breaths.

breathlessness that initially occurs during exercise and may progress to the point at which the person is totally incapacitated. Typically, a person with a restrictive lung disease breathes with a tachypneic pattern of breathing, in which the respiratory rate is increased and the tidal volume is decreased. This pattern of breathing serves to maintain minute volume yet reduces the work of breathing because it takes less work to move air through the airways at an increased rate than it does to stretch a stiff lung to accommodate a larger tidal volume. A nonproductive cough may develop, particularly with continued exposure to the inhaled irritant. Clubbing of the fingers and toes may develop.

Lung volumes, including vital capacity and TLC, are reduced in interstitial lung disease. In contrast to COPD, in which expiratory flow rates are reduced, the $FEV_{1.0}$ usually is preserved, even though the ratio of $FEV_{1.0}$ to FVC may increase. Although resting arterial blood gases usually are normal early in the course of the disease, arterial PO_2 levels may fall during exercise. In persons with advanced disease, hypoxemia often is present, even at rest. In the late stages of the disease, hypercapnia and respiratory acidosis develop. The impaired diffusion of gases in persons with interstitial lung disease is thought to be caused by alterations in the alveolar–capillary membrane as well as an increase in shunt resulting from unventilated regions of the lung.

The diagnosis of interstitial lung disease requires a careful personal and family history, with particular emphasis on exposure to environmental, occupational, and other injurious agents. Chest radiographs may be used as an initial diagnostic method, and serial chest films often are used to follow the progress of the disease. A biopsy specimen for histologic study and culture may be obtained by surgical incision or bronchoscopy using a fiberoptic bronchoscope. In bronchoalveolar lavage, fluid is instilled into the alveoli through a bronchoscope and then removed by suction to obtain inflammatory and immune cells for laboratory study. Gallium lung scans often are used to detect and quantify the chronic alveolitis that occurs in interstitial lung disease. Gallium does not localize in normal lung tissue, but uptake of the radionuclide is increased in interstitial lung disease and other diffuse lung diseases.

The treatment goals for persons with interstitial lung disease focus on identifying and removing the injurious agent, suppressing the inflammatory response, preventing progression of the disease, and providing supportive therapy for persons with advanced disease. In general, the treatment measures vary with the type of lung disease. Corticosteroid drugs frequently are used to suppress the inflammatory response. Many of the supportive treatment measures used in the late stages of the disease, such as oxygen therapy and measures to prevent infection, are similar to those discussed for persons with COPD.

Idiopathic Pulmonary Fibrosis

The most common diagnosis among persons with interstitial lung disease is idiopathic pulmonary fibrosis (IPF). The disease is characterized by diffuse interstitial fibrosis, which in severe cases results in severe hypoxemia and cyanosis. As the name implies, the cause of the disorder is unknown. Men are affected more commonly than women and approximately two thirds of persons are older than 60 years of age at the time of presentation.

Although the inciting agent of idiopathic fibrosing interstitial pneumonia is largely unknown, a number of conditions and risk factors are associated with the disease.[18,50,51] Cigarette smoking increases the risk of IPF, as does several occupational factors such as farming and exposure to livestock, hairdressing, stonecutting, and metal cutting. Although viruses have not been clearly implicated in the pathogenesis of IPF, several viral proteins and antibodies to viruses are associated with the disease. In addition, some people may have a genetic predisposition to the disease.

The disease is characterized by patchy interstitial fibrosis that causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II alveolar cells or bronchial epithelium. Secondary hypertensive changes due to intimal fibrosis and medial thickening of the pulmonary arteries are often present.

IPF usually presents insidiously, with gradual onset of a nonproductive cough and progressive dyspnea. Cyanosis, cor pulmonale, and peripheral edema may present late in the disease. Diagnosis is confirmed by surgical biopsy. Unfortunately, the progress of IPF is relentless despite current methods of treatment. The mean survival after diagnosis is 3 to 5 years.

Sarcoidosis

Sarcoidosis is a multisystem disorder in which granulomas are found in many tissues and organs, particularly the lung.[18,52,53] The disorder predominantly affects adults younger than 40 years of age, although it can occur in older persons. The incidence is highest among North American blacks and northern European whites; and women are affected more frequently than men.

The cause of sarcoidosis remains unclear. It is thought that the disorder may result from exposure of genetically predisposed persons to specific environmental agents. Support for a genetic influence comes from epidemiologic studies that have demonstrated the higher incidence in American blacks and Scandinavian populations. Additional evidence comes from familial clustering of the disease. Analysis of human leukocyte antigen (HLA) genes located in the major histocompatibility complex also suggests that unique HLA genes can be linked to disease susceptibility and prognosis. Despite advances, including the identification of sarcoidosis genetic factors, a specific etiologic agent has yet to be identified. Multiple lines of evidence suggest that the inciting agent triggers an immune response that depends on host susceptibility and is characterized by chronic inflammation, monocyte recruitment, and granuloma formation.

The characteristic lesion of sarcoidosis is the noncaseating granuloma. Unlike the granulomatous lesions that develop in tuberculosis and histoplasmosis, the collection of tissue macrophages composing the granulomas in sarcoidosis do not show evidence of necrosis or

caseation. In addition to granulomas, in which multinuclear giant cells are frequently seen (see Chapter 3), there is often alveolitis or inflammation of the alveoli. The inflammation is composed largely of macrophages and lymphocytes, with the latter thought to be of particular importance in the pathogenesis of the disease.

Sarcoidosis has variable manifestations and an unpredictable course of progression in which any organ system can be affected. The three systems that most commonly manifest symptoms are the lungs, skin, and eyes. Persons with sarcoidosis frequently seek health care either as a result of abnormalities detected on an incidental chest film or because of insidious onset of respiratory symptoms (shortness of breath, nonproductive cough, chest pain) or constitutional signs and symptoms (e.g., fever, sweating, anorexia, weight loss, fatigue, myalgia). Eye involvement (anterior uveitis) and skin involvement (skin papules and plaques) are particularly common extrathoracic manifestations, but there may be cardiac, neuromuscular, hematologic, hepatic, endocrine, and lymph node findings.

Sarcoidosis is characterized by either progressive chronicity or periods of activity interspersed with remissions, sometimes permanent, that may be spontaneous or induced by corticosteroid therapy. Approximately 65% to 75% of persons recover with minimal clinical and radiographic abnormalities.[18] Other persons have persistent radiographic abnormalities and progression of their respiratory symptoms, with or without additional extrathoracic disease.

The diagnosis of sarcoidosis is based on history and physical examination, tests to exclude other diseases, chest radiography, and biopsy to obtain confirmation of noncaseating granulomas. The use of CT scans and magnetic resonance imaging (MRI) as routine methods for diagnosis of sarcoidosis remains controversial. A thorough ophthalmologic evaluation is recommended for most persons, even those without ocular symptoms.

Treatment is directed at interrupting the granulomatous inflammatory process that is characteristic of the disease and managing the associated complications. When treatment is indicated, corticosteroid drugs are used. These agents produce clearing of the lung, as seen on the chest radiograph, and improve pulmonary function, but it is not known whether they affect the long-term outcome of the disease.

In summary, the diffuse interstitial lung diseases are a diverse group of lung disorders that produce similar inflammatory and fibrotic changes in the interstitium or alveolar septa of the lung. As a result, the lungs are stiff and difficult to expand despite normally functioning conductive airways. These diseases include hypersensitivity pneumonitis, drug- and radiation-induced lung disease, occupational lung diseases caused by inhalation of organic and inorganic dusts, immunologic lung disorders such as those that accompany rheumatoid arthritis and scleroderma, idiopathic pulmonary fibrosis, and lung diseases associated with granulomatous diseases such as sarcoidosis. These diseases reduce the diffusing capacity of the lung and cause various degrees of hypoxemia causing dyspnea, tachypnea, and eventual cyanosis, without evidence of wheezing or signs of airway obstruction.

Disorders of the Pulmonary Circulation

As blood moves through the pulmonary capillaries, oxygen content increases and carbon dioxide decreases. These processes depend on the matching of ventilation (i.e., gas exchange) and perfusion (i.e., blood flow). This section discusses two major problems of the pulmonary circulation: pulmonary embolism and pulmonary hypertension. Pulmonary edema, another major problem of the pulmonary circulation, is discussed in Chapter 20.

Pulmonary Embolism

Pulmonary embolism develops when a blood-borne substance lodges in a branch of the pulmonary artery and obstructs blood flow.[54–56] The embolism may consist of a thrombus (Fig. 23-13), air that has accidentally been

Disorders of the Pulmonary Circulation

- The pulmonary circulation is a low-pressure system that links the right heart and systemic venous system with the left heart and the systemic arterial system and functions as a conduit for exchange between the dissolved gases in the blood and the ventilated air in the alveoli.
- Pulmonary thromboemboli are blood clots that originate in the systemic venous system and become lodged in a pulmonary blood vessel as they move from the right heart into and through the pulmonary circulation.
- Pulmonary hypertension is an elevated pulmonary arterial pressure. It may arise as a primary disorder of the pulmonary arteries in which an abnormal thickening of the vessel wall increases the resistance to blood flow, or as a secondary disorder due to chronic lung disorders or environmental conditions that produce hypoxemia and a resultant constriction of small pulmonary arteries, cardiac disorders that increase pulmonary venous pressure, or thromboembolic disorders that occlude pulmonary blood vessels.

FIGURE 23-13. Pulmonary embolism. The main pulmonary artery and its bifurcation have been opened to reveal a large saddle embolus. (From McManus B.M., Allard M.F., Yanagawa R. [2008]. Hemodynamic disorders. In Rubin R., Strayer D.S. [Eds.]. *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 236]. Philadelphia: Lippincott Williams & Wilkins.)

injected during intravenous infusion, fat that has been mobilized from the bone marrow after a fracture or from a traumatized fat depot, or amniotic fluid that has entered the maternal circulation during childbirth.

Almost all pulmonary emboli are thrombi that arise from deep vein thrombosis (DVT) in the large veins of the lower legs, typically originating in the popliteal vein or larger veins above it (see Chapter 18). The presence of thrombosis in the deep veins of the legs or pelvis often is unsuspected until embolism occurs. Among the physiologic factors that contribute to venous thrombosis are venous stasis, venous endothelial injury, and hypercoagulability states. Venous stasis and venous endothelial injury can result from prolonged bed rest (particularly with immobilization of the legs), severe trauma (including burns and fractures), surgery (particularly orthopedic surgery of the knee or hip), childbirth, myocardial infarction and congestive heart failure, and spinal cord injury. Hypercoagulability is related to various factors. Cancer cells can produce thrombin and synthesize procoagulation factors, increasing the risk for thromboembolism. Use of oral contraceptives, pregnancy, and hormone replacement therapy are thought to increase the resistance to endogenous anticoagulants. There is increased risk for pulmonary embolism among users of oral contraceptives, particularly in women who smoke. The thrombophilias (e.g., antithrombin III deficiency, protein C and S deficiencies, factor V Leiden mutation) are a group of inherited disorders affecting coagulation that make an individual prone to the development of venous thromboemboli (see Chapter 12).

The pathophysiologic effects of thromboembolism depend largely on the size of the embolus and degree of pulmonary blood flow obstruction. Obstruction of pulmonary blood flow causes reflex bronchoconstriction in the affected area of the lung, wasted ventilation and impaired gas exchange, and loss of alveolar surfactant. Pulmonary hypertension and right heart failure may develop when there is massive vasoconstriction because of a large embolus.

Although small areas of infarction may occur, pulmonary infarction is uncommon. This is because the lung is oxygenated not only by the pulmonary arteries but also by the bronchial arteries and air from the alveoli. If the bronchial circulation is normal and adequate ventilation is maintained, a decrease in pulmonary artery perfusion does not usually cause infarction.

Clinical Features

Manifestations. The clinical manifestations of pulmonary embolism depend on the size and location of the obstruction. Small emboli that become lodged in the peripheral branches of the pulmonary artery are clinically silent and may go unrecognized unless the person is compromised, such as occurs in the elderly or acutely ill. Persons with moderate-sized emboli often present with breathlessness accompanied by pleuritic pain, apprehension, slight fever, and cough productive of blood-streaked sputum. Tachycardia often occurs to compensate for decreased oxygenation, and the breathing pattern is rapid and shallow. Patients with massive emboli usually present with sudden collapse, crushing substernal chest pain, shock, and sometimes loss of consciousness. The pulse is rapid and weak, the blood pressure is low, the neck veins are distended, and the skin is cyanotic and diaphoretic. Massive pulmonary emboli often are fatal.

Diagnosis and Treatment. The diagnosis of pulmonary embolism is based on clinical signs and symptoms, blood gas determinations, venous thrombosis studies, D-dimer testing, lung scans, helical CT scans of the chest, and, in selected cases, pulmonary angiography.[54–56] Laboratory studies and radiologic films are useful in ruling out other conditions that might give rise to similar symptoms. Because emboli can cause an increase in pulmonary vascular resistance, the electrocardiogram (ECG) may be used to detect signs of right heart strain. There has been recent interest in combining several noninvasive methods (lower limb compression ultrasonography, D-dimer measurements, and clinical assessment measures) as a means of establishing a diagnosis of pulmonary embolism.

Because most pulmonary emboli originate from DVT, venous studies such as *lower limb compression ultrasonography, impedance plethysmography,* and *contrast venography* are often used as initial diagnostic procedures. Of these, lower limb compression ultrasonography

has become an important noninvasive means for detecting DVT. *D-dimer testing* involves the measurement of plasma D-dimer, a degradation product of coagulation factors that have been activated as a result of a thromboembolic event. The *ventilation–perfusion scan* uses radiolabeled albumin, which is injected intravenously, and a radiolabeled gas, which is inhaled. A scintillation (gamma) camera is used to scan the various lung segments for blood flow and distribution of the radiolabeled gas. Ventilation–perfusion scans are useful only when their results are either normal or indicate a high probability of pulmonary embolism. *Helical (spiral) CT angiography* requires administration of an intravenous radiocontrast medium. It is sensitive for the detection of emboli in the proximal pulmonary arteries and provides another method of diagnosis. *Pulmonary angiography* involves the passage of a venous catheter through the right heart and into the pulmonary artery under fluoroscopy. Although it remains the most accurate method of diagnosis, it is an invasive procedure; therefore, its use is reserved for selected cases.

The treatment goals for pulmonary emboli focus on preventing DVT and the development of thromboemboli, protecting the lungs from exposure to thromboemboli when they occur, and in the case of large and life-threatening pulmonary emboli, sustaining life and restoring pulmonary blood flow.[55,56] Thrombolytic therapy using streptokinase, urokinase, or recombinant tissue plasminogen activator may be indicated in persons with life-threatening pulmonary emboli. Thrombolytic therapy is followed by anticoagulant therapy (e.g., heparin and then warfarin) to prevent clot reoccurrence. Surgical interruption of the vena cava or insertion of a filter to prevent emboli from traveling to the lung may be indicated in life-threatening situations.

Venous thromboembolism is often clinically silent until it presents with significant morbidity and mortality. Thus, recognition of risk factors and appropriate preventative treatment is essential. Prophylactic measures include early ambulation for postoperative and postpartum patients and the use of graded compression elastic stockings and intermittent pneumatic compression (IPC) boots for bedridden patients. IPC boots provide intermittent inflation of air-filled sleeves that prevent venous stasis. Some devices produce sequential gradient compression that moves blood upward in the leg. Anticoagulant therapy may be used to decrease the likelihood of deep vein thrombosis, thromboembolism, and fatal pulmonary embolism after major surgical procedures (see Chapter 12). Low–molecular-weight heparin, which can be administered subcutaneously on an outpatient basis, often is used. Warfarin, an oral anticoagulation drug, may be used for persons with a long-term risk for development of thromboemboli.

Pulmonary Hypertension

The pulmonary circulation is normally a low-pressure system designed to accommodate varying amounts of blood delivered from the right heart. The main pulmonary artery and major branches are relatively thin-walled, compliant vessels. The distal pulmonary arterioles also are thin walled and have the capacity to dilate, collapse, or constrict depending on the presence of vasoactive substances released from the endothelial cells of the vessel, neurohumoral influences, flow velocity, oxygen tension, and alveolar ventilation.

Pulmonary hypertension is a disorder characterized by an abnormal elevation of pressure within the pulmonary circulation, namely, the pulmonary arterial system. Once present, pulmonary hypertension is self-perpetuating. It introduces secondary structural abnormalities of pulmonary vessels including smooth muscle hypertrophy and proliferation of the vessel intima. Although pulmonary hypertension can develop as a primary disorder, most cases develop secondary to other conditions.[57,58]

Secondary Pulmonary Hypertension

Secondary pulmonary hypertension refers to an increase in pulmonary pressures associated with other disease conditions, usually cardiac or pulmonary.[57,58] Secondary pulmonary hypertension may develop at any age. Secondary causes, or mechanisms, of pulmonary hypertension can be divided into four major categories: (1) elevation of pulmonary venous pressure, (2) increased pulmonary blood flow, (3) pulmonary vascular obstruction, and (4) hypoxemia. Often more than one factor, such as COPD, heart failure, and sleep apnea, contributes to the elevation in pulmonary pressures.

Elevation of pulmonary venous pressure is common in conditions such as mitral valve disorders or left ventricular diastolic dysfunction. In each of these alterations, the elevated left atrial pressure is transmitted to the pulmonary circulation. Continued increases in left atrial pressure can lead to medial hypertrophy and intimal thickening of the small pulmonary arteries, causing sustained hypertension.

Increased pulmonary blood flow results from increased flow through left-to-right shunts in congenital heart diseases such as atrial or ventricular septal defects and patent ductus arteriosus. If the high-flow state is allowed to continue, morphologic changes occur in the pulmonary vessels, leading to sustained pulmonary hypertension. The pulmonary vascular changes that occur with congenital heart disorders are discussed in Chapter 19.

Another cause of secondary pulmonary hypertension is obstruction of pulmonary blood flow due to pulmonary thromboemboli. Persons who are promptly treated for acute pulmonary thromboembolism with anticoagulants rarely develop pulmonary hypertension. However, in some persons chronic obstruction of the pulmonary vascular bed develops because of impaired resolution of the thromboemboli.

Continued exposure of the pulmonary vessels to hypoxemia is a common cause of pulmonary hypertension. Unlike blood vessels in the systemic circulation, most of which dilate in response to hypoxemia and hypercapnia, the pulmonary vessels constrict. The stimuli for constriction are thought to originate in the air spaces near the smaller branches of the pulmonary arteries. In regions of the lung that are poorly ventilated, the

response is adaptive in that it diverts blood flow away from the poorly ventilated areas to those areas that are more adequately ventilated. This effect, however, becomes less beneficial as more and more areas of the lung become poorly ventilated. Pulmonary hypertension is a common problem resulting from hypoxemia that develops in persons with advanced COPD or interstitial lung disease. It also may develop at high altitudes in persons with normal lungs. Persons who experience marked hypoxemia during sleep (such as those with sleep apnea) often experience marked elevations in pulmonary arterial pressure.

Clinical Features. Secondary pulmonary hypertension is difficult to recognize in its early stages, when the signs and symptoms are primarily those of the underlying disease. Pulmonary hypertension may cause, or contribute to, dyspnea, present initially with exertion and later at rest. Fatigue and syncope on exertion also occur, presumably the result of reduced cardiac output and related to elevated pulmonary artery pressures.

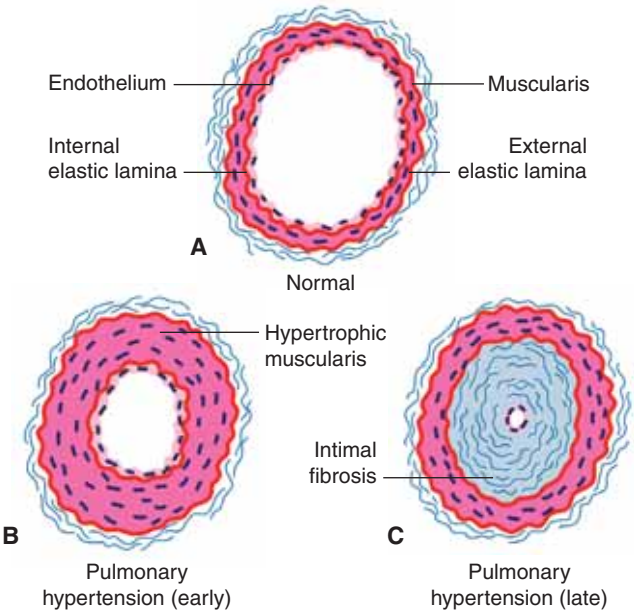
Diagnosis is based on radiographic findings and echocardiography. Doppler ultrasonography is a reliable noninvasive method for estimating pulmonary artery systolic pressure. Treatment measures are directed toward the underlying disorder. Vasodilator therapy may be indicated for some persons.

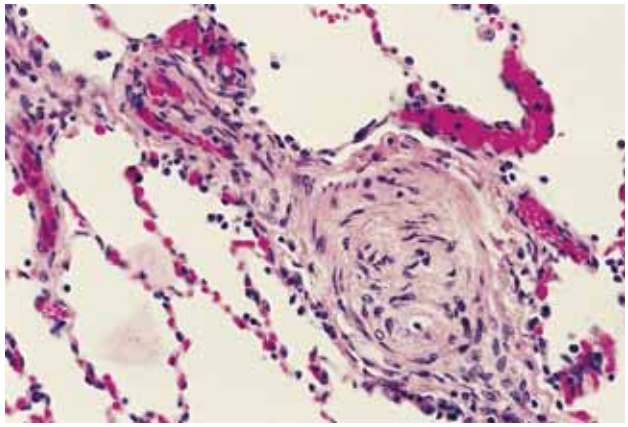
Primary Pulmonary Arterial Hypertension

Primary pulmonary arterial hypertension (PAH) is persistent elevation in pulmonary artery pressure that occurs in the absence of identified cardiopulmonary or other secondary causes of pulmonary hypertension.[59,60] It is a rare and debilitating disorder characterized by abnormal proliferation and contraction of vascular smooth muscle, coagulation abnormalities, and marked intimal fibrosis leading to obliteration or obstruction of the pulmonary arteries and arterioles (Fig. 23-14). The resulting increase in pulmonary artery pressure results in progressive right heart failure, low cardiac output, and death if left untreated.

A familial form of PAH appears to be inherited as an autosomal dominant trait with a variable but low penetrance, with some individuals inheriting the trait without exhibiting the disease. Other conditions associated with PAH include drugs and toxins, human immunodeficiency virus (HIV) infection, portal hypertension, and persistent pulmonary hypertension in the newborn.[57,59,60] A causal relationship has been established between several appetite suppressant drugs, including fenfluramine, and the development of PAH. Although the drug has been removed from the world market, there are still persons who were exposed to the drug before that time. The mechanism by which HIV infection produces PAH remains unknown, but treatment of HIV infection does not appear to affect the severity or natural history of the underlying pulmonary hypertension.

Although the specific mechanisms responsible for the vascular changes that occur in PAH remain unknown, a number of mechanisms have been proposed. These include diminished levels of nitric oxide and prostacyclin and increased levels of several growth factors, including endothelin, vascular endothelial growth factor, and platelet-derived growth factor. Nitric oxide, previously known as the *endothelium relaxing factor*, is a potent pulmonary vasodilator that is produced locally in the lung and has profound effects on smooth muscle relaxation and proliferation. Endothelin-1 is a peptide produced by the vascular endothelium that has potent vasoconstrictor and paracrine effects on vascular smooth muscle. The endothelium also produces prostacyclin





D

FIGURE 23-14. **(A)** Normal pulmonary artery. **(B)** Mild pulmonary hypertension with thickening of the media of the pulmonary artery. **(C)** Pulmonary artery with extensive intimal fibrosis and thickening of vascular smooth muscle. **(D)** Micrograph of a small pulmonary artery that is virtually occluded by concentrically thickened intimal fibrosis and thickening of the media due to pulmonary arterial hypertension. (From Bearsley M.B., Travis W.D., Rubin E. [2008]. The respiratory system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 537]. Philadelphia: Lippincott Williams & Wilkins.)

(PGI2), an inhibitor of platelet aggregation and a potent vasodilator. Results of studies relating these mechanisms to the structure and function of the pulmonary arterial circulation have already been translated into targeted therapies for PAH, with the probability that more will be investigated in the future.

Clinical Features. Symptoms of PAH typically progress from shortness of breath and decreasing exercise tolerance to right heart failure, with marked peripheral edema and functional limitations. Other common symptoms include fatigue, angina, and syncope (fainting) or near-syncope. The diagnosis of primary pulmonary hypertension is based on an elevated pulmonary artery pressure and an absence of disorders that cause secondary pulmonary hypertension.

Treatment consists of measures to improve right heart function as a means of reducing fatigue and peripheral edema. Supplemental oxygen may be used to increase exercise tolerance. The calcium channel blockers (nifedipine, diltiazem) may be effective early in the course of the disease but offer little in advanced stages. More advanced disease has been managed with epoprostenol, a prostacyclin that has potent pulmonary vasodilator effects.[58,60] Because of its short half-life (3 to 5 minutes), the drug must be administered by continuous infusion through an indwelling catheter with an automatic ambulatory pump. Properties of the drug other than its vasodilating effects include inhibition of platelet aggregation and beneficial vascular remodeling effects. This agent often improves symptoms, sometimes dramatically, in persons who have not responded to other vasodilators. Bosentan, an oral endothelin antagonist, has proved to be effective in treating moderate to severe primary pulmonary hypertension and may become the treatment of choice for all stages of the disease.[61] Sildenafil (e.g., Viagra), a highly selective phosphodiesterase-5 inhibitor, which acts in a manner similar to nitric oxide to produce vasodilation, has recently been approved for treatment of pulmonary hypertension. Lung transplantation may be an alternative for persons who do not respond to other forms of treatment.

Cor Pulmonale

The term *cor pulmonale* refers to right heart failure resulting from primary lung disease or pulmonary hypertension. The increased pressures and work result in hypertrophy and eventual failure of the right ventricle. The manifestations of cor pulmonale include the signs and symptoms of the primary lung disease and the signs of right-sided heart failure (see Chapter 20). Signs of right-sided heart failure include venous congestion, peripheral edema, shortness of breath, and a productive cough, which becomes worse during periods of heart failure. Plethora (i.e., redness), cyanosis, and warm, moist skin may result from the compensatory polycythemia and desaturation of arterial blood that accompany chronic lung disease. Drowsiness and altered consciousness may occur as the result of carbon dioxide retention. Management of cor pulmonale focuses on the treatment of the lung disease and heart failure. Low-flow oxygen therapy may be used to reduce the pulmonary hypertension and polycythemia associated with severe hypoxemia caused by chronic lung disease.

In summary, pulmonary vascular disorders include pulmonary embolism and pulmonary hypertension. Pulmonary embolism develops when a blood-borne substance lodges in a branch of the pulmonary artery and obstructs blood flow. The embolus can consist of a thrombus, air, fat, or amniotic fluid. The most common form is thromboemboli arising from the deep venous channels of the lower extremities. Pulmonary hypertension is the elevation of pulmonary arterial pressure. It can be divided into two types: (1) primary pulmonary arterial hypertension, which has its origin in the pulmonary arteries and includes both primary (idiopathic or familial) pulmonary hypertension and pulmonary hypertension associated with disease entities that produce a similar pathologic process, and (2) pulmonary hypertension that develops secondary to lung disease and hypoxemia (e.g., chronic lung diseases, sleep-disordered breathing, or chronic exposure to high altitude), conditions that elevate pulmonary venous pressures (left ventricular dysfunction, mitral valve disease), or chronic obstruction of the pulmonary vasculature due to thromboemboli. *Cor pulmonale* describes right heart failure caused by primary pulmonary disease and long-standing pulmonary hypertension.

Acute Respiratory Disorders

The function of the respiratory system is to add oxygen to the blood and remove carbon dioxide. Disruptions in this function occur with acute lung injury/acute respiratory distress syndrome and acute respiratory failure. Although the mechanisms that disrupt gas exchange may vary, both conditions represent a life-threatening situation with high risks of morbidity and mortality.

Acute Lung Injury/Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a clinical syndrome that is characterized by severe dyspnea of rapid onset, hypoxemia, and pulmonary infiltrates. Acute lung injury (ALI) is a less severe form of the disorder, but has the potential for evolving into ARDS. The two conditions are differentiated by the extent of hypoxemia as determined by the ratio of partial pressure of arterial blood (PO_2) to fraction of inspired oxygen (FIO_2).[62,63] The incidence of ALI/ARDS is not consistently reported, although it is estimated to occur in approximately 150,000 to 200,000 persons each year in North America. Despite the most sophisticated interventions, the mortality rate varies from 35% to

CHART 23-2 Conditions in Which ARDS Can Develop*

Aspiration
Near-drowning
Aspiration of gastric contents

Drugs, Toxins, Therapeutic Agents
Free-base cocaine smoking
Heroin
Inhaled gases (e.g., smoke, ammonia)
Breathing high concentrations of oxygen
Radiation

Infections
Septicemia

Trauma and Shock
Burns
Fat embolism
Chest trauma

Disseminated Intravascular Coagulation

Multiple Blood Transfusions

*This list is not intended to be inclusive.

60% and morbidity is extensive, including physical, cognitive, and emotional sequelae.[18,64]

Both ARDS and ALI can result from a number of conditions, including aspiration of gastric contents, major trauma (with or without fat emboli), sepsis secondary to pulmonary or nonpulmonary infections, acute pancreatitis, hematologic disorders, metabolic events, and reactions to drugs and toxins (Chart 23-2). Chronic alcohol abuse increases both the risk for and severity of ALI/ARDS.[65]

In the United States, there is a risk of transfusion-related acute lung injury,[66] which is rare in Europe, Canada, Australia, and the United Kingdom owing to their practice of washing of packed red blood cells. It is hypothesized that levels of mediators and cytokines are higher in unwashed red blood cells.

Etiology and Pathogenesis

Although a number of conditions may lead to ALI/ARDS, they all produce similar pathologic lung changes that include diffuse epithelial cell injury with increased permeability of the alveolar–capillary membrane (Fig. 23-15). The increased permeability permits fluid, plasma proteins, and blood cells to move out of the vascular compartment into the interstitium and alveoli of the lung.[67,68] Diffuse alveolar cell damage leads to accumulation of fluid, surfactant inactivation, and formation of a hyaline membrane that is impervious to gas exchange. As the disease progresses, the work of breathing becomes greatly increased as the lung stiffens and becomes more difficult to inflate. There is increased intrapulmonary shunting of blood, impaired gas exchange, and hypoxemia despite high supplemental oxygen therapy. Gas exchange is further compromised by alveolar collapse resulting from abnormalities in surfactant production. When injury to the alveolar epithelium is severe, disorganized epithelial repair may lead to fibrosis.

The pathogenesis of ALI/ARDS is unclear, although both local and systemic inflammatory responses occur. Neutrophils accumulate early in the course of the disorder and are considered to play a role in the pathogenesis of ALI/ARDS.[69] Activated neutrophils synthesize and release a variety of products, including proteolytic enzymes, toxic oxygen species, and phospholipid products that increase the inflammatory response and cause further injury to the capillary endothelium and alveolar epithelium.

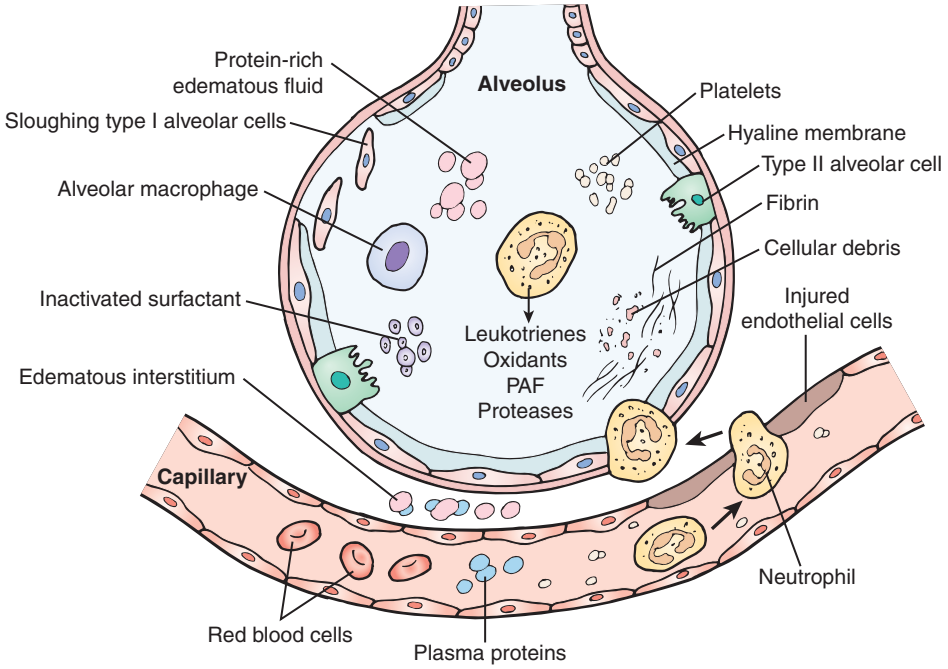


FIGURE 23-15. Mechanism of lung changes in acute respiratory distress syndrome. Injury and increased permeability of the alveolar capillary membrane allow fluid, protein, cellular debris, platelets, and blood cells to move out of the vascular compartment and enter the interstitium and alveoli. Activated neutrophils release a variety of products that damage the alveolar cells and lead to edema, surfactant inactivation, and formation of a hyaline membrane. PAF, platelet activating factor.

Clinical Features

Clinically, ALI/ARDS is marked by a rapid onset, usually within 12 to 18 hours of the initiating event, of respiratory distress, an increase in respiratory rate, and signs of respiratory failure. Chest radiography shows diffuse bilateral infiltrates of the lung tissue in the absence of cardiac dysfunction. Marked hypoxemia occurs that is refractory to treatment with supplemental oxygen therapy. Many persons with ARDS have a systemic response that results in multiple organ failure, particularly of the renal, gastrointestinal, cardiovascular, and central nervous systems.

Treatment. The treatment goals in ARDS are to supply oxygen to vital organs and provide supportive care until the condition causing the pathologic process has been reversed and the lungs have had a chance to heal. Assisted ventilation using high concentrations of oxygen may be required to correct the hypoxemia. Positive end-expiratory pressure breathing, which increases the pressure in the airways during expiration, may be used to assist in reinflating the collapsed areas of the lung and to improve the matching of ventilation and perfusion.

Acute Respiratory Failure

Respiratory failure can be viewed as a failure in gas exchange due to either pump (heart) or lung failure, or both. It is not a specific disease, but can occur in the course of a number of conditions that impair ventilation, compromise the matching of ventilation and perfusion, or impair gas diffusion. Acute respiratory failure may occur in previously healthy persons as the result of acute disease or trauma involving the respiratory system, or it may develop in the course of a chronic neuromuscular or lung disease.

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions—oxygenation of mixed venous blood and elimination of carbon dioxide. The function of the respiratory system can be said to consist of two aspects: (1) gas exchange (movement of gases across the alveolar–capillary membrane) and (2) ventilation (movement of gases into and out of the alveoli due to the action of the respiratory muscles, the respiratory center in the central nervous system [CNS], and the pathways that connect the centers in the CNS with the respiratory muscles). Thus, respiratory failure is commonly divided into two types: (1) hypoxemic respiratory failure due to failure of the gas exchange function of the lung and (2) hypercapnic/hypoxemic respiratory failure due to ventilatory failure.[3,70,71] The classification should not be viewed as rigid since lung disorders that cause impaired gas exchange can be complicated by ventilatory failure and ventilatory failure can be accompanied by lung disorders that impair gas diffusion. Causes of the two types of respiratory failure are summarized in Chart 23-3.

CHART 23-3 Causes of Respiratory Failure*

Hypoxemic Respiratory Failure
- Chronic obstructive pulmonary disease
- Restrictive lung disease
- Severe pneumonia
- Atelectasis
- Impaired diffusion
  - Pulmonary edema
  - Acute lung injury/acute respiratory distress syndrome

Hypercapnic/Hypoxemic Respiratory Failure
- Upper airway obstruction
  - Infection (e.g., epiglottitis)
  - Laryngospasm
  - Tumors
- Weakness or paralysis of respiratory muscles
  - Brain injury
  - Drug overdose
  - Guillain-Barré syndrome
  - Muscular dystrophy
  - Spinal cord injury
- Chest wall injury

*This list is not intended to be inclusive.

Hypoxemic Respiratory Failure

In persons with hypoxemic respiratory failure, two major pathophysiologic factors contribute to the lowering of arterial PO_2: ventilation–perfusion mismatching and impaired diffusion.

Mismatching of Ventilation and Perfusion. The mismatching of ventilation and perfusion occurs when areas of the lung are ventilated but not perfused or when areas are perfused but not ventilated. Usually the hypoxemia seen in situations of ventilation–perfusion mismatching is more severe in relation to hypercapnia than that seen in hypoventilation. Severe mismatching of ventilation and perfusion often is seen in persons with advanced COPD. These disorders contribute to the retention of carbon dioxide by reducing the effective alveolar ventilation, even when total ventilation is maintained. This occurs because a region of the lung is not perfused and gas exchange cannot take place or because an area of the lung is not being ventilated. Maintaining a high ventilation rate effectively prevents hypercapnia but also increases the work of breathing.

The hypoxemia associated with ventilation–perfusion disorders often is exaggerated by conditions such as hypoventilation and decreased cardiac output. For example, sedation can cause hypoventilation in persons with severe COPD, resulting in further impairment of ventilation. Likewise, a decrease in cardiac output because of myocardial infarction can exaggerate the ventilation–perfusion impairment in a person with mild pulmonary edema or COPD.

The beneficial effect of oxygen administration on PO_2 levels in ventilation–perfusion disorders depends on the degree of mismatching that is present. Because oxygen administration increases the diffusion gradient in ventilated portions of the lung, it usually is effective in raising

arterial PO_2 levels. However, high-flow oxygen may decrease the respiratory drive and produce an increase in PCO_2.

Impaired Diffusion. Impaired diffusion describes a condition in which gas exchange between the alveolar air and pulmonary blood is impeded because of an increase in the distance for diffusion or a decrease in the permeability or surface area of the respiratory membranes to the movement of gases. It most commonly occurs in conditions such as interstitial lung disease, ALI/ARDS, pulmonary edema, and pneumonia.

Conditions that impair diffusion may produce severe hypoxemia but no hypercapnia because of the increase in ventilation and greater diffusion rate of carbon dioxide. Hypoxemia resulting from impaired diffusion can be partially or completely corrected by the administration of high concentrations of oxygen. In this case, the high concentration of oxygen serves to overcome the decrease in diffusion by establishing a larger alveolar-to-capillary diffusion gradient.

Hypercapnic/Hypoxemic Respiratory Failure

In the hypercapnic form of respiratory failure, patients are unable to maintain a level of alveolar ventilation sufficient to eliminate CO_2 and keep arterial O_2 levels within normal range. Because ventilation is determined by a sequence of events ranging from the generation of impulses in the CNS to movement of air through the conducting airways, there are several stages at which problems can adversely affect the total minute ventilation.

Hypoventilation or ventilatory failure occurs when the volume of "fresh" air moving into and out of the lung is significantly reduced. It is commonly caused by conditions outside the lung such as depression of the respiratory center (e.g., drug overdose, brain injury), diseases of the nerves supplying the respiratory muscles (e.g., Guillain-Barré syndrome, spinal cord injury), disorders of the respiratory muscles (e.g., muscular dystrophy), exacerbation of chronic lung disease (e.g., COPD), or thoracic cage disorders (e.g., severe scoliosis or crushed chest).

Hypoventilation has two important effects on arterial blood gases. First, it almost always causes an increase in PCO_2. The rise in PCO_2 is directly related to the level of ventilation; reducing the ventilation by one half causes a doubling of the PCO_2. Thus, the PCO_2 level is a good diagnostic measure for hypoventilation. Second, it may cause hypoxemia, although the hypoxemia that is caused by hypoventilation can be readily abolished by the administration of supplemental oxygen.

Clinical Features

Acute respiratory failure is usually manifested by varying degrees of hypoxemia and hypercapnia. There is no absolute definition of the levels of PO_2 and PCO_2 that indicate respiratory failure. Respiratory failure is conventionally defined by an arterial PO_2 of less than 60 mm Hg, an arterial PCO_2 of more than 45 mm Hg, or both when prior blood values have been normal.[71] It is important to emphasize that these cut-off values are not rigid, but simply serve as a general guide in combination with history and physical assessment information. The signs and symptoms of acute respiratory failure are those of the underlying disease combined with signs of hypoxemia and hypercapnia/hypoxemia. Respiratory acidosis is usually present because the retention of CO_2 results in increased production of acids.

Hypoxemia is accompanied by increased respiratory drive and increased sympathetic tone. Potential signs of hypoxemia include cyanosis, restlessness, confusion, anxiety, delirium, fatigue, tachypnea, hypertension, cardiac arrhythmias, and tremor. The initial cardiovascular effects are tachycardia with increased cardiac output and increased blood pressure. Serious arrhythmias may be triggered. The pulmonary vasculature constricts in response to low alveolar PO_2. If severe, the pulmonary vasoconstriction may result in acute right ventricular failure with manifestations such as jugular vein distention and dependent edema. Profound acute hypoxemia can cause convulsions, retinal hemorrhages, and permanent brain damage. Hypotension and bradycardia often are preterminal events in persons with hypoxemic respiratory failure, indicating the failure of compensatory mechanisms.

Many of the adverse consequences of hypercapnia are the result of respiratory acidosis. Direct effects of acidosis include depression of cardiac contractility, decreased respiratory muscle contractility, and arterial vasodilation (see Chapter 8). Raised levels of PCO_2 greatly increase cerebral blood flow, which may result in headache, increased cerebrospinal fluid pressure, and sometimes papilledema (see Chapter 38, Fig. 38-9). The headache is due to dilation of the cerebral vessels. Additional indicators of hypercapnia are warm and flushed skin and hyperemic conjunctivae. Hypercapnia has nervous system effects similar to those of an anesthetic—hence the term *carbon dioxide narcosis*. There is progressive somnolence, disorientation, and, if the condition is untreated, coma. Mild to moderate increases in blood pressure are common. Air hunger and rapid breathing occur when alveolar PCO_2 levels rise to approximately 60 to 75 mm Hg; as PCO_2 levels reach 80 to 100 mm Hg, the person becomes lethargic and sometimes semicomatose.

Treatment. The treatment of respiratory failure focuses on correcting the problem causing impaired gas exchange when possible and on relieving the hypoxemia and hypercapnia. A number of treatment modalities are available, including the establishment of an airway, use of bronchodilating drugs, and antibiotics for respiratory infections. Controlled oxygen therapy and mechanical ventilation are used in treating blood gas abnormalities associated with respiratory failure.

When alveolar ventilation is inadequate to maintain PO_2 or PCO_2 levels because of respiratory or neurologic failure, mechanical ventilation may be lifesaving. Usually a nasotracheal, orotracheal, or tracheotomy tube is inserted into the trachea to provide the patient with the airway needed for mechanical ventilation. There has been recent interest in noninvasive forms of mechanical ventilation that use a face mask to deliver positive-pressure ventilation.[57]

In summary, the hallmark of acute lung injury and acute respiratory distress syndrome is a pronounced inflammatory response that affects the lung and may result in systemic organ failure. The acute inflammatory response results in damage and dysfunction of the alveolar–capillary membrane of the lung. Classically, there is interstitial edema of lung tissue, an increase in surface tension caused by inactivation of surfactant, collapse of alveolar structures, a stiff and noncompliant lung that is difficult to inflate, and impaired diffusion of the respiratory gases with severe hypoxia that is resistant to oxygen therapy.

Acute respiratory failure is a condition in which the lungs fail to oxygenate the blood adequately (hypoxemic respiratory failure) or prevent undue retention of carbon dioxide (hypercapnic/hypoxemic respiratory failure). The causes of respiratory failure are many. It may arise acutely in persons with previously healthy lungs, or it may be superimposed on chronic lung disease. Treatment of acute respiratory failure is directed toward treatment of the underlying disease, maintenance of adequate gas exchange and tissue oxygenation, and general supportive care. When alveolar ventilation is inadequate to maintain PO_2 or PCO_2 levels because of impaired respiratory function or neurologic failure, mechanical ventilation may be necessary.

REVIEW EXERCISES

1. A 30-year-old man is brought to the emergency department with a knife wound to the chest. On visual inspection, asymmetry of chest movement during inspiration, displacement of the trachea, and absence of breath sounds on the side of the wound are noted. His neck veins are distended, and his pulse is rapid and weak. A rapid diagnosis of tension pneumothorax is made.

- **A.** Explain the observed respiratory and cardiovascular function in terms of the impaired lung expansion and the air that has entered the chest as a result of the injury.
- **B.** What type of emergent treatment is necessary to save this man's life?

2. A 10-year-old boy who is having an acute asthmatic attack is brought to the emergency department by his parents. The boy is observed to be sitting up and struggling to breathe. His breathing is accompanied by use of the accessory muscles, a weak cough, and audible wheezing sounds. His pulse is rapid and weak and both heart and breath sounds are distant on auscultation. His parents relate that his asthma began to worsen after he developed a "cold," and now he doesn't even get relief from his "albuterol" inhaler.

- **A.** Explain the changes in physiologic function underlying this boy's signs and symptoms.
- **B.** What is the most probable reason for the progression of this boy's asthma in terms of the early- and late-phase responses?
- **C.** The boy is treated with a systemic corticosteroid and inhaled anticholinergic and β_2-adrenergic agonist and then transferred to the intensive care unit. Explain the action of each of these medications in terms of relieving this boy's symptoms.

3. A 62-year-old man with an 8-year history of chronic bronchitis reports to his health care provider with complaints of increasing shortness of breath, ankle swelling, and a feeling of fullness in his upper abdomen. The expiratory phase of his respirations is prolonged and expiratory wheezes and crackles are heard on auscultation. His blood pressure is 160/90 mm Hg, his red blood cell count is 6.0×10^6 μL (normal 4.2 to 5.4×10^6 μL), his hematocrit is 65% (normal male value 40% to 50%), his arterial PO_2 is 55 mm Hg, and his O_2 saturation, which is 85% while he is resting, drops to 55% during walking exercise.

- **A.** Explain the physiologic mechanisms responsible for his edema, hypertension, and elevated red blood cell count.
- **B.** His arterial PO_2 and O_2 saturation indicate that he is a candidate for continuous low-flow oxygen. Explain the benefits of this treatment in terms of his activity tolerance, blood pressure, and red blood cell count.
- **C.** Explain why the oxygen flow rate for persons with COPD is normally titrated to maintain the arterial PO_2 between 60 and 65 mm Hg.

4. An 18-year-old woman is admitted to the emergency department with a suspected drug overdose. Her respiratory rate is slow (4 to 6 breaths/minute) and shallow. Arterial blood gases reveal a PCO_2 of 80 mm Hg and a PO_2 of 60 mm Hg.

- **A.** What is the cause of this woman's high PCO_2 and low PO_2?
- **B.** Hypoventilation almost always causes an increase in PCO_2. Explain.
- **C.** Even though her PO_2 increases to 90 mm Hg with institution of oxygen therapy, her PCO_2 remains elevated. Explain.

REFERENCES

1. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 491–501, 524–533, 867). Philadelphia: W.B. Saunders.
2. Berne R.M., Levy M.N., Koeppen B.M. (2004). *Physiology* (5th ed., pp. 480–510). St. Louis: Elsevier Mosby.
3. West J.B. (2008). *Pulmonary pathophysiology: The essentials* (8th ed., p. 75). Philadelphia: Lippincott Williams & Wilkins.

4. Grap M.J. (2002). Pulse oximetry. *Critical Care Nurse* 22(3), 69–74.
5. Hudak C.M., Gallo B.M., Morton P.G. (1998). *Critical care nursing* (7th ed., pp. 449–455, 476–489). Philadelphia: Lippincott Williams & Wilkins.
6. Weinberger S.E., Schwartzstein R.M., Weiss J.W. (1989). Hypercapnia. *New England Journal of Medicine* 321, 1223–1230.
7. Kass S.M., Williams P.M., Beamy B.Y. (2007). Pleurisy. *American Family Physician* 75, 1357–1364.
8. Yataco J.C., Dweik R.A. (2005). Pleural effusions: Evaluation and management. *Cleveland Clinic Journal* 72, 854–871.
9. Light R.W. (2005). Disorders of the pleura, mediastinum, and diaphragm. In Kasper A.S., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1565–1569). New York: McGraw-Hill.
10. Romero S. (2000). Nontraumatic chylothorax. *Current Opinion in Pulmonary Medicine* 6, 287–291.
11. Sahn S.A., Heffner J.E. (2000). Spontaneous pneumothorax. *New England Journal of Medicine* 342, 868–874.
12. Baumann M.H. (2006). Management of spontaneous pneumothorax. *Clinics in Chest Medicine* 27, 369–381.
13. Baumann M.H., Nopeen M. (2004). Invited review: Pneumothorax. *Respirology* 9, 157–164.
14. Gotway M.B., Marder S.R., Hanks D.K., et al. (2002). Thoracic complications of illicit drug use: An organ system approach. *Radiographics* 22, S119–S135.
15. Chesnutt M.S., Murray J.A., Prendergast T.J. (2009). Pulmonary disorders. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 210–235). New York: McGraw-Hill Medical.
16. American Lung Association. (2009). *Asthma in adults fact sheet*. [Online] Available: http://www.lungusa.org. Accessed April 9, 2008.
17. National Asthma Education and Prevention Program. (2007). *Expert Panel report 3: Guidelines for the diagnosis and management of asthma*. NIH publication no. 07-4051. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute.
18. Husain A.N. (2010). The lung. In Kumar R.S., Abbas A.K., Fausto N., Aster J.C. *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 677–737). Philadelphia: Saunders Elsevier.
19. Elias J.A., Lee C.G., Zheng T., et al. (2003). New insights into the pathogenesis of asthma. *Journal of Clinical Investigation* 111, 291–297.
20. Fireman P. (2003). Understanding asthma pathophysiology. *Allergy and Asthma Proceedings* 24(2), 79–83.
21. Busse W.W., Lemanske R.F. (2001). Asthma. *New England Journal of Medicine* 344, 350–362.
22. Weiler J.M., Bonini S., Coifman R., et al. (2007). American Academy of Allergy, Asthma & Immunology Work Group report: Exercise-induced asthma. *Journal Allergy and Clinical Immunology* 119, 1349–1358.
23. Young S., LeSouef P.N., Geelhoed G.C., et al. (1991). The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *New England Journal of Medicine* 324, 1168–1173.
24. Bardana E.J. (2008). Occupational asthma. *Journal Allergy and Clinical Immunology* 121, S408–S411.
25. Stevenson D.D., Szczeklik F. (2006). Clinical and pathologic perspectives on aspirin sensitivity and asthma. *Journal Allergy and Clinical Immunology* 118, 773–786.
26. Tan K.S., McFarlane L.C., Lipworth B.J. (1997). Loss of normal cyclical B2 adrenoreceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. *Thorax* 52, 608–611.
27. Haxhiu M.A., Rust C.F., Brooks C., et al. (2006). CNS determinants of sleep-related worsening of airway functions: Implications for nocturnal asthma. *Respiratory Physiology and Neurobiology* 151, 1–30.
28. Sutherland E.R. (2005). Nocturnal asthma. *Journal of Allergy and Clinical Immunology* 116, 1179–1186.
29. Fanta C.H. (2009). Asthma. *New England Journal of Medicine* 360(10), 1002–1014.
30. Wenzel S. (2006). Physiologic and pathologic abnormalities in severe asthma. *Clinics in Chest Medicine* 27, 29–40.
31. Holgate S.T., Polosa R. (2006). The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 368, 780–793.
32. Magadle R., Berar-Yanay N., Weiner P. (2002). The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest* 121, 329–333.
33. Centers for Disease Control. *State of childhood asthma United States: 1980-2005*. [Online] Available: http://www.cdc.gov/nchs/pressroom/06facts/asthma1980-2005.htm. Accessed April 21, 2009.
34. Lui A.H., Covar R.A., Spahn J.D., et al. (2007). Childhood asthma. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (16th ed., pp. 953–970). Philadelphia: Saunders Elsevier.
35. Stewart L.J. (2008). Pediatric asthma. Primary care. *Clinics in Office Practice* 35, 25–40.
36. Courtney A.U., McCarter D.F., Pollart S.M. (2005). Childhood asthma: Treatment update. *American Family Physician* 71, 1959–1968.
37. Barnes P.J. (2000). Chronic obstructive pulmonary disease. *New England Journal of Medicine* 343, 269–280.
38. Calverley P.M.A., Walker P. (2003). Chronic obstructive pulmonary disease. *Lancet* 362, 1053–1061.
39. Rabe K.F. Hurd S., Anzuelo A., et al. (2007). Global strategy for diagnosis, management, and prevention of chronic obstructive lung disease: GOLD executive summary. *American Journal of Respiratory Critical Care Medicine* 176, 532–555.
40. MacNee W. (2007). The pathogenesis of chronic obstructive pulmonary disease. *Clinics in Chest Medicine* 28, 479–513.
41. Bearsley M.B., Travis W.D., Rubin E. (2008). The respiratory system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 510–518, 525–534, 536–545). Philadelphia: Lippincott Williams & Wilkins.
42. Reilly J.J., Silverman E.K., Shapiro S.D. (2005). Chronic obstructive pulmonary disease. In Kasper A.S., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1547–1554). New York: McGraw-Hill.
43. Barker A.F. (2002). Bronchiectasis. *New England Journal of Medicine* 346, 1383–1393.
44. Rowe S.M., Miller S., Sorscher E.J. (2005). Cystic fibrosis. *New England Journal of Medicine* 352, 1992–2001.
45. Strausbaugh S.D., Davis P.B. (2007). Cystic fibrosis: A review of epidemiology and pathobiology. *Clinics in Chest Medicine* 28, 279–288.
46. Boat T.F., Acton J.D. (2007). Cystic fibrosis. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1803–1817). Philadelphia: Saunders Elsevier.
47. Gibsen R.L., Burns J.L., Ramsey B.W. (2003). Pathophysiology and management of pulmonary infections in cystic fibrosis. *American Journal Respiratory Critical Care Medicine* 168, 918–951.
48. Gross F.H.Y. (2002). Overview of pulmonary fibrosis. *Chest* 122(6 Suppl), 334S–335S.
49. Ryu J.H., Daniels C.E., Hartman T., et al. (2007). Diagnosis of interstitial lung diseases. *Mayo Clinic Proceedings* 82(8), 976–986.
50. Gross T.J., Hunninghake G.W. (2001). Idiopathic pulmonary fibrosis. *New England Journal of Medicine* 345, 517–525.
51. Khalil N., O'Connor R.O. (2004). Idiopathic pulmonary fibrosis: Current understanding of the pathogenesis and status of treatment. *CMAJ* 171(2), 153–160.

52. Iannuzzi M.C., Rybicki B.A., Teirstein A.S. (2007). Sarcoidosis. *New England Journal of Medicine* 357(21), 2153–2165.
53. Mihailovic-Vucinic V., Jovanovic D. (2008). Pulmonary sarcoidosis. *Clinical Chest Medicine* 29, 459–473.
54. Sadosty A.T., Boie E.T., Stead L.G. (2003). Pulmonary embolism. *Emergency Medicine Clinics of North America* 21, 363–384.
55. Cardin T., Marinelli A. (2004). Pulmonary embolism. *Critical Care Nursing Quarterly* 27, 310–332.
56. Tapson V.F. (2008). Acute pulmonary embolism. *New England Journal Medicine* 358, 1037–1053.
57. McLaughlin V.V. (2004). Classification and epidemiology of pulmonary hypertension. *Cardiology Clinics* 22, 327–341.
58. Farber H.W., Lascalzo J. (2004). Pulmonary arterial hypertension. *New England Journal of Medicine* 351, 1655–1365.
59. Ghambra Z., Dweik R.A. (2003). Primary pulmonary hypertension: An overview of epidemiology and pathogenesis. *Cleveland Clinic Journal of Medicine* 70(Suppl 1), S2–S8.
60. Runo J.R., Loyd J.E. (2003). Primary pulmonary hypertension. *Lancet* 361, 1533–1544.
61. Rubin L.J., Badesch D.B. (2005). Evaluation and management of the patient with pulmonary arterial hypertension. *Annals Internal Medicine* 143, 282–292.
62. Avecillas J.F., Freire A.X., Arroliga A.C. (2006). Clinical epidemiology of acute lung injury and acute respiratory distress syndrome: Incidence, diagnosis, and outcomes. *Clinics in Chest Medicine* 27, 549–557.
63. Bernard G.R.A., Artigas K.L., Brigham J., et al. (Consensus Committee). (1994). The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *American Journal of Respiratory Critical Care Medicine* 149, 1807–1814.
64. Rubenfeld G.D., Caldwell E., Peabody E., et al. (2005). Incidence and outcomes of acute lung injury. *New England Journal of Medicine* 353, 1685–1693.
65. Moss M., Burnham E.L. (2003). Chronic alcohol abuse, acute respiratory distress syndrome, and multiple organ dysfunction. *Critical Care Medicine* 31, S207–S212.
66. Moore S.B. (2006). Transfusion-related acute lung injury (TRALI): Clinical presentation, treatment, and prognosis. *Critical Care Medicine* 34, S114–S117.
67. Mendez J.L., Hubmar R.D. (2005). New insights into the pathology of acute respiratory failure. *Current Opinion in Critical Care* 11, 29–36.
68. Abraham E. (2003). Neutrophils and acute lung injury. *Critical Care Medicine* 31, S195–S199.
69. Acute Respiratory Distress Syndrome Network. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and acute respiratory distress syndrome. *New England Journal of Medicine* 342, 1301–1308.
70. Roussos C., Koutsoukou A. (2003). Respiratory failure. *European Respiratory Journal* 22(Suppl 47), 3s–14s.
71. Markou N.K., Myrianthefs P.M., Batlopoulos G.J. (2004). Respiratory failure: An overview. *Critical Care Nursing Quarterly* 27, 353–379.

UNIT 7

Kidney and Urinary Tract Function

Kidney Structure and Function
- *Gross Structure and Location*
- *The Nephron*
  - The Glomerulus
  - Tubular Components of the Nephron
- *Urine Formation*
  - Glomerular Filtration
  - Tubular Reabsorption and Secretion
  - Regulation of Urine Concentration
- *Regulation of Renal Blood Flow*
  - Neural and Humoral Control Mechanisms
  - Autoregulatory Mechanisms
  - Effect of Increased Protein and Glucose Load
- *Elimination Functions of the Kidney*
  - Renal Clearance
  - Regulation of Sodium and Potassium Elimination
  - Regulation of pH
  - pH-Dependent Elimination of Organic Ions
  - Uric Acid Elimination
  - Urea Elimination
- *Drug Elimination*
- *Endocrine Functions of the Kidney*
  - The Renin-Angiotensin-Aldosterone Mechanism
  - Erythropoietin
  - Vitamin D

Tests of Renal Function
- *Urine Tests*
- *Glomerular Filtration Rate*
- *Blood Tests*
  - Serum Creatinine
  - Blood Urea Nitrogen

Chapter 24

Structure and Function of the Kidney

It is no exaggeration to say that the composition of the blood is determined not so much by what the mouth takes in as by what the kidneys keep.
—Homer Smith, *From Fish to Philosopher*

The kidneys are remarkable organs. Each is smaller than a person's fist, but in a single day the two organs process approximately 1700 L of blood and combine their waste products into approximately 1.5 L of urine. As part of their function, the kidneys filter physiologically essential substances, such as sodium (Na^+) and potassium (K^+) ions, from the blood and selectively reabsorb those substances that are needed to maintain the normal composition of internal body fluids. Substances that are not needed or are in excess of those needed for this purpose pass into the urine. In regulating the volume and composition of body fluids, the kidneys also perform endocrine functions. The renin-angiotensin mechanism participates in the regulation of blood pressure and the maintenance of circulating blood volume, and erythropoietin stimulates red blood cell production.

Kidney Structure and Function

Gross Structure and Location

The kidneys are paired, bean-shaped organs that lie outside the peritoneal cavity in the back of the upper abdomen, one on each side of the vertebral column at the level of the 12th thoracic to 3rd lumbar vertebrae (Fig. 24-1). The right kidney normally is situated lower

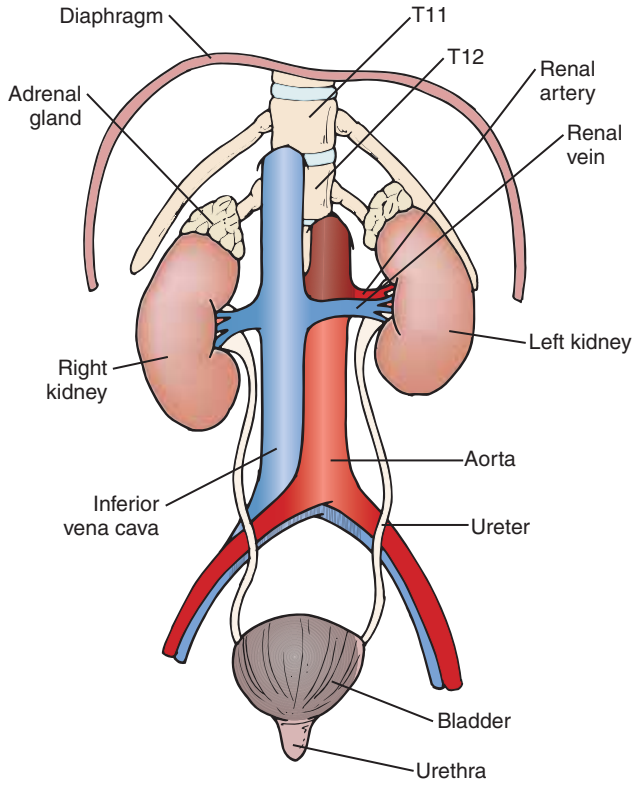


FIGURE 24-1. Kidneys, ureters, and bladder. (The right kidney is usually lower than the left.)

than the left, presumably because of the position of the liver. In the adult, each kidney is approximately 10 to 12 cm long, 5 to 6 cm wide, and 2.5 cm deep and weighs approximately 113 to 170 g. The medial border of the kidney is indented by a deep fissure called the *hilus*. It is here that blood vessels and nerves enter and leave the kidney. The ureters, which connect the kidneys with the bladder, also enter the kidney at the hilus.

The kidney is a multilobular structure, composed of up to 18 lobes. Each lobe is composed of nephrons, which are the functional units of the kidney. Each nephron has a glomerulus that filters the blood and a system of tubular structures that selectively reabsorb material from the filtrate back into the blood and secrete materials from the blood into the filtrate as urine is being formed.

On longitudinal section, a kidney can be divided into an outer cortex and an inner medulla (Fig. 24-2). The cortex, which is reddish-brown, contains the glomeruli and convoluted tubules of the nephron and blood vessels. The medulla consists of light-colored, cone-shaped masses—the renal pyramids—that are divided by the columns of the cortex (i.e., columns of Bertin) that extend into the medulla. Each pyramid, topped by a region of cortex, forms a lobe of the kidney. The apices of the pyramids form the papillae (i.e., 8 to 18 per kidney, corresponding to the number of lobes), which are perforated by the openings of the collecting ducts. The renal pelvis is a wide, funnel-shaped structure at the upper end of the ureter. It is made up of the calyces or cuplike structures that drain the upper and lower halves of the kidney.

The kidney is sheathed in a fibrous external capsule and surrounded by a mass of fatty connective tissue, especially at its ends and borders. The adipose tissue protects the kidney from mechanical blows and assists, together with the attached blood vessels and fascia, in holding the kidney in place. Although the kidneys are relatively well protected, they may be bruised by blows to the loin or by compression between the lower ribs and the ileum. Because the kidneys are located outside the peritoneal cavity, injury and rupture do not produce the same threat of peritoneal involvement as that of other organs such as the liver or spleen.

Each kidney is supplied by a single renal artery that arises on either side of the aorta. As the renal artery approaches the kidney, it divides into five segmental arteries that enter the hilus of the kidney. In the kidney, each segmental artery branches into several lobular arteries that

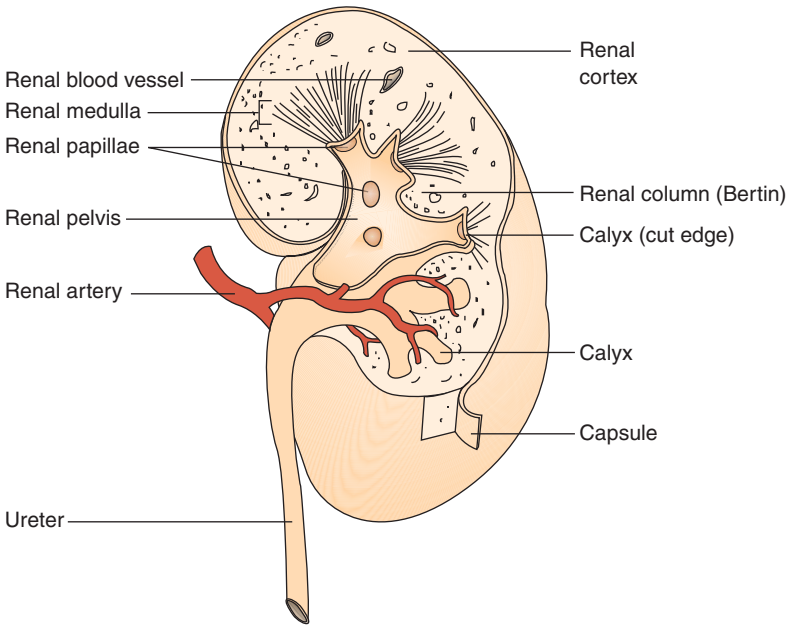


FIGURE 24-2. Internal structure of the kidney.

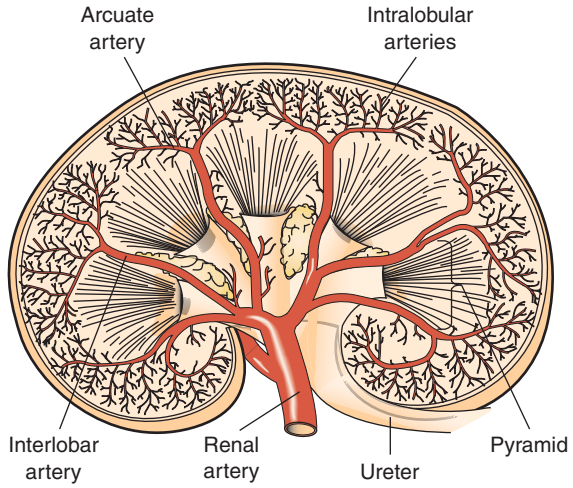


FIGURE 24-3. Simplified illustration of the arterial supply of the kidney. (From Cormack D.H. [1987]. *Ham's histology* [9th ed.]. Philadelphia: J.B. Lippincott.)

supply the upper, middle, and lower parts of the kidney. The lobular arteries further subdivide to form the interlobular arteries at the level of the corticomedullary junction (Fig. 24-3). These arteries give off branches, the arcuate arteries, that arch across the top of the pyramids. Small intralobular arteries radiate from the arcuate arteries to supply the cortex of the kidney. The afferent arterioles that supply the glomeruli arise from the intralobular arteries.

Although nearly all the blood flow to the kidneys passes through the cortex, less than 10% is directed to the medulla and only approximately 1% goes to the papillae. Under conditions of decreased perfusion or increased sympathetic nervous system stimulation, blood flow is redistributed away from the cortex toward the medulla. This redistribution of blood flow decreases glomerular filtration while maintaining the urine-concentrating ability of the kidneys, a factor that is important during conditions such as shock.

The Nephron

Each kidney is composed of more than 1 million tiny, closely packed functional units called *nephrons* (Fig. 24-4A). Each nephron consists of a glomerulus, where blood is filtered, and a proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct or tubule, where water, electrolytes, and other substances needed to maintain the constancy of the internal

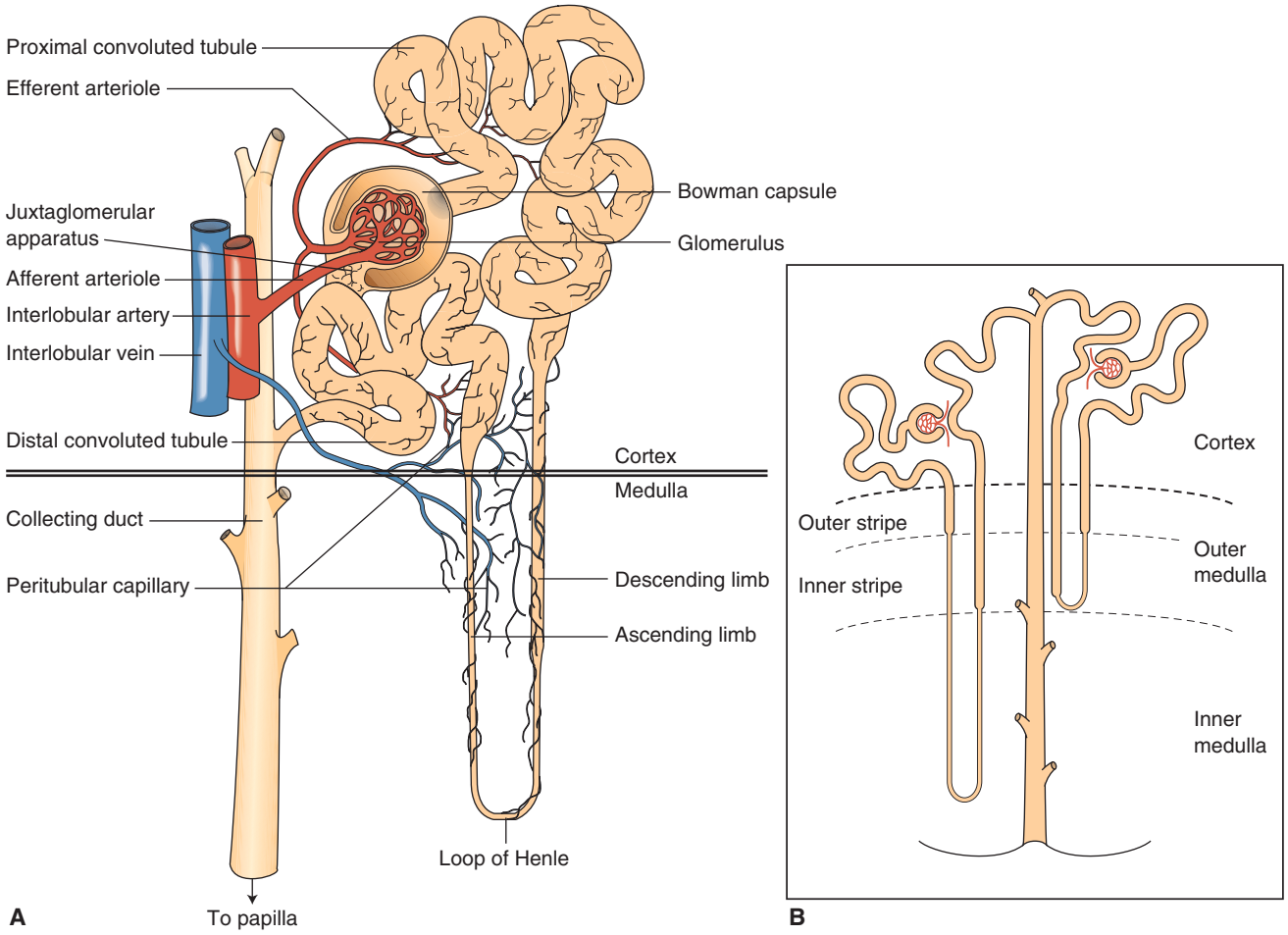


FIGURE 24-4. **(A)** Nephron showing the glomerular and tubular structures along with the blood supply. **(B)** Comparison of differences in location of tubular structures of the cortical and juxtamedullary nephrons.

The Nephron

- The nephron, which is the functional unit of the kidney, is composed of a vascular component, which connects to the circulatory system, and a tubular component, which has connections to both the circulatory system and the elimination functions of the kidney.
- The vascular component of the nephron consists of two arterioles closely associated with two capillary beds: the glomerulus (where water-soluble nutrients, wastes, and other small particles are filtered from the blood) and the peritubular capillaries (which surround the tubular structures).
- The tubular portion of the nephron processes the glomerular filtrate (urine), facilitating the reabsorption of substances from the tubular fluid into the peritubular capillaries and the secretion of substances from the peritubular capillaries into the urine filtrate.

environment are reabsorbed into the bloodstream while other, unneeded materials are secreted into the tubular filtrate for elimination.

Nephrons can be roughly grouped into two categories. Approximately 85% of the nephrons originate in the superficial part of the cortex and are called *cortical nephrons* (see Fig. 24-4B). They have short, thick loops of Henle that penetrate only a short distance into the medulla. The remaining 15% are called *juxtamedullary nephrons*. They originate deeper in the cortex and have longer and thinner loops of Henle that penetrate the entire length of the medulla. The juxtamedullary nephrons are largely concerned with urine concentration.

The nephrons are supplied by two capillary systems, the glomerulus and the peritubular capillary network (see Fig. 24-4A). The *glomerulus* is a unique, high-pressure capillary filtration system located between two arterioles, the afferent and the efferent arterioles. Because the arterioles are high-resistance vessels and the afferent arteriole has a larger diameter than the efferent arteriole, the blood pressure in the glomerulus is extraordinarily high for a capillary bed and easily forces fluid and solutes out of the blood into the glomerular capillary along its entire length. The *peritubular capillaries* originate from the efferent arteriole. They are low-pressure vessels that are adapted for reabsorption rather than filtration. These capillaries surround all portions of the tubules, an arrangement that permits rapid movement of solutes and water between the fluid in the tubular lumen and the blood in the capillaries. In the deepest part of the renal cortex, the efferent arterioles serving the juxtaglomerular complex also continue into long, thin-walled looping vessels called the *vasa recta*. The vasa recta accompany the long loops of Henle in the medullary portion of the kidney to assist in the exchange of substances flowing in and out of that portion of the kidney. The peritubular capillaries rejoin to form the venous channels by which blood leaves the kidneys and empties into the inferior vena cava.

The Glomerulus

The glomerulus consists of a compact tuft of capillaries encased in a thin, double-layered capsule called the *Bowman capsule*. Blood flows into the glomerular capillaries from the afferent arteriole and flows out of the glomerular capillaries into the efferent arteriole, which leads into the peritubular capillaries. Fluid and particles from the blood are filtered through the capillary membrane into a fluid-filled space in the Bowman capsule, called the *Bowman space*. The portion of the blood that is filtered into the capsule space is called the *glomerulary filtrate*. The mass of capillaries and its surrounding epithelial capsule are collectively referred to as the *renal corpuscle* (Fig. 24-5A).

The filtration apparatus enclosed by the parietal layer of the Bowman capsule consists of three components: the glomerular capillary endothelium, the glomerular basement membrane, and the visceral layer of the Bowman capsule (Fig. 24-5B). The endothelium of the glomerular capillary, which interfaces with blood as it moves through the capillary, contains many small perforations, called *fenestrations*. These fenestrations are larger than those in other capillaries; hence, they only restrict the movement of blood cells and macromolecules whose effective diameter exceeds the size of the fenestrae. Endothelial cells of glomerular capillaries also possess a number of aquaporin-1 water channels that allow for fast movement of water.

The glomerular basement membrane consists of a homogeneous acellular meshwork of collagen fibers, glycoproteins, and mucopolysaccharides (see Fig. 24-5C). Because the endothelial and epithelial layers of the glomerular capillary have porous structures, the basement membrane determines the permeability of the glomerular capillary membrane. The spaces between the fibers that make up the basement membrane represent the pores of a filter and determine the size-dependent permeability barrier of the glomerulus. The size of the pores in the basement membrane normally prevents red blood cells and plasma proteins from passing through the glomerular membrane into the filtrate. Alterations in the structure and function of the glomerular basement membrane are responsible for the leakage of proteins and blood cells into the filtrate that occurs in many forms of glomerular disease.

The visceral layer of the Bowman capsule is composed of epithelial cells that are highly modified to perform a filtering function. These large cells, called *podocytes* or *visceral epithelial* cells, have numerous tentacle-like cytoplasmic extensions that extend around the glomerular capillaries (see Fig. 24-5B). The elongated spaces between the interdigitating foot processes, called *filtration slits*, are about 25 nm wide and allow the ultrafiltrate from the blood to enter the Bowman space.

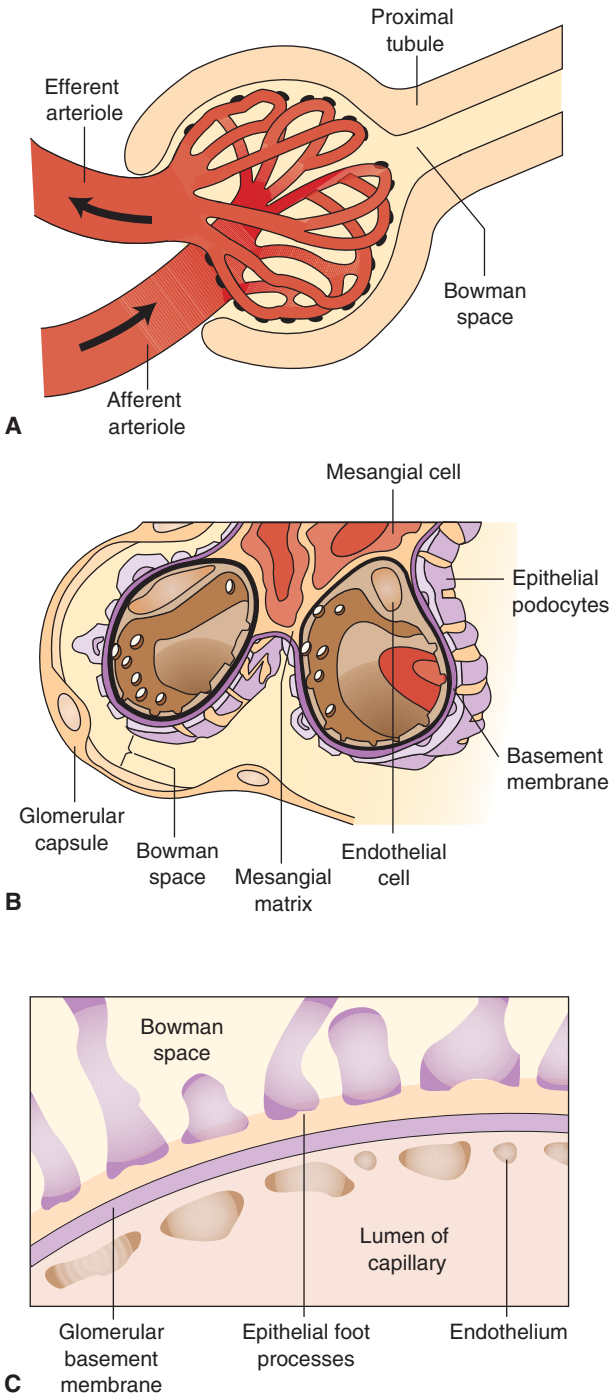


FIGURE 24-5. Renal corpuscle. **(A)** Structures of the glomerulus. **(B)** Cross-section of the glomerular membrane, showing the position of the endothelium, basement membrane, and epithelial foot processes. **(C)** Position of the mesangial cells in relation to the capillary loops and Bowman capsule.

Another important component of the glomerulus is the *mesangium*. In some areas, the capillary endothelium and the basement membrane do not completely surround each capillary. Instead, the mesangial cells, which lie between the capillary tufts, provide support for the glomerulus in these areas (see Fig. 24-5B). The mesangial cells produce an intercellular substance similar to that of the basement membrane. This substance covers the endothelial cells where they are not covered by basement membrane. The mesangial cells possess (or can develop) phagocytic properties and remove macromolecular materials that enter the intercapillary spaces. Mesangial cells also exhibit contractile properties in response to neurohumoral substances and are thought to contribute to the regulation of blood flow through the glomerulus. In normal glomeruli, the mesangial area is narrow and contains only a small number of cells. Mesangial hyperplasia and increased mesangial matrix occur in a number of glomerular diseases.

Tubular Components of the Nephron

The nephron tubule is divided into four segments: a highly coiled segment called the *proximal convoluted tubule,* which drains Bowman capsule; a thin, looped structure called the *loop of Henle;* a distal coiled portion called the *distal convoluted tubule;* and the final segment, called the *collecting tubule,* which joins with several tubules to collect the filtrate (see Fig. 24-4). The filtrate passes through each of these segments before reaching the pelvis of the kidney.

The proximal tubule is a highly coiled structure that dips toward the renal pelvis to become the descending limb of the loop of Henle. The ascending loop of Henle returns to the region of the renal corpuscle, where it becomes the distal tubule. The distal convoluted tubule, which begins at the juxtaglomerular complex, is divided into two segments: the *diluting segment* and the *late distal tubule*. The late distal tubule fuses with the collecting tubule. Like the distal tubule, the collecting duct is divided into two segments: the *cortical collecting tubule* and the *inner medullary collecting tubule*.

Throughout its course, the tubule is composed of a single layer of epithelial cells resting on a basement membrane. The structure of the epithelial cells varies with tubular function. The cells of the proximal tubule have a fine, villous structure that increases the surface area for reabsorption; they also are rich in mitochondria, which support active transport processes. The epithelial layer of the thin segment of the loop of Henle has few mitochondria, indicating minimal metabolic activity and reabsorptive function.

Urine Formation

Urine formation involves the filtration of blood by the glomerulus to form an *ultrafiltrate of urine* and the tubular reabsorption of electrolytes and nutrients needed to maintain the constancy of the internal environment while eliminating waste materials.

Glomerular Filtration

Urine formation begins with the filtration of essentially protein-free plasma through the glomerular capillaries into the Bowman space. The movement of fluid through the glomerular capillaries is determined by the same factors (i.e., capillary filtration pressure, colloidal osmotic

pressure, and capillary permeability) that affect fluid movement through other capillaries in the body (see Chapter 17). The glomerular filtrate has a chemical composition similar to plasma, but it contains almost no proteins because large molecules do not readily cross the glomerular wall. Approximately 125 mL of filtrate is formed each minute. This is called the *glomerular filtration rate* (GFR). This rate can vary from a few milliliters per minute to as high as 200 mL/minute.

The location of the glomerulus between two arterioles allows for maintenance of a high-pressure filtration system. The capillary filtration pressure (approximately 60 mm Hg) in the glomerulus is approximately two to three times higher than that of other capillary beds in the body. The filtration pressure and the GFR are regulated by the constriction and relaxation of the afferent and efferent arterioles. Constriction of the efferent arteriole increases resistance to outflow from the glomeruli and increases the glomerular pressure and the GFR. Constriction of the afferent arteriole causes a reduction in the renal blood flow, glomerular filtration pressure, and GFR. The afferent and the efferent arterioles are innervated by the sympathetic nervous system and are sensitive to vasoactive hormones, such as angiotensin II, as well. During periods of strong sympathetic stimulation, such as shock, constriction of the afferent arteriole causes a marked decrease in renal blood flow and thus glomerular filtration pressure. Consequently, urine output can fall almost to zero.

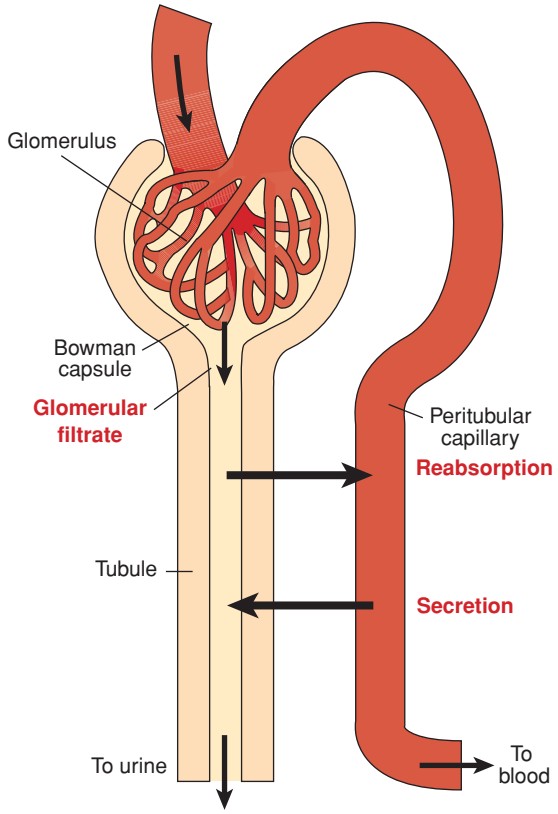


FIGURE 24-6. Reabsorption and secretion of substances between the renal tubules and the peritubular capillaries.

Tubular Reabsorption and Secretion

From the Bowman capsule, the glomerular filtrate moves into the tubular segments of the nephron. In its movement through the lumen of the tubular segments, the glomerular filtrate is changed considerably by the tubular transport of water and solutes. Tubular transport can result in reabsorption of substances from the tubular fluid into the peritubular capillaries or secretion of substances into the tubular fluid from the blood in the peritubular capillaries (Fig. 24-6).

The basic mechanisms of transport across the tubular epithelial cell membrane are similar to those of other cell membranes in the body and include active and passive transport mechanisms. Water and urea are passively absorbed along concentration gradients. Sodium, potassium, chloride (Cl^-), calcium (Ca^{++}), and phosphate (PO_4^-) ions, as well as urate, glucose, and amino acids, are reabsorbed using primary or secondary active transport mechanisms to move across the tubular membrane. Some substances, such as hydrogen, potassium, and urate ions, are secreted into the tubular fluids. Under normal conditions, only approximately 1 mL of the 125 mL of glomerular filtrate that is formed each minute is excreted in the urine. The other 124 mL is reabsorbed in the tubules. This means that the average output of urine is approximately 60 mL/hour.

Renal tubular cells have two membrane surfaces through which substances must pass as they are reabsorbed from the tubular fluid. The outside membrane that lies adjacent to the interstitial fluid is called the *basolateral membrane*, and the side that is in contact with the tubular lumen and tubular filtrate is called the *luminal membrane*. In most cases, substances move from the tubular filtrate into the tubular cell along a concentration gradient, but they require facilitated transport or carrier systems to move across the basolateral membrane into the interstitial fluid, where they are absorbed into the peritubular capillaries.

The bulk of energy used by the kidney is for active sodium transport mechanisms that facilitate sodium reabsorption and cotransport of other electrolytes and substances such as glucose and amino acids. This is called *secondary active transport* or *cotransport* (Fig. 24-7). In secondary active transport, two or more substances interact with a specific membrane protein (a carrier protein) and are transported across the membrane. As one of the substances (in this case sodium) diffuses down its concentration gradient, the energy released is used to move another substance (for instance, glucose or an amino acid) against its concentration gradient. Thus, the secondary active transport of a substance such as glucose does not require energy directly from adenosine triphosphate (ATP), but depends on the energy-dependent Na^+/K^+-adenosine triphosphatase (ATPase) pump on the basolateral side of renal tubular cells. This pump maintains a low intracellular sodium concentration that facilitates the downhill movement of sodium across the luminal membrane; it is this downhill diffusion of

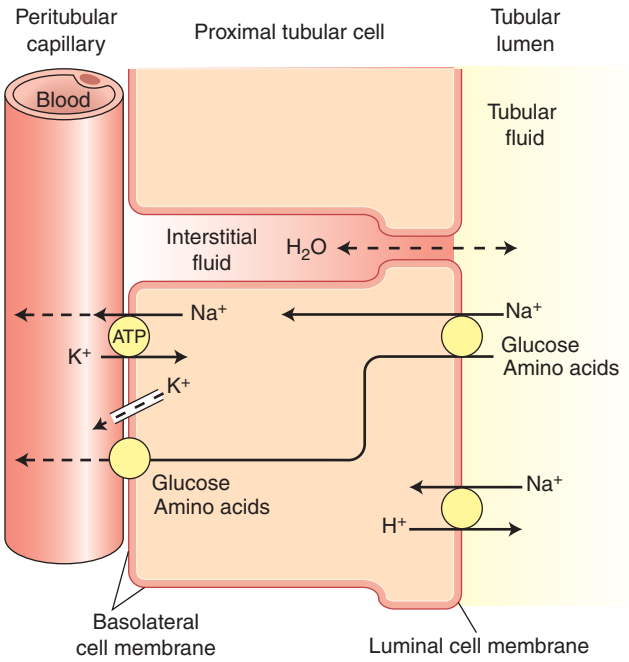


FIGURE 24-7. Mechanism for secondary active transport or cotransport of glucose and amino acids in the proximal tubule. The energy-dependent sodium-potassium pump on the basal lateral surface of the cell maintains a low intracellular gradient that facilitates the downhill movement of sodium and glucose or amino acids (cotransport) from the tubular lumen into the tubular cell and then into the peritubular capillary.

sodium to the interior of cell that provides the energy for the simultaneous uphill transport of glucose across the luminal membrane. A few substances, such as the hydrogen ion (H^+), are secreted into the tubule using secondary active transport, in which the movement of one substance, such as sodium, enables the movement of a second substance in the opposite direction.

Proximal Tubule. Approximately 65% of all reabsorptive and secretory processes that occur in the tubular system take place in the proximal tubule. There is almost complete reabsorption of nutritionally important substances, such as glucose, amino acids, lactate, and water-soluble vitamins (Fig. 24-8). Electrolytes, such as Na^+, K^+, Cl^-, and bicarbonate (HCO_3^-), are 65% to 80% reabsorbed. As these solutes move into the tubular cells, their concentration in the tubular lumen decreases, providing a concentration gradient for the osmotic reabsorption of water and urea. The proximal tubule is highly permeable to water, and the osmotic movement of water occurs so rapidly that the concentration difference of solutes on either side of the membrane seldom is more than a few milliosmoles.

Many substances, such as glucose, are freely filtered in the glomerulus and reabsorbed by energy-dependent cotransport carrier mechanisms. The maximum amount of substance that these transport systems can reabsorb per unit time is called the *transport maximum*. The transport maximum is related to the number of carrier proteins that are available for transport and usually is sufficient to ensure that all of a filtered substance such as glucose can be reabsorbed rather than being eliminated in the urine. The plasma level at which the substance appears in the urine is called the *renal threshold* (Fig. 24-9). Under some circumstances, the amount of substance filtered in the glomerulus exceeds the transport maximum. For example, when the blood glucose level is elevated in uncontrolled diabetes mellitus, the amount that is filtered in the glomerulus often exceeds the transport maximum (approximately 320 mg/minute), and glucose spills into the urine.

In addition to *reabsorbing* solutes and water, cells in the proximal tubule also *secrete* organic cations and

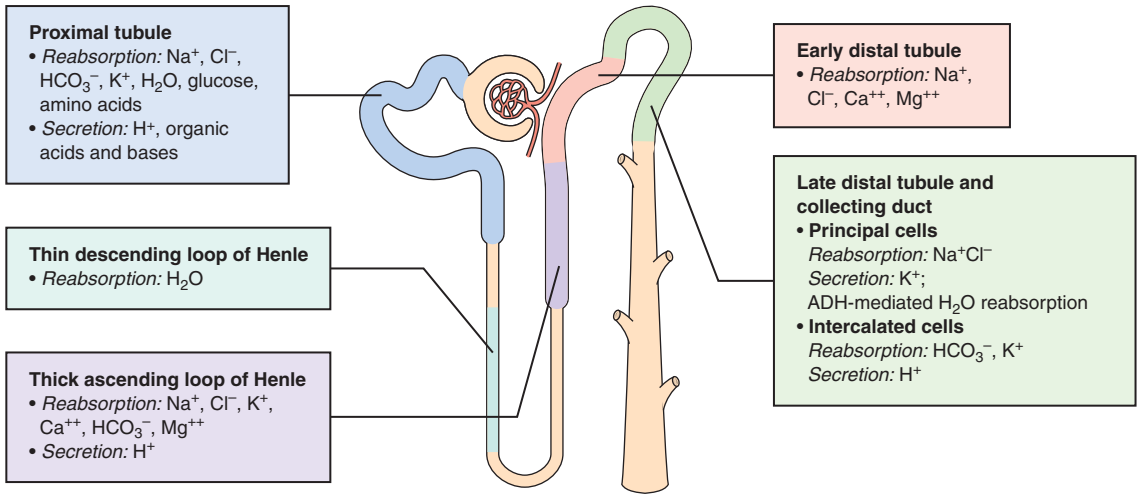


FIGURE 24-8. Sites of tubular water (H_2O), glucose, amino acids, Na^+ (sodium), Cl^- (chloride), HCO_3^- (bicarbonate), K^+ (potassium), Ca^{++} (calcium), and Mg^{++} (magnesium) reabsorption, and organic acids and bases, H^+ (hydrogen), and K^+ secretion.

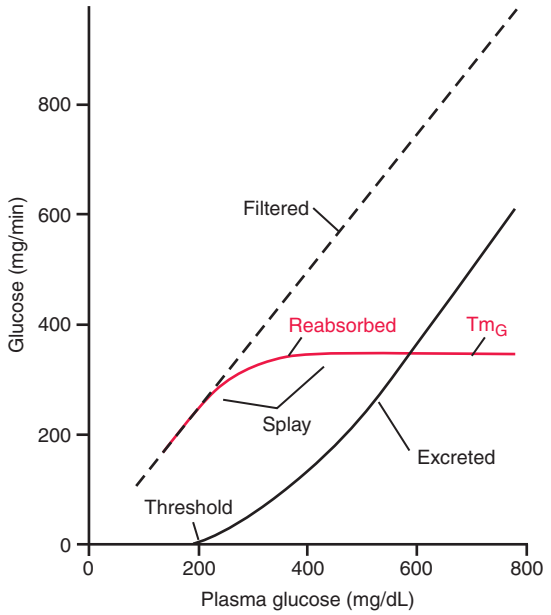


FIGURE 24-9. Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the rate of glucose excretion in the urine. The tubular transport maximum for glucose (Tm_G) is the maximum rate at which glucose can be reabsorbed from the tubules. The *threshold* for glucose refers to the filtered load of glucose at which glucose first begins to appear in the urine. The splay or rounding of the graph represents the fact that some nephrons reach their tubular maximum before others do. (From Rhoades R.A., Tanner G.A. [2003]. *Medical physiology* [2nd ed., p. 384]. Philadelphia: Lippincott Williams & Wilkins.)

anions into the urine filtrate (see Figs. 24-6 and 24-8). Many of these organic anions and cations are end products of metabolism (e.g., urate, oxalate) that circulate in the plasma. The proximal tubule also secretes exogenous organic compounds such as penicillin, aspirin, and morphine. Many of these compounds can be bound to plasma proteins and are not freely filtered in the glomerulus. Therefore, excretion by filtration alone eliminates only a small portion of these potentially toxic substances from the body.

The Loop of Henle. The loop of Henle plays an important role in controlling the concentration of the urine. It does this by establishing a high concentration of osmotically active particles in the interstitium surrounding the medullary collecting tubules where the antidiuretic hormone exerts its effects (to be discussed).

The loop of Henle is divided into three segments: the thin descending segment, the thin ascending segment, and the thick ascending segment. The loop of Henle, taken as a whole, always reabsorbs more sodium and chloride than water. This is in contrast to the proximal tubule, which reabsorbs sodium and water in equal proportions. The thin descending limb is highly permeable to water and moderately permeable to urea, sodium, and other ions. As the urine filtrate moves down the descending limb, water moves out of the filtrate into the surrounding interstitium. Thus, the osmolality of the filtrate reaches its highest point at the elbow of the loop of Henle. In contrast to the descending limb, the ascending limb of the loop of Henle is impermeable to water. In this segment, solutes are reabsorbed, but water cannot follow and remains in the filtrate; as a result, the tubular filtrate becomes more and more dilute, often reaching an osmolality of 100 mOsm/kg of H_2O as it enters the distal convoluted tubule, compared with the 285 mOsm/kg of H_2O in plasma. This allows for excretion of free water from the body. For this reason, it is often called the *diluting segment*.

The thick segment of the loop of Henle begins in the ascending limb where the epithelial cells become thickened. As with the thin ascending limb, this segment is impermeable to water. The thick segment contains a $Na^+/K^+/2Cl^-$ cotransport system (Fig. 24-10). This system involves the cotransport of a positively charged Na^+ and a positively charged K^+ ion accompanied by two negatively charged Cl^- ions. The gradient for the operation of this cotransport system is provided by the basolateral Na^+/K^+-ATPase pump, which maintains a low intracellular sodium concentration. Approximately 20% to 25% of the filtered load of sodium, potassium, and chloride is reabsorbed in the thick loop of Henle. Movement of these ions out of the tubule leads to the development of a transmembrane potential that favors the passive reabsorption of small divalent cations such as calcium and magnesium. The thick ascending loop of Henle is the site of the powerful "loop" diuretics (e.g., furosemide [Lasix]), which exert their action by inhibiting the $Na^+/K^+/2Cl^-$ cotransporters.

Distal and Collecting Tubules. Like the thick ascending loop of Henle, the distal convoluted tubule is relatively

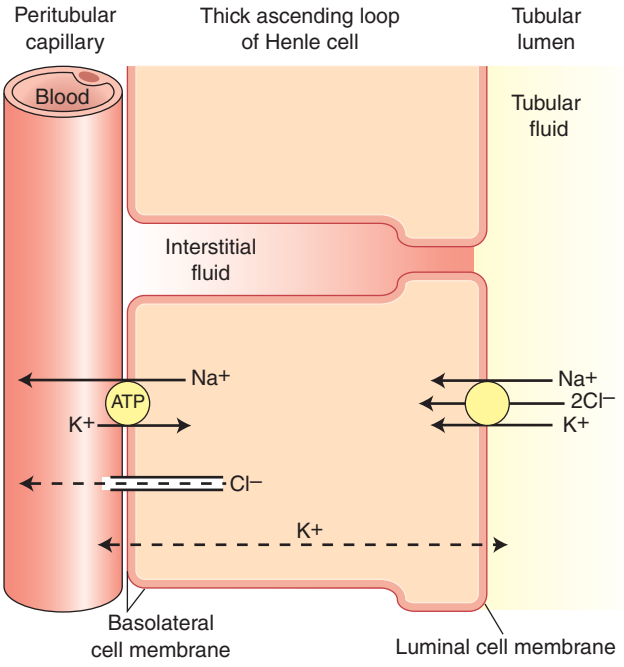


FIGURE 24-10. Sodium, chloride, and potassium reabsorption in the thick segment of the loop of Henle.

impermeable to water, and reabsorption of sodium chloride from this segment further dilutes the tubular fluid. Sodium reabsorption occurs through a Na^+/Cl^- cotransport mechanism. Approximately 5% of filtered sodium chloride is reabsorbed in this section of the tubule. Unlike the thick ascending loop of Henle, neither Ca^{++} nor Mg^{++} is passively absorbed in this segment of the tubule. Instead, Ca^{++} ions are actively reabsorbed in a process that is largely regulated by parathyroid hormone and possibly by vitamin D. The thiazide diuretics exert their action by inhibiting sodium chloride reabsorption in this segment of the renal tubules.

The late distal tubule and the cortical collecting tubule constitute the site where aldosterone exerts its action on sodium reabsorption and potassium secretion and elimination. Although responsible for only 2% to 5% of sodium chloride reabsorption, this site is largely responsible for determining the final sodium concentration of the urine. The late distal tubule with the cortical collecting tubule also is the major site for regulation of potassium excretion by the kidney. When the body is confronted with a potassium excess, as occurs with a diet high in potassium content, the amount of potassium secreted at this site may exceed the amount filtered in the glomerulus.

The mechanism for sodium reabsorption and potassium secretion in this section of the nephron is distinct from other tubular segments. This tubular segment is composed of two types of cells, the *intercalated cells,* where potassium is reabsorbed and hydrogen is secreted, and the *principal cells,* where aldosterone exerts its action. The secretion of H^+ ions into the tubular fluid by the intercalated cells is accompanied by the reabsorption of HCO_3^- ions. The intercalated cells can also reabsorb K^+ ions. The principal cells reabsorb Na^+ and facilitate the movement of K^+ into the urine filtrate (Fig. 24-11). Under the influence of aldosterone, sodium moves from the urine filtrate into principal cells; from there, it moves into the surrounding interstitial fluid and peritubular capillaries. Potassium moves from the peritubular capillaries into the principal cells and then into the urine filtrate.

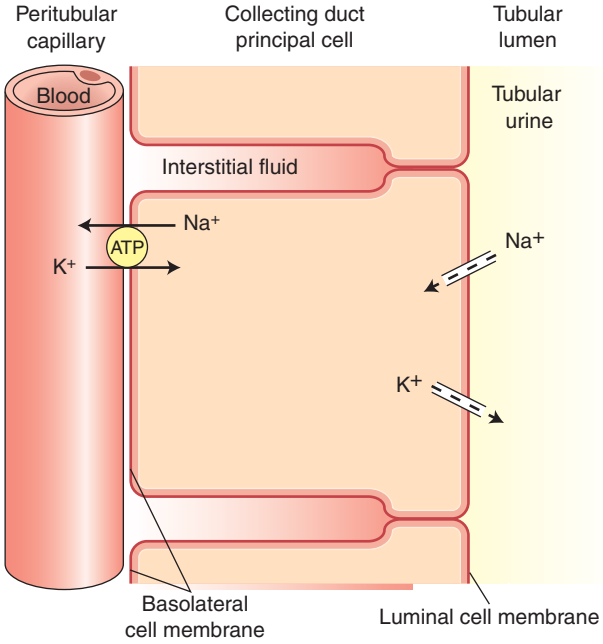


FIGURE 24-11. Mechanism of sodium reabsorption and potassium secretion by principal cells of the late distal and collecting tubules. Aldosterone exerts its action by increasing the activity of the Na^+/K^+-ATPase pump that transports sodium outward through the basolateral membrane of the cell and into the blood at the same time it pumps potassium into the cell. Aldosterone also increases the permeability of the luminal membrane for potassium.

Regulation of Urine Concentration

The ability of the kidney to respond to changes in the osmolality of the extracellular fluids by producing either a concentrated or dilute urine depends on the establishment of a high concentration of osmotically active particles (approximately 1200 mOsm/kg of H_2O) in the interstitium of the kidney medulla and the action of the antidiuretic hormone (ADH) in regulating the water permeability of the surrounding medullary collecting tubules (see Understanding How the Kidney Concentrates Urine).

In approximately one fifth of the juxtamedullary nephrons, the loops of Henle and special hairpin-shaped capillaries called the *vasa recta* descend into the medullary portion of the kidney, forming a countercurrent system that controls water and solute movement so that water is kept out of the area surrounding the tubule and solutes are retained. The term *countercurrent* refers to a flow of fluids in opposite directions in adjacent structures. In this case, there is an exchange of solutes between the adjacent descending and ascending loops of Henle and between the ascending and descending sections of the vasa recta. Because of these exchange processes, a high concentration of osmotically active particles (approximately 1200 mOsm/kg of H_2O) collects in the interstitium of the kidney medulla. The presence of these osmotically active particles in the interstitium surrounding the medullary collecting tubules facilitates the ADH-mediated reabsorption of water.

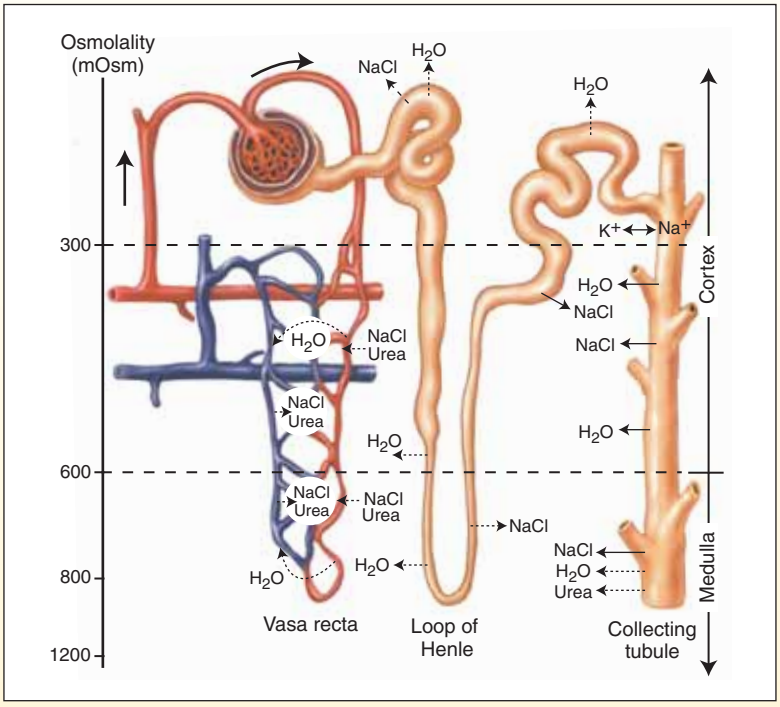
ADH assists in the maintenance of the extracellular fluid volume by controlling the permeability of the medullary collecting tubules. Osmoreceptors in the hypothalamus sense an increase in osmolality of extracellular fluids and stimulate the release of ADH from the posterior pituitary gland. In exerting its effect, ADH, also known as *vasopressin,* binds to receptors on the basolateral side of the tubular cells. Binding of ADH to the vasopressin receptors causes water channels, known as *aquaporin-2 channels,* to move into the luminal side of the tubular cell membrane, producing a marked increase in water permeability. At the basolateral side of the membrane, water exits the tubular cell into the hyperosmotic interstitium of the medullary area, where it enters the peritubular capillaries for return to the vascular system. The aquaporin-2 channels are thought to have a critical role in inherited and acquired disorders of water reabsorption by the kidney (e.g., diabetes insipidus).

UNDERSTANDING → How the Kidney Concentrates Urine

The osmolarity of body fluids relies heavily on the ability of the kidney to produce dilute or concentrated urine. Urine concentration depends on three factors: (1) the osmolarity of interstitial fluids in the urine-concentrating part of the kidney, (2) the antidiuretic hormone (ADH), and (3) the action of ADH on the cells in the collecting tubules of the kidney.

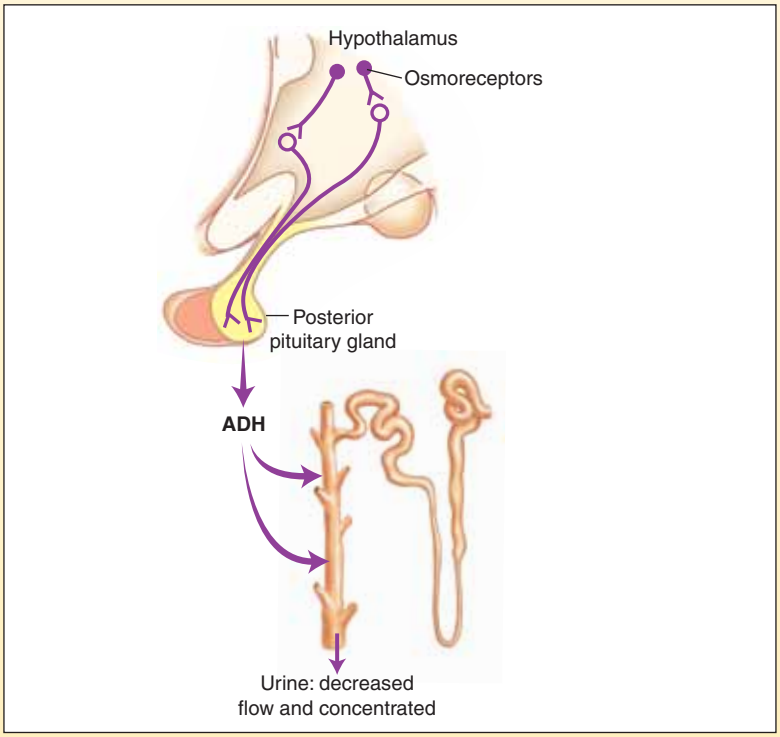
1

Osmolarity. In approximately one fifth of the juxtamedullary nephrons, the loops of Henle and special hairpin-shaped capillaries called the *vasa recta* descend into the medullary portion of the kidney to form a countercurrent system—a set of parallel passages in which the contents flow in opposite directions. The countercurrent design serves to increase the osmolarity in this part of the kidney by promoting the exchange of solutes between the adjacent descending and ascending loops of Henle and between the descending and ascending sections of the vasa recta. Because of these exchange processes, a high concentration of osmotically active particles (approximately 1200 mOsm/kg of H_2O) collects in the interstitium surrounding the collecting tubules where the ADH-mediated reabsorption of water takes place.



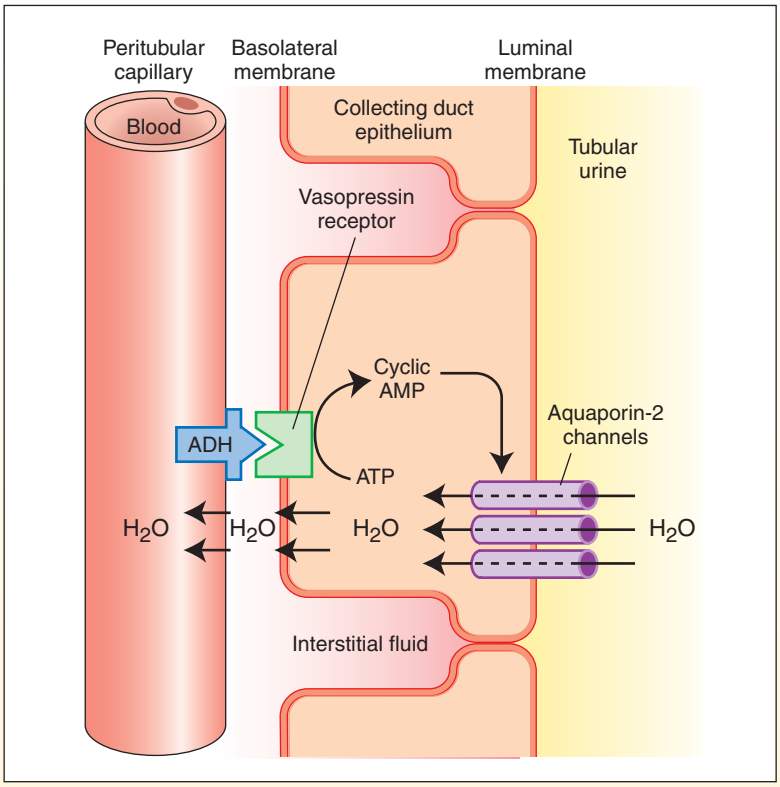
2

Antidiuretic Hormone. ADH, which regulates the ability of the kidneys to concentrate urine, is synthesized by neurons in the hypothalamus and transported down their axons to the posterior pituitary gland and then released into the circulation. One of the main stimuli for synthesis and release of ADH is an increase in serum osmolarity. ADH release is also controlled by cardiovascular reflexes that respond to changes in blood pressure or blood volume.



3

Action of ADH. ADH, also known as vasopressin, acts at the level of the collecting tubule to increase water absorption. It exerts its action by binding to vasopressin receptors on the basolateral membrane of the tubular cell. Binding of ADH to the vasopressin receptors causes water channels (*aquaporin-2 channels*) to move into the luminal side of the cell membrane, which is normally impermeable to water. Insertion of the channels allows water from the tubular fluids to move into the tubular cell and then out into the surrounding hyperosmotic interstitial fluid on the basolateral side of the cell, and from there it moves into the peritubular capillaries for return to the circulatory system. Thus, when ADH is present, the water that moved from the blood into the urine filtrate in the glomeruli is returned to the circulatory system, and when ADH is absent, the water is excreted in the urine.



Regulation of Renal Blood Flow

In the adult, the kidneys are perfused with 1000 to 1300 mL of blood per minute, or 20% to 25% of the cardiac output. This large blood flow is mainly needed to ensure a sufficient GFR for the removal of waste products from the blood, rather than for the metabolic needs of the kidney. Feedback mechanisms, both intrinsic (e.g., autoregulation, local hormones) and extrinsic (e.g., sympathetic nervous system, blood-borne hormones), normally keep blood flow and GFR constant despite changes in arterial blood pressure.

Neural and Humoral Control Mechanisms

The kidney is richly innervated by the sympathetic nervous system. Increased sympathetic activity causes constriction of the afferent and efferent arterioles and thus a decrease in renal blood flow. Intense sympathetic stimulation such as occurs in shock and trauma can produce marked decreases in renal blood flow and GFR, even to the extent of causing blood flow to cease altogether.

Several humoral substances, including angiotensin II, ADH, and the endothelins, produce vasoconstriction of renal vessels. The endothelins are a group of peptides released from damaged endothelial cells in the kidney and other tissues. Although not thought to be an important regulator of renal blood flow during everyday activities, endothelin I may play a role in the reduction of blood flow in conditions such as postischemic acute renal failure (see Chapter 26).

Other substances such as dopamine, nitric oxide, and prostaglandins (i.e., E_2 and I_2) produce vasodilation. Nitric oxide, a vasodilator produced by the vascular endothelium, appears to be important in preventing excessive vasoconstriction of renal blood vessels and allowing normal excretion of sodium and water. Prostaglandins are a group of mediators of cell function that are produced locally and exert their effects locally. Although prostaglandins do not appear to be of major importance in regulating renal blood flow and GFR under normal conditions, they may protect the kidneys against the vasoconstricting effects of sympathetic stimulation and angiotensin II. Nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit prostaglandin synthesis may cause reduction in renal blood flow and GFR under certain conditions.

Autoregulatory Mechanisms

The constancy of renal blood flow is maintained by a process called *autoregulation* (see Chapter 17). Normally, autoregulation of blood flow is designed to

maintain blood flow at a level consistent with the metabolic needs of the tissues. In the kidney, autoregulation of blood flow also must allow for precise regulation of solute and water excretion. For autoregulation to occur, the resistance to blood flow through the kidneys must be varied in direct proportion to the arterial pressure. The exact mechanisms responsible for the intrarenal regulation of blood flow are unclear. One of the proposed mechanisms is a direct effect on vascular smooth muscle that causes the blood vessels to relax when there is an increase in blood pressure and to constrict when there is a decrease in pressure. A second proposed mechanism is the juxtaglomerular complex.

The Juxtaglomerular Complex. The juxtaglomerular complex is thought to represent a feedback control system that links changes in the GFR with renal blood flow. The juxtaglomerular complex is located at the site where the distal tubule extends back to the glomerulus and then passes between the afferent and efferent arterioles (Fig. 24-12A). The distal tubular site that is nearest the glomerulus is characterized by densely nucleated cells called the *macula densa*. In the adjacent afferent arteriole, the smooth muscle cells of the media are modified as special secretory cells called *juxtaglomerular cells*. These cells contain granules of inactive renin, an enzyme that functions in the conversion of angiotensinogen to angiotensin. Renin functions by means of angiotensin II to produce vasoconstriction of the efferent arteriole as a means of preventing large decreases in the GFR. Angiotensin II also increases sodium reabsorption indirectly by stimulating aldosterone secretion from the adrenal gland, and directly by increasing sodium reabsorption by the proximal tubule cells.

Because of its location between the afferent and efferent arterioles, the juxtaglomerular complex is thought to play an essential feedback role in linking the level of arterial blood pressure and renal blood flow to the GFR and the composition of the distal tubular fluid (see Fig. 24-12B). It is thought to monitor the systemic arterial blood pressure by sensing the stretch of the afferent arteriole and the concentration of sodium chloride in the tubular filtrate as it passes through the macula densa. This information is then used in determining how much renin should be released to keep the arterial blood pressure within its normal range and maintain a relatively constant GFR. Studies suggest that a decrease in the GFR slows the flow rate of the urine filtrate in the ascending loop of Henle, thereby increasing sodium and chloride reabsorption. This, in turn, decreases the delivery of sodium chloride to the macula densa. The decrease in delivery of sodium chloride to the macula densa has two effects: it decreases resistance in the afferent arterioles, which raises glomerular filtration pressure, and it increases the release of renin from the juxtaglomerular cells. The renin from these cells functions as an enzyme to convert angiotensinogen to angiotensin I, which is converted to angiotensin II (see Chapter 18, Fig. 18-12). Finally, angiotensin II acts to constrict the efferent arteriole as a means of producing a further increase in the

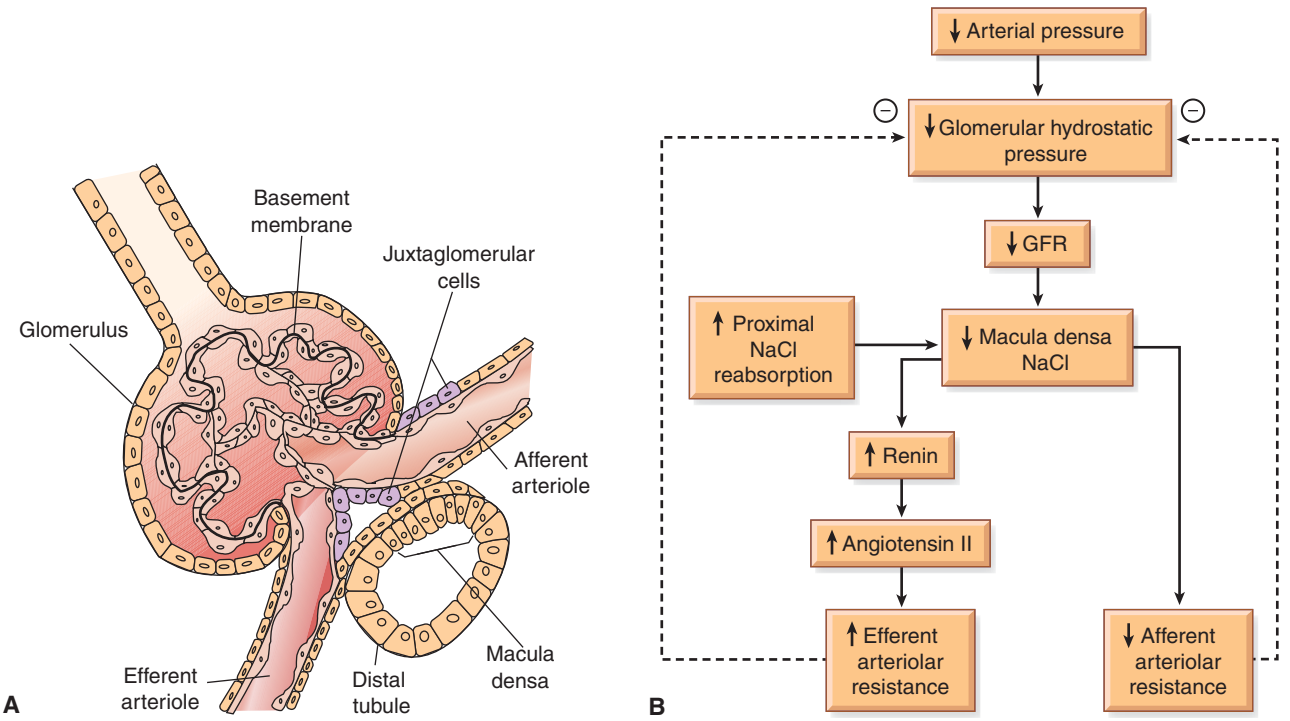


FIGURE 24-12. **(A)** Juxtaglomerular apparatus showing the close contact of the distal tubule with the afferent arteriole, the macula densa, and the juxtaglomerular cells. **(B)** Flow chart depicting the macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during changes in renal arterial pressure. (From Guyton A.C., Hall J.E. [2006]. *Textbook of medical physiology* [11th ed., p. 324]. Philadelphia: Elsevier Saunders.)

glomerular filtration pressure and thereby returning the GFR toward a more normal range.

Effect of Increased Protein and Glucose Load

Even though renal blood flow and glomerular filtration are relatively stable under most conditions, two conditions can increase renal blood flow and glomerular filtration. These conditions are an increased amount of protein in the diet and an increase in blood glucose. With ingestion of a high-protein diet, renal blood flow increases 20% to 30% within 1 to 2 hours. Although the exact mechanism for this increase is uncertain, it is thought to be related to the fact that amino acids and sodium are absorbed together in the proximal tubule (secondary active transport). As a result, delivery of sodium to the macula densa is decreased, which elicits an increase in renal blood flow through the juxtaglomerular complex feedback mechanism. The resultant increase in blood flow and GFR allows sodium excretion to be maintained at a near-normal level while increasing the excretion of the waste products of protein metabolism, such as urea. The same mechanism is thought to explain the large increases in renal blood flow and GFR that occur with high blood glucose levels in persons with uncontrolled diabetes mellitus.

Elimination Functions of the Kidney

The functions of the kidney focus on elimination of water, waste products, excess electrolytes, and unwanted substances from the blood. Blood tests can provide valuable information about the kidneys' ability to remove metabolic wastes and maintain the blood's normal electrolyte and pH composition. As renal function declines, there is an increase in serum levels of substances such as urea, creatinine, phosphate, and potassium. The effect of renal failure on the concentration of serum electrolytes and metabolic end products is discussed in Chapter 26.

Renal Clearance

Renal clearance is the volume of plasma that is completely cleared each minute of any substance that finds its way into the urine. It is determined by the ability of the glomeruli to filter the substance and the capacity of the renal tubules to reabsorb or secrete it. Every substance has its own clearance rate, the units of which are always volume of plasma per unit time. It can be determined by measuring the amount of a substance that is excreted in the urine (i.e., urine concentration × urine flow rate in milliliters per minute) and dividing by its plasma concentration. Inulin, a large polysaccharide, is freely filtered in the glomeruli and neither reabsorbed nor secreted by the tubular cells. After intravenous injection, the amount of inulin that appears in the urine is equal to the amount that is filtered in the glomeruli (i.e., the clearance rate is equal to the GFR). Because of these properties, inulin can be used as a laboratory measure of the GFR. Some substances, such as urea, are freely filtered in the glomeruli, but the volume that is cleared from the plasma is less than the GFR, indicating that at least some of the substance is being reabsorbed. At normal plasma levels, glucose has a clearance of zero because it is reabsorbed in the tubules and none appears in the urine.

The Functions of the Kidney

- The kidney regulates the composition and pH of body fluids through the reabsorption and elimination or conservation of sodium, potassium, hydrogen, chloride, and bicarbonate ions.
- It functions in the elimination of metabolic wastes (urea, uric acid, creatinine) and drugs and their metabolites.
- It serves to regulate the osmolality of the extracellular fluid through the action of antidiuretic hormone (ADH).
- It plays a central role in blood pressure regulation through the renin-angiotensin-aldosterone mechanism and the regulation of salt and water elimination.
- It contributes to the metabolic functions of the skeletal system through activation of vitamin D and regulation of calcium and phosphate conservation and elimination.
- It controls the production of red blood cells in the bone marrow through the production of erythropoietin.

Regulation of Sodium and Potassium Elimination

Elimination of sodium and potassium is regulated by the GFR and by humoral agents that control their reabsorption. Aldosterone functions in the regulation of sodium and potassium elimination. Atrial natriuretic peptide (ANP) contributes to the regulation of sodium elimination. Sodium reabsorption in the distal tubule and collecting duct is highly variable and depends on the presence of aldosterone, a hormone secreted by the adrenal gland. In the presence of aldosterone, almost all the sodium in the distal tubular fluid is reabsorbed, and the urine essentially becomes sodium free. In the absence of aldosterone, virtually no sodium is reabsorbed from the distal tubule. The remarkable ability of the distal tubular and collecting duct cells to alter sodium reabsorption in relation to changes in aldosterone allows the kidneys to excrete urine with sodium levels that range from a few tenths of a gram to 40 g per day.

Like sodium, potassium is freely filtered in the glomerulus, but unlike sodium, potassium is reabsorbed from and secreted into the tubular fluid. The secretion of potassium into the tubular fluid occurs in the distal tubule and, like that of sodium, is regulated by aldosterone. Only approximately 70 mEq of potassium is delivered to the distal tubule each day, but the average

person consumes this much and more potassium in the diet. Excess potassium that is not filtered in the glomerulus and delivered to the collecting tubule therefore must be secreted (i.e., transported from the blood) into the tubular fluid for elimination from the body. In the absence of aldosterone (as in Addison disease; see Chapter 32), potassium secretion becomes minimal. In these circumstances, potassium reabsorption exceeds secretion, and blood levels of potassium increase.

Atrial natriuretic peptide, discovered in 1981, is a hormone believed to have an important role in salt and water excretion by the kidney. It is synthesized in muscle cells of the atria of the heart and released when the atria are stretched. The actions of ANP include vasodilation of the afferent and efferent arterioles, which results in an increase in renal blood flow and glomerular filtration rate. ANP inhibits aldosterone secretion by the adrenal gland and sodium reabsorption from the collecting tubules through its action on aldosterone and through direct action on the tubular cells. It also inhibits ADH release from the posterior pituitary gland, thereby increasing excretion of water by the kidneys. ANP also has vasodilator properties. Whether these effects are sufficient to produce long-term changes in blood pressure is uncertain.

Regulation of pH

The kidneys regulate body pH by conserving base bicarbonate and eliminating hydrogen ions. Neither the blood buffer systems nor the respiratory control mechanisms for carbon dioxide elimination can eliminate hydrogen ions from the body. This is accomplished by the kidneys. The average North American diet results in the liberation of 40 to 80 mmol of hydrogen ions each day. Virtually all the hydrogen ions excreted in the urine are secreted into the tubular fluid by means of tubular secretory mechanisms. The lowest tubular fluid pH that can be achieved is 4.4 to 4.5. The ability of the kidneys to excrete hydrogen ions depends on buffers in the urine that combine with the hydrogen ion. The three major urine buffers are bicarbonate, phosphate (HPO_4^{2-}), and ammonia (NH_3). Bicarbonate ions, which are present in the urine filtrate, combine with hydrogen ions that have been secreted into the tubular fluid; this results in the formation of carbon dioxide and water. The carbon dioxide is then absorbed into the tubular cells and bicarbonate is regenerated. The phosphate ion is a metabolic end product that is filtered into the tubular fluid; it combines with a secreted hydrogen ion and is not reabsorbed. Ammonia is synthesized in tubular cells by deamination of the amino acid glutamine; it diffuses into the tubular fluid and combines with the hydrogen ion. An important aspect of this buffer system is that the deamination process increases whenever the body's hydrogen ion concentration remains elevated for 1 to 2 days. These mechanisms for pH regulation are described more fully in Chapter 8.

pH-Dependent Elimination of Organic Ions

The proximal tubule actively secretes large amounts of different organic anions. Foreign anions (e.g., salicylates, penicillin) and endogenously produced anions (e.g., bile acids, uric acid) are actively secreted into the tubular fluid. Most of the anions that are secreted use the same transport system, allowing the kidneys to rid the body of many different drugs and environmental agents. Because the same transport system is shared by different anions, there is competition for transport such that elevated levels of one substance tend to inhibit the secretion of other anions. The proximal tubules also possess an active transport system for organic cations that is analogous to that for organic anions.

Uric Acid Elimination

Uric acid is a product of purine metabolism (see Chapter 44). Excessively high blood levels (i.e., hyperuricemia) can cause gout, and excessive urine levels can cause kidney stones. Uric acid is freely filtered in the glomerulus and is reabsorbed and secreted into the proximal tubules. Uric acid is one of the anions that use the previously described anion transport system in the proximal tubule. Tubular reabsorption normally exceeds secretion, and the net effect is removal of uric acid from the filtrate. Although the rate of reabsorption exceeds secretion, the secretory process is homeostatically controlled to maintain a constant plasma level. Many persons with elevated uric acid levels secrete less uric acid than do persons with normal uric acid levels.

Uric acid uses the same transport systems as other anions, such as aspirin, sulfinpyrazone, and probenecid. Small doses of aspirin compete with uric acid for secretion into the tubular fluid and reduce uric acid secretion, and large doses compete with uric acid for reabsorption and increase uric acid excretion in the urine. Because of its effect on uric acid secretion, aspirin is not recommended for treatment of gouty arthritis. Thiazide and loop diuretics (i.e., furosemide and ethacrynic acid) also can cause hyperuricemia and gouty arthritis, presumably through a decrease in extracellular fluid volume and enhanced uric acid reabsorption.

Urea Elimination

Urea is an end product of protein metabolism. The normal adult produces 25 to 30 g/day; the quantity rises when a high-protein diet is consumed, when there is excessive tissue breakdown, or in the presence of gastrointestinal bleeding. With gastrointestinal bleeding, the blood proteins are broken down to form ammonia in the intestine; the ammonia is then absorbed into the portal circulation and converted to urea by the liver before being released into the bloodstream. The kidneys, in their role as regulators of blood urea nitrogen (BUN) levels, filter urea in the glomeruli and then reabsorb it in the tubules. This enables maintenance of a normal BUN, which is in the range of 8 to 25 mg/dL (2.9 to 8.9 mmol/L). During periods of dehydration, the blood volume and GFR drop, and BUN levels increase. The renal tubules are permeable to urea, which means that the longer the tubular fluid remains in the kidneys, the greater is the reabsorption of urea into the blood. Only small amounts

of urea are reabsorbed into the blood when the GFR is high, but relatively large amounts of urea are returned to the blood when the GFR is reduced.

Drug Elimination

Many drugs are eliminated in the urine. These drugs are selectively filtered in the glomerulus and reabsorbed or secreted into the tubular fluid. Only drugs that are not bound to plasma proteins are filtered in the glomerulus and therefore able to be eliminated by the kidneys. Many drugs are weak acids or weak bases and are present in the renal tubular fluid partly as ionized water-soluble and nonionized lipid-soluble molecules. The nonionized lipid-soluble form of a drug diffuses more readily through the lipid membrane of the tubule and then back into the bloodstream, whereas the ionized water-soluble form remains in the urine filtrate. The ratio of ionized to nonionized drug depends on the pH of the urine. For example, aspirin is highly ionized in alkaline urine and in this form is rapidly excreted in the urine, and it is largely nonionized in acid urine and is reabsorbed rather than excreted. Alkaline or acid diuresis may be used to increase elimination of drugs in the urine, particularly in situations of drug overdose.

Endocrine Functions of the Kidney

In addition to their function in regulating body fluids and electrolytes, the kidneys function as an endocrine organ in that they produce chemical mediators that travel through the blood to distant sites where they exert their actions. The kidneys participate in control of blood pressure through the renin-angiotensin-aldosterone mechanism, in calcium metabolism by activating vitamin D, and in regulating red blood cell production through the synthesis of erythropoietin.

The Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanism plays an important part in short- and long-term regulation of blood pressure (see Chapter 18). Renin is an enzyme that is synthesized and stored in the juxtaglomerular cells of the kidney. This enzyme is thought to be released in response to a decrease in renal blood flow or a change in the composition of the distal tubular fluid, or as the result of sympathetic nervous system stimulation. Renin itself has no direct effect on blood pressure. Rather, it acts enzymatically to convert a circulating plasma protein called *angiotensinogen* to angiotensin I. Angiotensin I, which has few vasoconstrictor properties, leaves the kidneys and enters the circulation; as it is circulated through the lungs, the *angiotensin-converting enzyme* catalyzes its conversion to angiotensin II. Angiotensin II is a potent vasoconstrictor, and it acts directly on the kidneys to decrease salt and water excretion. Both mechanisms have relatively short periods of action. Angiotensin II also stimulates the secretion of aldosterone by the adrenal gland, thereby exerting a more long-term effect on maintenance of blood pressure by increasing the reabsorption of sodium in the distal tubule. Renin also functions via angiotensin II to produce constriction of the efferent arteriole as a means of preventing a serious decrease in glomerular filtration pressure.

Erythropoietin

Erythropoietin is a polypeptide hormone that regulates the differentiation of red blood cells in the bone marrow (see Chapter 13). Between 89% and 95% of erythropoietin is formed in the kidneys. The synthesis of erythropoietin is stimulated by tissue hypoxia, which may be brought about by anemia, residence at high altitudes, or impaired oxygenation of tissues due to cardiac or pulmonary disease. Persons with chronic kidney disease often are anemic because of an inability of the kidneys to produce erythropoietin. This anemia usually is managed by the administration of a recombinant erythropoietin (epoetin alfa) produced through DNA technology to stimulate erythropoiesis.

Vitamin D

Activation of vitamin D occurs in the kidneys. Vitamin D increases calcium absorption from the gastrointestinal tract and helps to regulate calcium deposition in bone. It also has a weak stimulatory effect on renal calcium absorption. Although vitamin D is not synthesized and released from an endocrine gland, it often is considered as a hormone because of its pathway of molecular activation and mechanism of action.

Vitamin D exists in two forms: natural vitamin D (cholecalciferol), produced in the skin from ultraviolet irradiation, and synthetic vitamin D (ergocalciferol), derived from irradiation of ergosterol. The active form of vitamin D is 1,25-dihydroxycholecalciferol. Cholecalciferol and ergocalciferol must undergo chemical transformation to become active: first to 25-hydroxycholecalciferol in the liver and then to 1,25-dihydroxycholecalciferol in the kidneys. Persons with end-stage renal disease are unable to transform vitamin D to its active form and may require pharmacologic preparations of the active vitamin (calcitriol) for maintaining mineralization of their bones.

In summary, the kidneys rid the body of metabolic wastes, regulate fluid volume, control the concentration of electrolytes, assist in maintaining acid-base balance, and aid in the regulation of blood pressure. The nephron is the functional unit of the kidney. It is composed of a glomerulus, which filters the blood, and a tubular component, where electrolytes and other substances needed to maintain the constancy of the internal environment are reabsorbed back into the bloodstream while unneeded materials are secreted into the tubular filtrate for elimination. Urine concentration occurs in the collecting tubules under the influence of ADH. ADH maintains extracellular volume by returning water to the vascular

compartment, producing concentrated urine by removing water from the tubular filtrate.

Renal clearance is the volume of plasma that is completely cleared each minute of any substance that finds its way into the urine. It is determined by the ability of the glomeruli to filter the substance and the capacity of the renal tubules to reabsorb or secrete it. The GFR is the amount of filtrate that is formed each minute as blood moves through the glomeruli. It is regulated by the arterial blood pressure and renal blood flow in the normally functioning kidney. The juxtaglomerular complex is thought to represent a feedback control system that links changes in the GFR with renal blood flow.

In addition to their function in regulating body fluids and electrolytes, the kidneys function as an endocrine organ in that they produce chemical mediators that travel through the blood to distant sites where they exert their actions. The kidneys participate in control of blood pressure by way of the renin-angiotensin-aldosterone mechanism, regulate red blood cell production through the synthesis of erythropoietin, and aid in calcium metabolism by activating vitamin D.

Tests of Renal Function

The function of the kidneys is to filter the blood, selectively reabsorb those substances that are needed to maintain the constancy of body fluid, and excrete metabolic wastes. The composition of urine and blood provides valuable information about the adequacy of renal function. Radiologic tests, endoscopy, and renal biopsy afford means for viewing the gross and microscopic structures of the kidneys and urinary system.

Urine Tests

Urine is a clear, amber-colored fluid that is approximately 95% water and 5% dissolved solids. The kidneys normally produce approximately 1.5 L of urine each day. Normal urine contains metabolic wastes and few or no plasma proteins, blood cells, or glucose molecules. Urine tests can be performed on a single urine specimen or on a 24-hour urine specimen. First-voided morning specimens are useful for qualitative protein and specific gravity testing. A freshly voided specimen is most reliable. Urine specimens that have been left standing may contain lysed red blood cells, disintegrating *casts*, and rapidly multiplying bacteria. Table 24-1 describes urinalysis values for normal urine.

Casts are molds of the distal nephron lumen. A gel-like substance called *Tamm-Horsfall mucoprotein*, which is formed in the tubular epithelium, is the major protein constituent of urinary casts. Casts composed of this gel but devoid of cells are called *hyaline casts*. These casts develop when the protein concentration of the urine is high (as in nephrotic syndrome), urine osmolality is high, and urine pH is low. The inclusion of granules or cells in the matrix of the protein gel leads to the formation of various other types of casts.

Proteinuria represents excessive protein excretion in the urine. Because of the glomerular capillary filtration barrier, less than 150 mg/L of protein is excreted in the urine over 24 hours in a healthy person. Urine tests for proteinuria are used to detect abnormal filtering of albumin in the glomeruli or defects in its reabsorption in the renal tubules. A protein reagent dipstick can be used as a rapid screening test for the presence of proteins in the urine. Once the presence of proteinuria has been detected, a 24-hour urine test is often used to quantify the amount of protein that is present.

Albumin, which is the smallest of the plasma proteins, is filtered more readily than globulins or other plasma proteins. Thus, *microalbuminuria* tends to occur long before clinical proteinuria becomes evident. A dipstick test for microalbuminuria is available for screening purposes. The microalbuminuria dipstick method, however, only indicates an increase in urinary albumin that is below the detectable range of the standard proteinuria test. It does not specify the amount of albumin that is present in the urine. Therefore, a 24-hour urine collection is the standard method for detecting microalbuminuria (an albumin excretion >30 mg/day is abnormal).

TABLE 24-1 Normal Values for Routine Urianalysis

General Characteristics and Measurements	Chemical Determinations	Microscopic Examination of Sediment
Color: yellow-amber—indicates a high specific gravity and small output of urine Turbidity: clear to slightly hazy Specific gravity: 1.010–1.025 with a normal fluid intake pH: 4.5–8.0	Glucose: negative Ketones: negative Blood: negative Protein: negative Bilirubin: negative Urobilinogen: 0.5–4.0 mg/d Nitrate for bacteria: negative Leukocyte esterase: negative	Casts negative: occasional hyaline casts Red blood cells: negative or rare Crystals: negative (none) White blood cells; negative or rare Epithelial cells: few

From Fischbach F. (2004). *A manual of laboratory and diagnostic tests* (7th ed., p. 178). Philadelphia: Lippincott Williams & Wilkins.

The *specific gravity* of urine is a measure of its concentration of solutes. Urine specific gravity provides a valuable index of the hydration status and functional ability of the kidneys. The usual range is from 1.010 to 1.025 with normal fluid intake. Healthy kidneys can produce concentrated urine with a specific gravity of 1.030 to 1.040 during periods of dehydration, and during periods of marked hydration, the specific gravity can approach 1.000. With diminished renal function, there is a loss of renal concentrating ability, and the urine specific gravity may fall to levels of 1.006 to 1.010. These low levels are particularly significant if they occur during periods that follow a decrease in water intake (e.g., during the first urine specimen on arising in the morning).

Urine osmolality, which depends on the number of particles of solute in a unit of solution, is a more exact measurement of urine concentration than specific gravity. More information concerning renal function can be obtained if the serum and urine osmolality tests are done at the same time. The normal ratio between urine and serum osmolality is 3:1. A high urine-to-serum ratio is seen in concentrated urine. With poor concentrating ability, the ratio is low.

Glomerular Filtration Rate

The GFR provides a gauge of renal function. It can be measured clinically by collecting timed samples of blood and urine. *Creatinine,* a product of creatine metabolism by the muscle, is filtered by the kidneys but not reabsorbed in the renal tubule. Creatinine levels in the blood and urine can be used to calculate the GFR. The clearance rate for creatinine is the amount that is completely cleared by the kidneys in 1 minute. The formula is expressed as $C = UV/P$, in which C is the clearance rate (mL/minute), U is the urine concentration (mg/dL), V is the urine volume excreted (mL/minute or 24 hours), and P is plasma concentration (mg/dL).

Normal creatinine clearance is 115 to 125 mL/minute. This value is corrected for body surface area, which reflects the muscle mass where creatinine metabolism takes place. The test may be done on a 24-hour basis, with blood being drawn when the urine collection is completed. In another method, two 1-hour urine specimens are collected, and a blood sample is drawn in between.

Blood Tests

Blood tests can provide valuable information about the kidneys' ability to remove metabolic wastes from the blood and maintain normal electrolyte and pH composition of the blood. Normal blood values are listed in Table 24-2. Serum levels of potassium, phosphate, BUN, and creatinine increase in renal failure. Serum pH, calcium, and bicarbonate levels decrease in renal failure. The effect of renal failure on the concentration of serum electrolytes and metabolic end products is discussed in Chapter 26.

TABLE 24-2 Normal Blood Chemistry Levels

Substance	Normal Value*
Blood urea nitrogen	8.0–20.0 mg/dL (2.9–7.1 mmol/L)
Creatinine	0.6–1.2 mg/dL (50–100 mmol/L)
Sodium	135–145 mEq/L (135–145 mmol/L)
Chloride	98–106 mEq/L (98–106 mmol/L)
Potassium	3.5–5 mEq/L (3.5–5 mmol/L)
Carbon dioxide (CO_2 content)	24–29 mEq/L (24–29 mmol/L)
Calcium	8.5–10.5 mg/dL (2.1–2.6 mmol/L)
Phosphate	2.5–4.5 mg/dL (0.77–1.45 mmol/L)
Uric acid	
Male	2.4–7.4 mg/dL (140–440 μmol/L)
Female	1.4–5.8 mg/dL (80–350 μmol/L)
pH	7.35–7.45

*Values may vary among laboratories, depending on the method of analysis used.

Serum Creatinine

Serum creatinine levels reflect the GFR. Because these measurements are easily obtained and relatively inexpensive, they often are used as a screening measure of renal function. Creatinine is a product of creatine metabolism in muscles; its formation and release are relatively constant and proportional to the amount of muscle mass present. Creatinine is freely filtered in the glomeruli, is not reabsorbed from the tubules into the blood, and is only minimally secreted into the tubules from the blood; therefore, its blood values depend closely on the GFR.

The normal creatinine value is approximately 0.7 mg/dL of blood for a woman with a small frame, approximately 1.0 mg/dL of blood for a normal adult man, and approximately 1.5 mg/dL of blood (60 to 130 mmol/L) for a muscular man. There is an age-related decline in creatinine clearance in many elderly persons because muscle mass and the GFR decline with age. A normal serum creatinine level usually indicates normal renal function. In addition to its use in calculating the GFR, the serum creatinine level is used in estimating the functional capacity of the kidneys (Fig. 24-13). If the value doubles, the

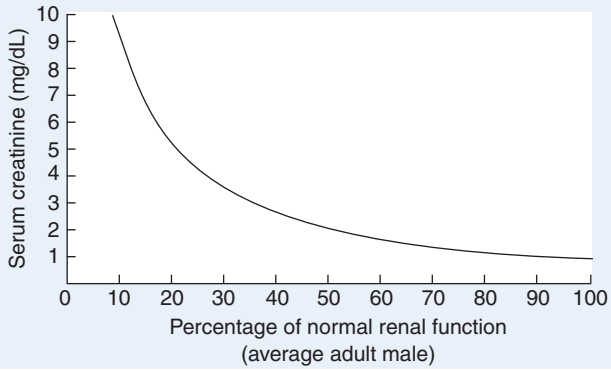


FIGURE 24-13. Relation between the percentage of renal function and serum creatinine levels.

GFR—and renal function—probably has fallen to one half of its normal state. A rise in the serum creatinine level to three times its normal value suggests that there is a 75% loss of renal function, and with creatinine values of 10 mg/dL or more, it can be assumed that approximately 90% of renal function has been lost.

Recently it has been proposed that another serum protein, *cystatin C* (a cysteine protease inhibitor), could be useful as a marker of GFR because it has a stable production rate, is freely filtered at the glomerulus, and in several studies has shown a greater sensitivity in detecting a decreased GFR. Further clinical studies are needed to determine the clinical efficacy of cystatin C as a marker and to determine whether there is an advantage to its use compared with creatinine.

Blood Urea Nitrogen

Urea is formed in the liver as a by-product of protein metabolism and is eliminated entirely by the kidneys. BUN therefore is related to the GFR but, unlike creatinine, also is influenced by protein intake, gastrointestinal bleeding, and hydration status. In gastrointestinal bleeding, the blood is broken down by the intestinal flora, and the nitrogenous waste is absorbed into the portal vein and transported to the liver, where it is converted to urea. During dehydration, elevated BUN levels result from increased concentration. Approximately two thirds of renal function must be lost before a significant rise in the BUN level occurs.

The BUN is less specific for renal insufficiency than creatinine, but the *BUN–creatinine ratio* may provide useful diagnostic information. The ratio normally is approximately 10:1. Ratios greater than 15:1 represent prerenal conditions, such as congestive heart failure and upper gastrointestinal tract bleeding, that produce an increase in BUN but not in creatinine. A ratio of less than 10:1 occurs in persons with liver disease and in those who receive a low-protein diet or chronic dialysis, because BUN is more readily dialyzable than creatinine.

In summary, urinalysis and blood tests that measure serum levels of pH, electrolytes, and by-products of metabolism provide valuable information about renal function. Urine specific gravity is used to assess the kidneys' ability to concentrate urine. Dipstick and 24-hour urine tests for proteinuria and microalbuminuria are used to detect abnormal filtering of albumin in the glomeruli or defects in its reabsorption in the renal tubules. Creatinine is a product of creatine metabolism in muscles that is freely filtered in the glomeruli and neither reabsorbed nor secreted in the tubules; therefore, serum creatinine levels are commonly used to estimate the GFR. Urea is formed in the liver as a by-product of protein metabolism and is eliminated entirely by the kidneys. BUN is therefore related to the GFR but, unlike creatinine, also is influenced by protein intake, gastrointestinal bleeding, and hydration status.

REVIEW EXERCISES

1. A 32-year-old woman with diabetes is found to have a positive result on a urine dipstick test for microalbuminuria. A subsequent 24-hour urine specimen reveals an albumin excretion of 50 mg (an albumin excretion >30 mg/day is abnormal).

A. Use the structures of the glomerulus in Figure 24-5 to provide a possible explanation for this finding. Why specifically test for the albumin rather than the globulins or other plasma proteins?

B. Strict control of blood sugars and treatment of hypertension have been shown to decrease the progression of kidney disease in persons with diabetes. Explain the physiologic rationale for these two types of treatments.

2. A 10-year-old boy with bed-wetting was placed on an ADH nasal spray at bedtime as a means of treating the disorder.

A. Explain the rationale for using ADH to treat bed-wetting.

3. A 54-year-old man, seen by his physician for an elevated blood pressure, was found to have a serum creatinine of 2.5. He complains that he has been urinating more frequently than usual and his first morning urine specimen reveals a dilute urine with a specific gravity of 1.010.

A. Explain the elevation of serum creatinine in terms of renal function.

B. Explain the inability of persons with early renal failure to produce a concentrated urine as evidenced by the frequency of urination and the low specific gravity of his first morning urine specimen.

BIBLIOGRAPHY

Berne R.M., Levy M.N. (2004). *Physiology* (3rd ed., pp. 408–432). Philadelphia: C.V. Mosby.

Ganong W.F. (2005). *Review of medical physiology* (22nd ed., pp. 699–730). New York: Lange Medical Books/McGraw-Hill.

Gartner L.P., Hiatt J.L. (2007). *Color textbook of histology* (3rd ed., pp. 437–458). Philadelphia: Saunders Elsevier.

Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 307–382). Philadelphia: Elsevier Saunders.

Junqueira L.C., Carneiro J. (2005). *Basic histology* (11th ed., pp. 373–391). New York: McGraw-Hill.

Koeppen B.M., Stanton B.A. (1997). *Renal physiology* (2nd ed.). St. Louis: C.V. Mosby.

Laterza O.F., Price C.P., Scott M.G. (2002). Cystatin C: An improved estimator of glomerular filtration rate. *Clinical Chemistry* 48, 699–707.

Price C.P., Finney H. (2000). Developments in the assessment of glomerular filtration rate. *Clinica Chimica Acta* 297, 55–66.

Rahn K.H., Heidenreich S., Bruckner D. (1999). How to assess glomerular function and damage in humans. *Journal of Hypertension* 17, 309–317.
Rhoades R.A., Tanner G.A. (2003). *Medical physiology* (2nd ed., pp. 377–402). Boston: Little, Brown.
Ross G.I., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 646–669). Philadelphia: Lippincott Williams & Wilkins.
Schrier R.W. (2003). *Renal and electrolyte disorders* (6th ed.). Philadelphia: Lippincott Williams & Wilkins.
Smith H. (1953). *From fish to philosopher* (p. 4). Boston: Little, Brown.
Stevens L.A., Levey A.S. (2005). Measurement of kidney function. *Medical Clinics of North America* 89, 457–473.
Thomson S.C., Vallon V., Blantz R.C. (2004). Kidney function in early diabetes: The tubular hypothesis of glomerular filtration. *American Journal of Physiology: Renal Physiology* 286, F8–F15.
Vallon V. (2003). Tubuloglomerular feedback and the control of glomerular filtration rate. *News in Physiological Sciences* 18, 169–174.
Vander A.J. (1995). *Renal physiology* (5th ed.). New York: McGraw-Hill.

Disorders of Glomerular Function
Etiology and Pathogenesis of Glomerular Injury
Types of Glomerular Disease
Acute Nephritic Syndrome
Rapidly Progressive Glomerulonephritis
Nephrotic Syndrome
Asymptomatic Hematuria or Proteinuria
Chronic Glomerulonephritis
Glomerular Lesions Associated with Systemic Disease
Tubulointerstitial Disorders
Pyelonephritis
Acute Pyelonephritis
Chronic Pyelonephritis
Drug-Related Nephropathies
Cystic Diseases of the Kidney
Polycystic Kidney Disease
Autosomal Dominant Polycystic Kidney Disease
Autosomal Recessive Polycystic Kidney Disease
Nephronophthisis–Medullary Cystic Disease Complex
Simple and Acquired Renal Cysts
Obstructive Disorders
Mechanisms of Renal Damage
Hydronephrosis
Clinical Features
Renal Calculi
Types of Stones
Clinical Features
Malignant Tumors of the Kidney
Wilms Tumor
Renal Cell Carcinoma

Chapter 25

Disorders of Renal Function

Diseases of the kidney and urologic tract can strike anyone at any age. Some of these diseases are progressive, eventually leading to chronic kidney disease and the need for dialysis or transplantation. The kidneys filter blood from all parts of the body, and although many forms of kidney disease originate in the kidneys, others develop secondary to disorders such as hypertension, diabetes mellitus, and systemic lupus erythematosus (SLE). As a major cause of work loss, physicians' visits, and hospitalizations, kidney diseases remain among the most costly illnesses throughout the industrial countries of the world.

The content in this chapter focuses on disorders of glomerular function, tubulointerstitial disorders, cystic diseases, obstructive disorders, and malignant neoplasms. Acute renal injury and failure and chronic kidney disease are discussed in Chapter 26, and disorders that predominantly affect the lower urinary tract and bladder are discussed in Chapter 27.

Disorders of Glomerular Function

The glomeruli are tufts of capillaries that lie between the afferent and efferent arterioles. The capillaries of the glomeruli are arranged in lobules and supported by a stalk consisting of mesangial cells and a basement membrane–like mesangial matrix (Fig. 25-1A). The glomerular capillary membrane is composed of three structural layers: an endothelial cell layer that lines the inner surface of the capillary, a basement membrane made up of a network of matrix proteins, and a layer of epithelial cells that surrounds the outer surface of the capillary and lines the inner surface of the Bowman capsule (see Chapter 24, Fig. 24-5). The epithelial cells are attached to the basement membrane by long, footlike processes (*podocytes*) that encircle the outer surface of the capillaries. The glomerular capillary membrane is selectively permeable, allowing water and small particles (e.g., electrolytes and dissolved particles, such as glucose and amino acids) to leave the blood and enter the Bowman space while preventing larger particles (e.g., plasma proteins and blood cells) from leaving the blood.

Glomerulonephritis, an inflammatory process that involves glomerular structures, is the second leading

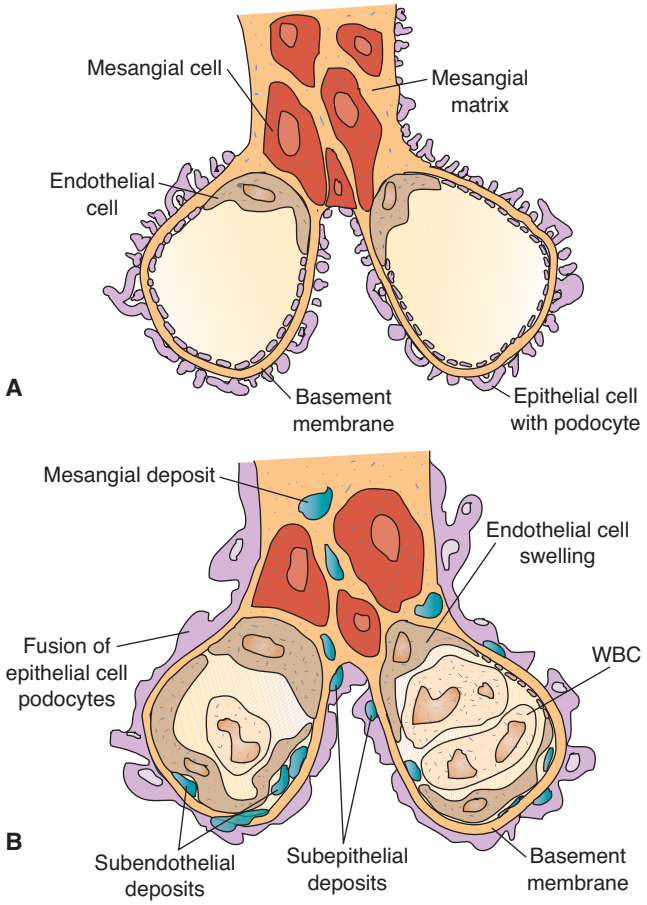


FIGURE 25-1. Schematic representations of a glomerulus. **(A)** Normal. **(B)** Localization of immune deposits (mesangial, subendothelial, subepithelial) and changes in glomerular architecture associated with injury. WBC, white blood cell. (From Whitley K., Keane W.F., Vernier R.L. [1984]. Acute glomerulonephritis: A clinical overview. *Medical Clinics of North America* 68, 263.)

cause of kidney failure worldwide, and it ranks third, after diabetes and hypertension, as a cause of chronic kidney disease in the United States and Canada.[1,2] There are many causes of glomerular disease. The disease may occur as a primary condition in which the glomerular abnormality is the only disease present, or it may occur as a secondary condition in which the glomerular abnormality results from another disease, such as diabetes mellitus or SLE.

Etiology and Pathogenesis of Glomerular Injury

The causative agents or triggering events that produce glomerular injury include immunologic, nonimmunologic, and hereditary mechanisms.[3–11] Most cases of primary and many cases of secondary glomerular disease probably have an immune origin. Although many glomerular diseases are driven by immunologic events, a variety of nonimmunologic metabolic (e.g., diabetes), hemodynamic (e.g., hypertension), and toxic (e.g., drugs, chemicals) stresses can induce glomerular injury, either alone or in concert with immunologic mechanisms. Hereditary glomerular diseases such as Alport syndrome, although relatively rare, are an important category of glomerular disease because of their association with progressive loss of renal function and transmission to future generations.

Two types of immune mechanisms have been implicated in the development of glomerular disease: (1) injury resulting from antibodies reacting with fixed glomerular antigens or antigens planted within the glomerulus and (2) injury resulting from circulating antigen–antibody complexes that become trapped in the glomerular membrane (Fig. 25-2). Antigens responsible for development of the immune response may be of endogenous origin, such as autoantibodies to deoxyribonucleic acid (DNA) in SLE, or they may be of exogenous origin, such as streptococcal membrane antigens in poststreptococcal glomerulonephritis. Frequently, the source of the antigen is unknown.

Glomerular diseases have traditionally been named according to tissue appearance (i.e., proliferative, membranous, or sclerotic) rather than according to the underlying cause.[6] Accordingly, the term *proliferative* is used to describe a hypercellular inflammatory process involving infiltrating leukocytes or white blood cells and proliferation of glomerular cells; *membranous,* an abnormal

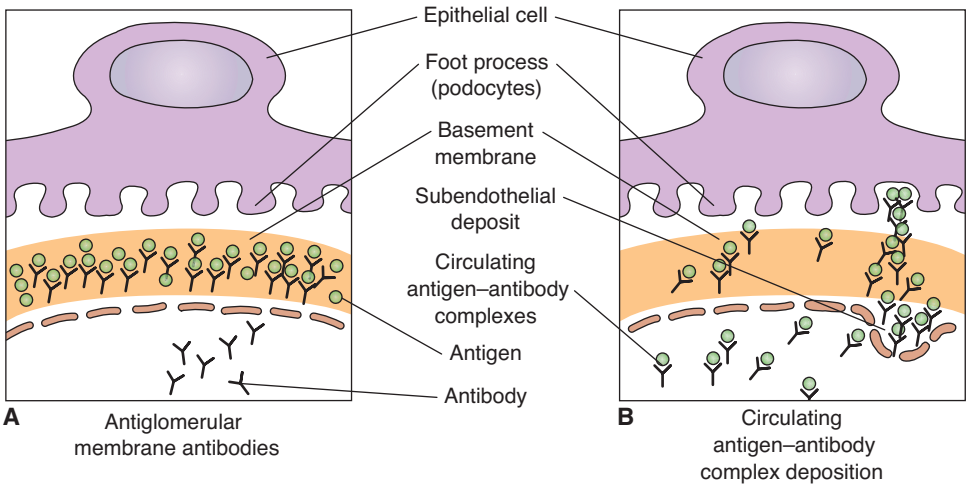


FIGURE 25-2. Immune mechanisms of glomerular disease. **(A)** Antiglomerular membrane antibodies leave the circulation and interact with antigens that are present in the basement membrane of the glomerulus. **(B)** Antigen–antibody complexes circulating in the blood become trapped as they are filtered in the glomerulus.

thickening of the glomerular basement membrane; and *sclerosis,* an increase in the amount of extracellular material in the mesangial, subendothelial, or subepithelial tissue of the glomerulus.[3–7] Glomerular changes can be *diffuse,* involving all glomeruli and all parts of the glomeruli; *focal,* in which only some glomeruli are affected and others are essentially normal; *segmental,* involving only a certain segment of each glomerulus; or *mesangial,* affecting only mesangial cells. Figure 25-1B illustrates the location of lesions associated with various types of glomerular disease.

Types of Glomerular Disease

The clinical manifestations of glomerular disorders generally fall into one of five categories: acute nephritic syndromes, rapidly progressive glomerulonephritis, nephrotic syndrome, asymptomatic disorders of urinary sediment (i.e., hematuria, proteinuria), and chronic glomerulonephritis[3,4] (Table 25-1). The nephritic syndromes produce a proliferative inflammatory response, whereas the nephrotic syndrome produces increased permeability of the glomerulus. Because most glomerular disorders can produce mixed nephritic and nephrotic syndromes, a definitive diagnosis often requires renal biopsy.

Acute Nephritic Syndrome

The acute nephritic syndrome is the clinical correlate of acute proliferative inflammation that occludes the glomerular capillary lumen and damages the capillary wall. It may occur as a renal-limited primary disorder, such as acute postinfectious glomerulonephritis, or as a secondary complicating disorder in systemic diseases, such as SLE. In its most dramatic form, the acute nephritic syndrome is characterized by sudden onset of hematuria (either microscopic or grossly visible, with red cell casts), variable degrees of proteinuria, diminished glomerular filtration rate (GFR), oliguria, and signs of impaired renal function. Extracellular fluid accumulation, edema, and hypertension develop because of the decreased GFR and enhanced tubular reabsorption of salt and water.

Acute Postinfectious Glomerulonephritis. Acute postinfectious glomerulonephritis usually occurs after infection with certain strains of group A β-hemolytic streptococci and is caused by deposition of immune complexes.[4–8,12] It also may occur after infections by other organisms, including staphylococci and a number of viral agents, such as those responsible for mumps, measles, and chickenpox. This type of glomerular disease is now rare in industrialized nations, but continues to be a common disorder in the underprivileged populations of the world.[12] Although the disease is seen primarily in children, persons of any age can be affected.

Glomerular Disorders

- Glomerular disorders affect the semipermeable properties of the glomerular capillary membrane that allow water and small particles to move from the blood into the urine filtrate, while preventing blood cells and plasma proteins from leaving the circulation.
- The nephritic syndromes produce a decrease in glomerular permeability and manifestations related to a decrease in glomerular filtration rate, fluid retention, and nitrogenous waste accumulation.
- The nephrotic syndrome produces an increase in glomerular permeability and manifestations of altered body function related to a massive loss of plasma proteins in the urine.

TABLE 25-1 Classification and Manifestations of Glomerular Syndromes

Classification	Manifestations
Acute nephritic syndrome	Recent onset of hematuria and proteinuria, impairment of kidney function (azotemia), and salt and water retention causing edema and hypertension
Rapidly progressive glomerulonephritis	Progression of renal failure over days to weeks, in most cases in the context of nephritic presentation, typically associated with pathologic finding of extensive glomerular crescent formation on renal biopsy
Nephrotic syndrome	Nephrotic-range proteinuria (>3.5 g/day in adults), hypoalbuminemia, hyperlipidemia, and lipiduria
Asymptomatic hematuria or proteinuria	Subnephrotic-range proteinuria, or hematuria, not accompanied by acute manifestations of impaired kidney function, edema, or hypertension
Chronic glomerulonephritis	Persistent proteinuria with or without hematuria and slowly progressive impairment of kidney function

Data from Chadban S.J., Atkins R.C. (2005). Glomerulonephritis. Lancet 365, 1797–1806; Kumar V., Abbas A.K., Fausto N. (2005). *Robbins and Cotran pathologic basis of disease* (7th ed., pp. 961–966, 971–979). Philadelphia: Elsevier Saunders; and Jennette J.C. (2008). The kidney. In Rubin R., Strayer D. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., p. 698). Philadelphia: Lippincott Williams & Wilkins.

The acute phase of postinfectious glomerulonephritis is characterized by diffuse glomerular enlargement and hypercellularity. The hypercellularity is caused by infiltration of leukocytes, both neutrophils and monocytes; proliferation of endothelial and mesangial cells; and in severe cases, formation of crescents (collections of proliferating epithelial cells and infiltrating leukocytes shaped like half-moons) in the Bowman space. There is also swelling of endothelial cells. The combination of proliferation, swelling, and leukocyte infiltration obliterates the glomerular capillary lumens. There may be interstitial edema and inflammation, and the tubules often contain red blood cells. In the first weeks of the disease, immunofluorescence microscopy typically reveals granular deposits of immunoglobulin G (IgG) and the complement component C3 in the mesangium and along the basement membrane (Fig. 25-3).

The classic case of poststreptococcal glomerulonephritis follows a streptococcal infection by approximately 7 to 12 days—the time needed for the development of antibodies. The primary infection usually involves the pharynx (pharyngitis), but can also result from a skin infection (impetigo). Oliguria, which develops as the GFR decreases, is one of the first symptoms. Proteinuria and hematuria follow because of increased glomerular capillary wall permeability. The red blood cells are degraded by materials in the urine, and cola-colored urine may be the first sign of the disorder. Sodium and water retention gives rise to edema (particularly of the face and hands) and hypertension. Important laboratory findings include an elevated antistreptococcal antibody (ASO) titer, a decline in serum concentrations of C3 and other components of the complement cascade, and cryoglobulins (i.e., large immune complexes) in the serum.

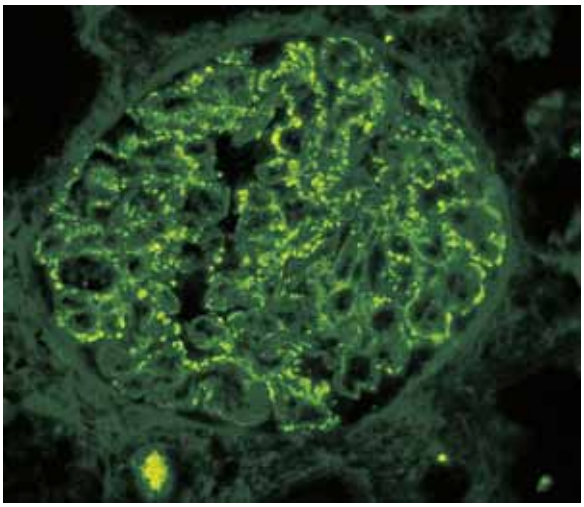


FIGURE 25-3. Acute postinfectious glomerulonephritis. An immunofluorescence micrograph demonstrates granular staining for complement C3 in capillary walls and the mesangium. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 713]. Philadelphia: Lippincott Williams & Wilkins.)

Treatment of acute poststreptococcal glomerulonephritis includes eliminating the streptococcal infection with antibiotics and providing supportive care. The disorder carries an excellent prognosis and rarely causes chronic kidney disease.[7] In children, spontaneous resolution of the glomerular lesion and nephritic syndrome is usually the norm and occurs within 6 to 8 weeks. Adults tend to recover more slowly, often with some degree of persistent azotemia that may, in some cases, progress to chronic kidney disease.

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis is a clinical syndrome characterized by signs of severe glomerular injury that does not have a specific cause. As its name indicates, this type of glomerulonephritis is rapidly progressive, often within a matter of months. The disorder involves focal and segmental proliferation of glomerular cells and recruitment of monocytes and macrophages with the formation of crescent structures that obliterate the Bowman space.[3–5] Rapidly proliferative glomerulonephritis may be caused by a number of immunologic disorders, some systemic and others restricted to the kidney. Among the diseases associated with this form of glomerulonephritis are immune complex disorders such as SLE, small vessel vasculitides (e.g., microscopic polyangiitis), and an immune disorder called *Goodpasture syndrome*.

Goodpasture Syndrome. Goodpasture syndrome is an uncommon and aggressive form of glomerulonephritis that is caused by antibodies to the glomerular basement membrane (GBM). The anti–glomerular membrane (anti-GBM) antibodies cross-react with the pulmonary alveolar basement membrane to produce the syndrome of pulmonary hemorrhage associated with renal failure. The pathologic hallmark of anti-GBM glomerulonephritis is diffuse linear staining of glomerular basement membranes for IgG (Fig. 25-4). The cause of the disorder is unknown, although influenza infection and exposure to hydrocarbon solvent (found in paints and dyes) have been implicated in some persons, as have various drugs and cancers. There is a high prevalence of certain human leukocyte antigen subtypes (e.g., HLA-DRB1) in those affected, suggesting a genetic predisposition.[4] Treatment includes plasmapheresis to remove circulating anti-GBM antibodies and immunosuppressive therapy (i.e., corticosteroids and cyclophosphamide) to inhibit antibody production.

Nephrotic Syndrome

The nephrotic syndrome is characterized by massive proteinuria (≥3.5 g/day in adults) and lipiduria (e.g., free fat, oval bodies, fatty casts), along with an associated hypoalbuminemia (<3 g/dL), generalized edema, and hyperlipidemia.[4,5,13,14] The nephrotic syndrome is not a specific glomerular disease, but a constellation of clinical findings that result from an increase in glomerular permeability and loss of plasma proteins in the urine[13,14] (Fig. 25-5).

The glomerular membrane acts as a size-specific barrier through which the glomerular filtrate must pass. An

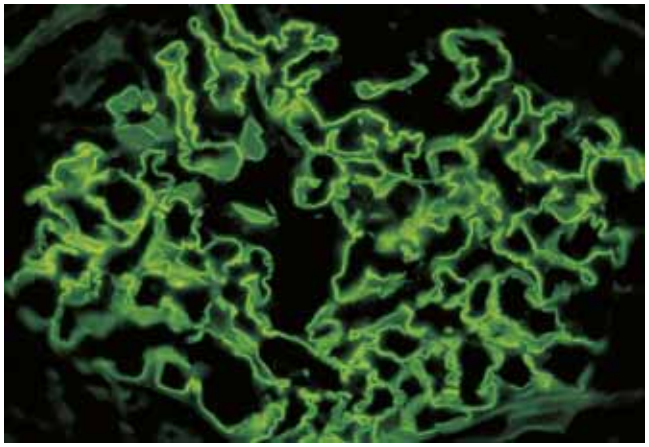


FIGURE 25-4. Anti–glomerular basement membrane glomerulonephritis. Linear immunofluorescence for IgG is seen along the glomerular basement membrane. Contrast this with the granular pattern of immunofluorescence typical of most types of immune complex deposition within the capillary wall. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 720]. Philadelphia: Lippincott Williams & Wilkins.)

increase in permeability allows proteins to escape from the plasma into the glomerular filtrate, often leading to an excessive loss of albumin—the smallest and most abundant of the plasma proteins. Generalized edema, which is a hallmark of the nephrotic syndrome, results from a decrease in the plasma colloidal osmotic pressure due to the hypoalbuminemia that develops as albumin is lost from the vascular compartment (see Chapter 8).[4,5]

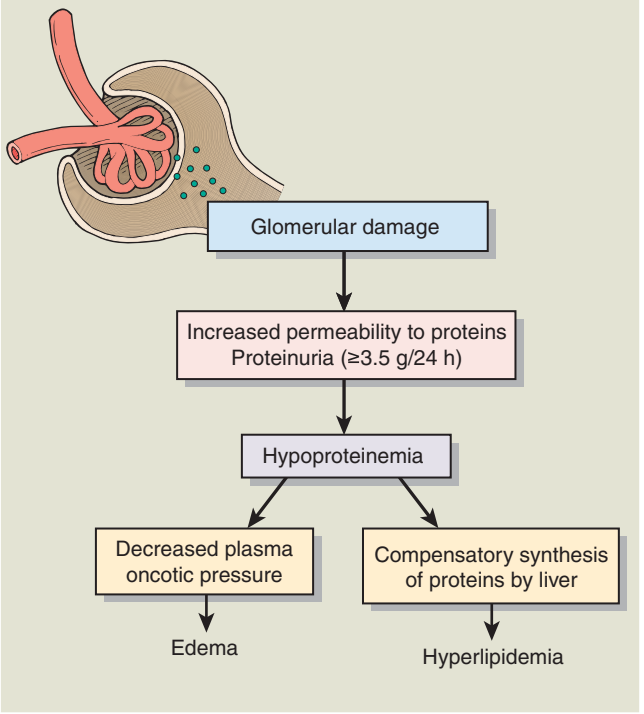


FIGURE 25-5. Pathophysiology of the nephrotic syndrome.

There is also salt and water retention, which aggravates the edema. This appears to be due to several factors, including a compensatory increase in aldosterone, stimulation of the sympathetic nervous system, and a reduction in the secretion of natriuretic factors. Initially, the edema presents in dependent parts of the body such as the lower extremities, but becomes more generalized as the disease progresses. Dyspnea due to pulmonary edema, pleural effusions, and diaphragmatic compromise due to ascites can develop in persons with nephrotic syndrome.

The hyperlipidemia that occurs in persons with nephrosis is characterized by elevated levels of triglycerides and low-density lipoproteins (LDLs). Levels of high-density lipoproteins (HDLs) usually are normal. It is thought that these abnormalities are related, at least in part, to increased synthesis of lipoproteins in the liver secondary to a compensatory increase in albumin production.[13] Because of the elevated LDL levels, persons with nephrotic syndrome are at increased risk for development of atherosclerosis.

The largest proportion of protein lost in the urine is albumin, but globulins also may be lost in some diseases. As a result, persons with nephrosis may be vulnerable to infections, particularly those caused by staphylococci and pneumococci.[4] This decreased resistance to infection probably is related to the loss of both immunoglobulins and low–molecular-weight complement components in the urine. Many binding proteins also are lost in the urine. Consequently, the plasma levels of many ions (iron, copper, zinc) and hormones (thyroid and sex hormones) may be low because of the decreased binding proteins. Many drugs require protein binding for transport. Hypoalbuminemia reduces the number of available protein-binding sites, thereby producing a potential increase in the amount of free (active) drug that is available.[14]

Persons with nephrotic syndrome are also at risk for thrombotic complications. These complications reflect a disruption in the function of the coagulation system brought about by a loss of coagulation and anticoagulation factors. Renal vein thrombosis, once thought to be a cause of the disorder, is more likely a consequence of the hypercoagulable state.[13] Other thrombotic complications include deep vein thrombosis and pulmonary emboli.

The glomerular derangements that occur with nephrosis can develop as a primary disorder or secondary to changes caused by systemic diseases such as diabetes mellitus and SLE.[4,5] Among the primary glomerular lesions leading to nephrotic syndrome are minimal-change disease (lipoid nephrosis), focal segmental glomerulosclerosis, and membranous glomerulonephritis. The relative frequency of these causes varies with age. In children younger than 15 years of age, nephrotic syndrome almost always is caused by primary idiopathic glomerular disease, whereas in adults, it often is a secondary disorder.[4,14]

Minimal-Change Disease (Lipoid Nephrosis). Minimal-change disease is characterized by diffuse loss (through fusion) of the foot processes of cells in the epithelial layer of the glomerular membrane. It is most commonly seen in children (peak incidence at 2 to 6 years of age),[4] but may occasionally occur in adults. The cause of minimal-change

nephrosis is unknown; however, children in whom the disease develops often have a history of recent upper respiratory infections or of receiving routine childhood immunizations.[4] Although minimal-change disease does not usually progress to renal failure, it can cause significant complications, including predisposition to infection with gram-positive organisms, tendency toward thromboembolic events, hyperlipidemia, and protein malnutrition. The prognosis in children with the disorder is good; more than 90% respond to a short course of glucocorticoids. Adults also respond to corticosteroids, but the response is slower.[4,13]

Membranous Glomerulonephritis. Membranous glomerulonephritis is the most common cause of primary nephrosis in adults, often in the fifth and sixth decades of life and almost always after 30 years of age.[4,5] The disorder is caused by diffuse thickening of the glomerular basement membrane due to deposition of immune complexes. The disorder may be idiopathic or associated with a number of disorders, including autoimmune diseases such as SLE, infections such as chronic hepatitis B, metabolic disorders such as diabetes mellitus and thyroiditis, and use of certain drugs such as gold compounds, penicillamine, and captopril.[4] The presence of immunoglobulins and complement in the subendothelial deposits suggests that the disease represents a chronic immune complex–mediated disorder (see Chapter 16).

The disorder usually begins with an insidious onset of the nephrotic syndrome or, in a small percentage of patients, with nonnephrotic proteinuria. Hematuria and mild hypertension may be present. The progress of the disease is variable. The nephrotic syndrome remits spontaneously in about 40% of patients, another 30% to 40% have repeated relapses and remissions, and 10% to 20% suffer a slow, progressive decline in GFR that terminates in kidney failure.[9] Spontaneous remissions and a relatively benign outcome occur more commonly in women and those with proteinuria in the nonnephrotic range. Treatment is controversial. Because of the variable course of the disease, the overall effectiveness of corticosteroids and other immunosuppressive therapy in controlling the progress of the disease has been difficult to evaluate.[3,4]

Focal Segmental Glomerulosclerosis. Focal segmental glomerulosclerosis is characterized by sclerosis (i.e., increased collagen deposition) of some but not all glomeruli, and in the affected glomeruli, only a portion of the glomerular tuft is involved.[4] The disorder has increased in prevalence since the late 1980s so that it now accounts for as much as one third of cases of nephrotic syndrome in adults.[3] It is a particularly common cause of nephrotic syndrome in Hispanic and African Americans.

Although focal segmental sclerosis often is an idiopathic syndrome, it may be associated with reduced oxygen in the blood (e.g., sickle cell disease and cyanotic congenital heart disease), human immunodeficiency virus (HIV) infection, or intravenous drug abuse, or it may occur as a secondary event reflecting glomerular scarring due to other forms of glomerulonephritis or reflux nephropathy.[4,5]

The presence of hypertension and decreased renal function distinguishes focal sclerosis from minimal-change disease. The disorder usually is treated with corticosteroids. Most persons with the disorder progress to kidney failure within 5 to 10 years.

Asymptomatic Hematuria or Proteinuria

Many cases of glomerulonephritis result in mild asymptomatic illness that is not recognized or is brought to the attention of a health care professional during routine screening or physical examination for another purpose. Population-based screening studies have shown that kidney damage as evidenced by proteinuria and/or hematuria is present in 16% of persons in Australia and a similar proportion in the United States.[15] Disorders such as IgA nephropathy and Alport syndrome often present with asymptomatic hematuria and/or proteinuria.

Immunoglobulin A Nephropathy. Immunoglobulin A nephropathy (i.e., Berger disease) is a primary glomerulonephritis characterized by the presence of glomerular IgA immune complex deposits. It can occur at any age, but most commonly has its onset in the second and third decades of life.[16,17] The disease occurs more commonly in men than women and is the most common cause of glomerular nephritis in Asians.

The disorder is characterized by the deposition of IgA-containing immune complexes in the mesangium of the glomerulus. Once deposited in the kidney, the immune complexes are associated with glomerular inflammation. The cause of the disorder is unknown. Some persons with the disorder have elevated serum IgA levels. Recent studies have focused on potential abnormalities of the IgA molecule as a factor in the pathogenesis of the disorder.[16]

Early in the disease, many persons with the disorder have no obvious symptoms and are unaware of the problem. In these persons, IgA nephropathy is evidenced during routine screening or examination for another condition. In other persons, the disorder presents with gross hematuria that is preceded by upper respiratory tract infection, gastrointestinal tract symptoms, or a flu-like illness. The hematuria usually lasts 2 to 6 days. Approximately one half of the persons with gross hematuria have a single episode, whereas the remainder experience a gradual progression of the disease with recurrent episodes of hematuria and mild proteinuria. Progression usually is slow, extending over several decades.

Immunofluorescence microscopy is essential for diagnosis of IgA nephropathy.[5] The diagnostic finding is mesangial staining for IgA that is more intense than staining for IgG or IgM (Fig. 25-6). At present, there are no satisfactory treatment measures for IgA nephropathy. The role of immunosuppressive drugs such as steroids and cytotoxic drugs is not clear. There has been recent interest in the use of omega-3 fatty acids (i.e., fish oil) in delaying the progression of the disease. Randomized, clinical control studies have yielded conflicting results.

Alport Syndrome. Alport syndrome represents a hereditary defect of the glomerular basement membrane that

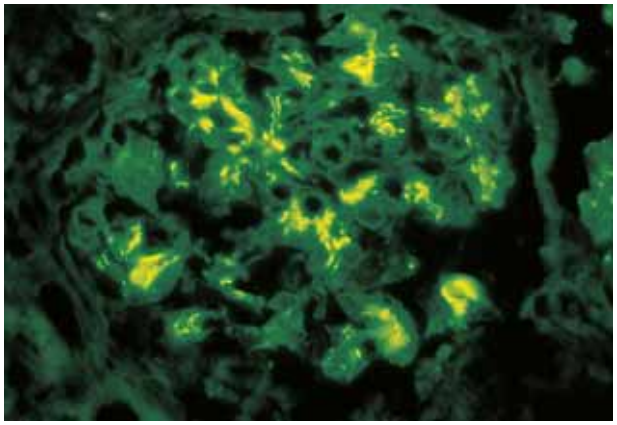


FIGURE 25-6. IgA nephropathy. An immunofluorescence micrograph shows deposits of IgA in the mesangial areas. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 718]. Philadelphia: Lippincott Williams & Wilkins.)

results in hematuria and may progress to chronic renal failure.[4,8] Approximately 80% of cases are inherited as an X-linked autosomal dominant trait, whereas others have autosomal dominant and recessive patterns of inheritance.[8] In X-linked pedigrees, boys are usually affected more seriously than girls. Affected boys usually progress to renal failure as adults, but progression may occur during adolescence. Although many girls never have more than mild hematuria with or without mild proteinuria, some have more significant disease and may even progress to kidney failure.

Diagnosis of Alport syndrome is often made after examination of the urine of a child from a family with multiple cases of hereditary nephritis. Children may initially present with heavy microscopic hematuria (large amount of blood on dipstick), followed by the development of proteinuria. Many, but not all, persons with Alport syndrome have sensorineural deafness and various eye disorders, including lens dislocation, posterior cataracts, and corneal dystrophy. The hearing loss is bilateral and often is first detected during adolescence.

Chronic Glomerulonephritis

Chronic glomerulonephritis represents the chronic phase of a number of specific types of glomerulonephritis.[4,5] Some forms of acute glomerulonephritis (e.g., poststreptococcal glomerulonephritis) undergo complete resolution, whereas others progress at variable rates to chronic glomerulonephritis. Some persons who present with chronic glomerulonephritis have no history of glomerular disease. These cases may represent the end result of relatively asymptomatic forms of glomerulonephritis. Histologically, the condition is characterized by small kidneys with sclerosed glomeruli. In most cases, chronic glomerulonephritis develops insidiously and slowly progresses to chronic kidney disease over a period of years (see Chapter 26).

Glomerular Lesions Associated with Systemic Disease

Many immunologic, metabolic, or hereditary systemic diseases are associated with glomerular injury. In some diseases, such as SLE, diabetes mellitus, and hypertension, the glomerular involvement may be a major clinical manifestation.

Systemic Lupus Erythematosus Glomerulonephritis. Renal involvement is one of the most common complications of SLE.[5,7–10] The pathogenesis of SLE (see Chapter 44) is uncertain, but appears to be related to dysregulated B-cell immunity with production of autoantibodies to a variety of nuclear, cytoplasmic, extracellular matrix, and cell membrane components. Most glomerular injury is triggered by the deposition of immune complexes within the glomerular wall. Immune complexes may derive from the circulation, develop locally, or both.

The clinical manifestations of lupus nephritis depend on the site of immune complex–mediated injury. Immune complexes confined to the mesangium cause less inflammation than subendothelial immune complexes, which have greater exposure to inflammatory cells and mediators in the blood, and which therefore are more likely to produce inflammation.[5,18] Immune complexes may also localize in the renal interstitium, walls of interstitial vessels, and basement membranes, causing the tubulointerstitial inflammation that occurs in persons with SLE.[5]

Because of the high risk for kidney disease, all persons with SLE should undergo routine urinalysis to monitor for the appearance of hematuria or proteinuria. If urinary abnormalities are noted, renal biopsy is often performed. Treatment depends on the extent of glomerular involvement. Oral corticosteroids and angiotensin-converting enzyme (ACE) inhibitors are the mainstays of treatment. Persons with more advanced disease may require treatment with immunosuppressive agents (e.g., intravenous cyclophosphamide or oral mycophenolate mofetil). Clinical trials using other immunosuppressant agents are ongoing.

Diabetic Glomerulosclerosis. Diabetic nephropathy is a major cause of chronic kidney disease and the most common cause of kidney failure treated by renal replacement therapy in the United States and Canada.[1,2,19–21] It occurs in both type 1 and type 2 diabetes mellitus.

The lesions of diabetic nephropathy most commonly involve the glomeruli and are associated with three glomerular syndromes: nonnephrotic proteinuria, nephrotic syndrome, and chronic renal failure.[4,5,19] Widespread thickening of the glomerular capillary basement membrane occurs in almost all persons with diabetes and can occur without evidence of proteinuria. This is followed by a diffuse increase in mesangial matrix, with mild proliferation of mesangial cells. As the disease progresses, the mesangial cells impinge on the capillary lumen, reducing the surface area for glomerular filtration. In nodular glomerulosclerosis, also known as *Kimmelstiel-Wilson syndrome,* there is nodular deposition of hyaline in the

mesangial portion of the glomerulus. As the sclerotic process progresses in the diffuse and nodular forms of glomerulosclerosis, there is complete obliteration of the glomerulus, with impairment of renal function.

Although the mechanisms of glomerular change in diabetes are uncertain, they are thought to represent enhanced or defective synthesis of the glomerular basement membrane and mesangial matrix with inappropriate incorporation of glucose into the noncellular components of these glomerular structures.[22] Alternatively, hemodynamic changes that occur secondary to elevated blood glucose levels may contribute to the initiation and progression of diabetic glomerulosclerosis.[4] It has been hypothesized that elevations in blood glucose produce an increase in GFR and glomerular pressure that leads to enlargement of glomerular capillary pores by a mechanism that is, at least partly, mediated by angiotensin II. This enlargement results in an increase in the protein content of the glomerular filtrate, which in turn requires increased endocytosis of the filtered proteins by tubular endothelial cells, a process that ultimately leads to nephron destruction and progressive deterioration of renal function.

The clinical manifestations of diabetic glomerulosclerosis are closely linked to those of diabetes. The increased GFR that occurs in persons with early alterations in renal function is associated with *microalbuminuria*, defined as urinary albumin excretion of 30 to 300 mg in 24 hours.[5] Microalbuminuria is an important predictor of future diabetic nephropathies.[4,19] In many cases, these early changes in glomerular function can be reversed by careful control of blood glucose levels (see Chapter 33). Inhibition of angiotensin by ACE inhibitors or angiotensin receptor blockers (ARBs) has been shown to have a beneficial effect, possibly by reversing increased glomerular pressure.[19] Hypertension and cigarette smoking have been implicated in the progression of diabetic nephropathy. Thus, control of blood pressure (to levels of 130/80 mm Hg or less) and smoking cessation are recommended as primary and secondary prevention strategies in persons with diabetes.

Hypertensive Glomerular Disease. Mild to moderate hypertension causes sclerotic changes in renal arterioles and small arteries, referred to as *benign nephrosclerosis*. The condition has been identified in approximately 15% of persons with benign hypertension[5] (see Chapter 18). It is most prevalent and most aggressive among blacks. In fact, among African Americans in the United States, hypertension is the leading cause of chronic kidney disease.[5]

Hypertensive nephropathy is associated with a number of changes in kidney structure and function. The kidneys are smaller than normal and are usually affected bilaterally.[5] On histologic examination, there is narrowing of the arterioles and small arteries, caused by thickening and hyalinization of the vessel walls. As the vascular structures thicken and perfusion diminishes, blood flow to the nephron decreases, causing patchy tubular atrophy, interstitial fibrosis, and a variety of changes in glomerular structure and function. Although uncomplicated hypertensive nephrosclerosis is not usually associated with significant abnormalities in renal function, a few persons may progress to chronic kidney disease.

In summary, diseases of the glomerulus disrupt glomerular filtration and alter the permeability of the glomerular capillary membrane to plasma proteins and blood cells. Glomerulonephritis is a term used to describe a group of diseases that result from inflammation and injury of the glomerulus. Glomerulonephritis may occur as a primary condition in which the glomerular abnormality is the only disease present, or it may occur as a secondary condition in which the glomerular abnormality results from another disease, such as diabetes mellitus or SLE. Most cases of primary and many cases of secondary glomerular disease probably have an immune origin.

The clinical manifestations of glomerular disorders generally fall into one of five categories: acute nephritic syndromes, rapidly progressive glomerulonephritis, nephrotic syndrome, asymptomatic disorders (i.e., hematuria, proteinuria), and chronic glomerulonephritis. The acute nephritic syndromes evoke an inflammatory response in the glomeruli and are characterized by hematuria with red cell casts in the urine, diminished GFR, azotemia, oliguria, and hypertension. The nephrotic syndrome affects the integrity of the glomerular capillary membrane and is characterized by massive proteinuria, hypoalbuminemia, generalized edema, lipiduria, and hyperlipidemia. Rapidly progressive, often within months, glomerulonephritis is a clinical syndrome of acute glomerular injury that does not have a specific cause. Asymptomatic hematuria and proteinuria represent glomerular disorders that are not recognized or brought to the attention of a health care professional, and therefore remain undiagnosed. Chronic glomerulonephritis represents the chronic phase of a number of specific types of glomerulonephritis. Secondary causes of glomerular kidney disease include systemic lupus erythematosus, diabetes mellitus, and hypertension.

Tubulointerstitial Disorders

Several disorders affect renal tubular structures, including the proximal and distal tubules. Most of these disorders also affect the interstitial tissue that surrounds the tubules. These disorders, sometimes referred to as *tubulointerstitial disorders*, include acute tubular necrosis (see Chapter 26), acute and chronic pyelonephritis, and the effects of drugs and toxins.

Tubulointerstitial renal diseases may be divided into acute and chronic disorders. The acute disorders are characterized by their sudden onset and by signs and symptoms of interstitial edema; they include acute pyelonephritis and acute hypersensitivity reaction to drugs. The chronic

disorders produce interstitial fibrosis, atrophy, and mononuclear infiltrates; most persons are asymptomatic until late in the course of the disease. In the early stages, tubulointerstitial diseases commonly are manifested by fluid and electrolyte imbalances that reflect subtle changes in tubular function. These manifestations can include inability to concentrate urine, as evidenced by polyuria and nocturia; interference with acidification of urine, resulting in metabolic acidosis; and diminished tubular reabsorption of sodium and other substances.[4]

Pyelonephritis

Pyelonephritis refers to infection of the kidney parenchyma and renal pelvis. There are two forms of pyelonephritis: acute and chronic. Chronic pyelonephritis is a more complex disorder involving not only bacterial infection but also other factors such as reflux.

Acute Pyelonephritis

Acute pyelonephritis represents a bacterial infection of the upper urinary tract, specifically the kidney parenchyma and the renal pelvis.[23] Gram-negative bacteria, including *Escherichia coli* and *Proteus, Klebsiella, Enterobacter,* and *Pseudomonas* species, are the most common causative agents. *Staphylococcus* species and *Streptococcus faecalis* may also cause pyelonephritis, but they are uncommon. There are two routes by which bacteria can gain access to the kidney: from the lower urinary tract (ascending infection) and through the bloodstream (hematogenous spread). Ascending infection from the lower urinary tract is the most important and common route by which bacteria reach the kidney.

Ascending infection reaches the kidney through the bladder, a process that requires a bacterial urinary tract infection, reflux of urine up the ureters into the renal pelvis and calyces, and bacterial entry into the renal parenchyma. Factors that contribute to the development of ascending infections are outflow obstruction, catheterization and urinary instrumentation, vesicoureteral reflux, pregnancy, and neurogenic bladder. Although outflow obstruction is an important predisposing factor in the pathogenesis of ascending infection, it is incompetence of the vesicoureteral orifice that allows bacteria to ascend the ureter into the renal pelvis. The normal ureteral insertion into the bladder is a competent one-way valve that prevents the retrograde flow of urine, especially during micturition. The ureter commonly inserts into the bladder at a steep angle and in its most distal portion courses parallel to the bladder wall, forming a mucosal flap (Fig. 25-7A). The flap is compressed against the bladder wall during micturition, preventing urine from being forced into the ureter. In persons with vesicoureteral reflux, the ureter enters the bladder at an approximate right angle such that urine is forced into the ureter during micturition (Fig. 25-7B). It is seen most commonly in children with urinary tract infections (UTIs) and is believed to result from congenital defects in length, diameter, muscle structure, or innervation of the submucosal segment of the ureter. Vesicoureteral reflux

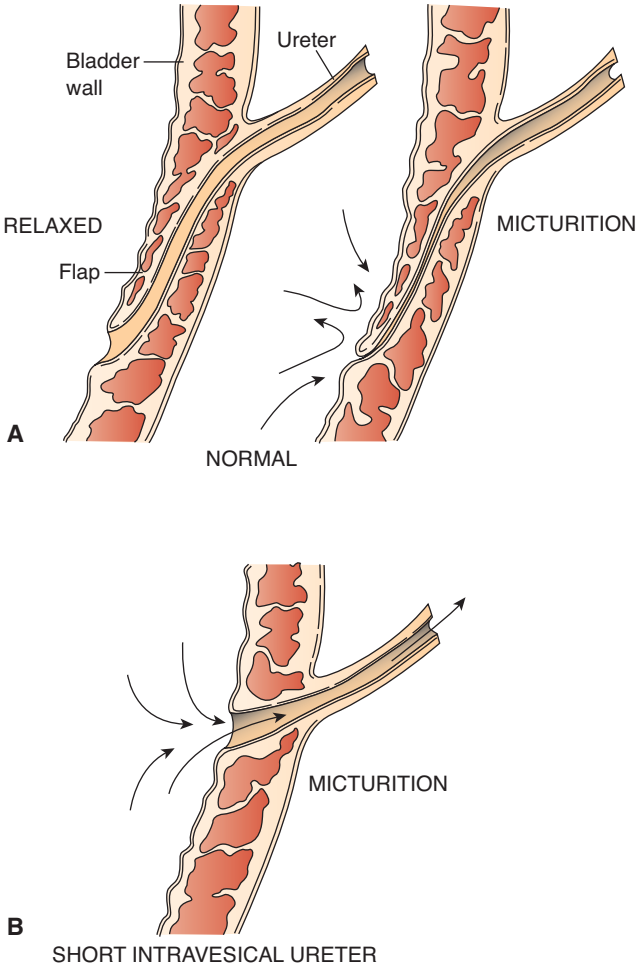


FIGURE 25-7. Anatomic features of the ureter and bladder and their relationship to vesicoureteral reflux. **(A)** In the normal bladder, the distal portion of the intravesical ureter courses between the mucosa and the muscularis of the bladder. A mucosal flap is thus formed. On micturition, the elevated intravesicular pressure compresses the flap against the bladder wall, thereby occluding the lumen. **(B)** Persons with a congenitally short intravesical ureter have no mucosal flap because the entry of the ureter into the bladder approaches a right angle. Thus, micturition forces urine into the ureter. (Adapted from Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 732]. Philadelphia: Lippincott Williams & Wilkins; Courtesy of Dmitri Karetnikov, artist.)

can also occur in persons with flaccid bladder due to spinal cord injury and with neurogenic bladder dysfunction secondary to diabetes mellitus.

Although hematogenous spread is far less common, acute pyelonephritis can result from seeding of the kidney in the course of septicemia or infective endocarditis. It occurs most often in debilitated, chronically ill persons and those receiving immunosuppressive therapy. Immunosuppression favors the development of subclinical (silent) pyelonephritis and infections caused by nonenteric, aerobic, gram-negative rods and *Candida*. Metastatic staphylococcal or fungal infections may spread to the kidney from distant foci in the skin or bone.

The onset of acute pyelonephritis is usually abrupt, with shaking chills, moderate to high fever, and a constant ache in the loin area of the back that is unilateral or bilateral.[23] Lower urinary tract symptoms, including dysuria, frequency, and urgency, also are common (see Chapter 27). There may be significant malaise, and the person usually looks and feels ill. Nausea and vomiting may occur along with abdominal pain. Palpation or percussion over the costovertebral angle on the affected side usually causes pain. Pyuria occurs but is not diagnostic because it also occurs in lower UTIs.

A second and infrequent form of acute pyelonephritis is characterized by ischemia and a condition known as *papillary necrosis*, the suppurative necrosis of one or several renal pyramids. It occurs most commonly in persons with diabetes mellitus who develop acute pyelonephritis and may also complicate acute pyelonephritis when there is significant urinary tract obstruction. The development of papillary necrosis is associated with a much poorer prognosis. These persons have evidence of overwhelming sepsis with frequent development of renal failure.

Acute pyelonephritis is treated with appropriate antimicrobial drugs. Unless obstruction or other complications occur, the symptoms usually disappear within several days. Treatment with an appropriate antimicrobial agent usually is continued for 10 to 14 days. Persons with complicated acute pyelonephritis and those who do not respond to outpatient treatment may require hospitalization.[23]

Chronic Pyelonephritis

Chronic pyelonephritis represents a progressive process. There is scarring and deformation of the renal calyces and pelvis, along with atrophy and thinning of the overlying cortex[4,5] (Fig. 25-8). The disorder involves a recurrent or persistent bacterial infection superimposed on urinary tract obstruction, urine reflux, or both. Chronic obstructive pyelonephritis can be bilateral, caused by conditions that obstruct bladder outflow, or unilateral, such as occurs with ureteral obstruction. Reflux, which is the most common cause of chronic pyelonephritis, results from superimposition of infection on congenital vesicoureteral reflux or intrarenal reflux. Reflux may be unilateral with involvement of a single kidney or bilateral, leading to scarring and atrophy of both kidneys.

The symptoms of chronic pyelonephritis may be similar to those of acute pyelonephritis, or its onset may be insidious. Often there is a history of recurrent episodes of UTI or acute pyelonephritis. Loss of tubular function and the ability to concentrate urine give rise to polyuria and nocturia, and mild proteinuria is common. Severe hypertension often is a contributing factor in the progress of the disease. Chronic pyelonephritis is a significant cause of chronic kidney disease.

Drug-Related Nephropathies

Drug-related nephropathies involve functional or structural changes in the kidneys that occur after exposure to a drug. Because of their large blood flow and high filtration pressure, the kidneys are exposed to any substance that is in the blood. The kidneys also are active in the metabolic transformation of drugs and therefore are exposed to a number of toxic metabolites. The tolerance to drugs varies with age and depends on renal function, state of hydration, blood pressure, and the pH of the urine. Elderly persons are particularly susceptible to kidney damage caused by drugs and toxins. The dangers of nephrotoxicity are increased when two or more drugs capable of producing kidney damage are given at the same time.

Drugs and toxic substances can damage the kidneys by causing a decrease in renal blood flow, obstructing

FIGURE 25-8. Chronic pyelonephritis. **(A)** The cortical surface contains many irregular depressed scars (reddish areas). **(B)** There is marked dilation of calyces caused by inflammatory destruction of papillae, with atrophy and scarring of the overlying cortex. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 734]. Philadelphia: Lippincott Williams & Wilkins.)

urine flow, directly damaging tubulointerstitial structures, or producing hypersensitivity reactions.[24,25] Some drugs, such as diuretics, high–molecular-weight radiocontrast media, the immunosuppressive drugs cyclosporine and tacrolimus, and the nonsteroidal anti-inflammatory drugs (NSAIDs), can cause acute prerenal failure by decreasing renal blood flow. Other drugs such as sulfonamides and vitamin C (due to oxalate crystals) can form crystals that cause kidney damage by obstructing urinary flow in the tubules.

Acute drug-related hypersensitivity reactions produce tubulointerstitial nephritis, with damage to the tubules and interstitium. This condition was observed initially in persons who were sensitive to the sulfonamide drugs; currently, it is observed most often with the use of methicillin and other synthetic antibiotics, and with the use of furosemide and the thiazide diuretics in persons sensitive to these drugs. The condition begins approximately 15 days (range, 2 to 40 days) after exposure to the drug.[4] At the onset, there is fever, eosinophilia, hematuria, mild proteinuria, and, in approximately one fourth of cases, a rash. In approximately 50% of cases, signs and symptoms of acute renal failure develop. Withdrawal of the drug commonly is followed by complete recovery, but there may be permanent damage in some persons, usually in older persons. Drug nephritis may not be recognized in its early stage because it is relatively uncommon.

Chronic analgesic nephritis, which is associated with analgesic abuse, causes tubulointerstitial nephritis with renal papillary necrosis.[24,25] When first observed, it was attributed to phenacetin, a then-common ingredient of over-the-counter medications containing aspirin, phenacetin, and caffeine. Although phenacetin is no longer contained in these preparations, it has been suggested that other ingredients, such as aspirin and acetaminophen, also may contribute to the disorder. Prostaglandins (particularly PGI_2 and PGE_2) are potent renal vasodilators that contribute to the regulation of renal blood flow. The deleterious effects of aspirin and the NSAIDs are thought to result from their ability to decrease prostaglandin synthesis and thus decrease renal blood flow. The susceptibility of the papillae to damage is believed to be related to the establishment of a renal gradient in which the papillary concentration of the drug is higher than in the cortex. How much analgesic it takes to impair renal function or produce papillary necrosis is unknown. Persons particularly at risk are the elderly because of age-related changes in renal function, individuals who are dehydrated or have a decrease in blood volume, and those with preexisting kidney disease or renal insufficiency.

Illicit drug use has also been implicated in a wide spectrum of kidney diseases.[25] For example, acute renal failure has been reported in persons presenting with acute cocaine intoxication. The cause is probably multifactorial and involves direct vasoconstriction, altered systemic hemodynamics, and myoglobin-induced renal failure. The chronic inhalation of solvents (e.g., glue, paint thinner), aerosols, gases, and nitrates has also been associated with a variety of toxic kidney effects, including acute and chronic renal failure. The tubular manifestations of solvent abuse probably result from the interference with intracellular metabolic processes involved in membrane transport.

In summary, tubulointerstitial diseases affect the tubules and the surrounding interstitium of the kidneys. These disorders include acute and chronic pyelonephritis and the effects of drugs and toxins. Pyelonephritis, or infection of the kidney and kidney pelvis, can occur as an acute or a chronic condition. Acute pyelonephritis typically is caused by ascending bladder infections or infections that come from the bloodstream; it usually is successfully treated with appropriate antimicrobial drugs. Chronic pyelonephritis is a progressive disease that produces scarring and deformation of the renal calyces and pelvis.

The susceptibility of the kidney to drug-induced damage reflects its significant exposure to administered medications leading to direct toxic injury, decreased renal blood flow, or hypersensitivity reactions. Some drugs, such as diuretics, high–molecular-weight radiocontrast media, the immunosuppressive drugs cyclosporine and tacrolimus, and the NSAIDs can cause acute prerenal failure by decreasing renal blood flow. Other drugs such as sulfonamides and vitamin C (due to oxalate crystals) can form crystals that cause kidney damage by obstructing urinary flow in the tubules. Illicit drug use has also been implicated in a wide spectrum of kidney diseases.

Cystic Diseases of the Kidney

Renal cysts are epithelium-lined cavities filled with fluid or semisolid material. The cysts may be single or multiple, can vary in size from microscopic to several centimeters in diameter, and can be symptomatic or asymptomatic. Although they may arise as a developmental abnormality or be acquired later in life, most forms are hereditary. Simple cysts are acquired cysts that develop in the kidney cortex as a consequence of aging, dialysis, or other conditions that affect tubular function. The inherited cystic kidney diseases, which are single-gene disorders and are inherited as mendelian traits, include autosomal dominant and recessive polycystic kidney disease and nephronophthisis–medullary cystic disease.

Polycystic Kidney Disease

Polycystic kidney diseases (PKDs) are a group of inherited kidney disorders characterized by fluid-filled sacs or segments that have their origin in the tubular structures of the kidney.[4,5,26–30] An emerging theme in the pathophysiology of the hereditary cystic diseases is that of an underlying defect in the cilia–centrosome complex of the epithelial cells.[30] Such deformities may interfere with fluid absorption or cellular maturation, resulting in cyst formation.[4] In the autosomal dominant form of polycystic kidney disease (ADPKD), cystic outpouchings are derived from every tubule segment and rapidly close off from the nephron (Fig. 25-9A). In the autosomal recessive form of polycystic kidney disease (ARPKD), small,

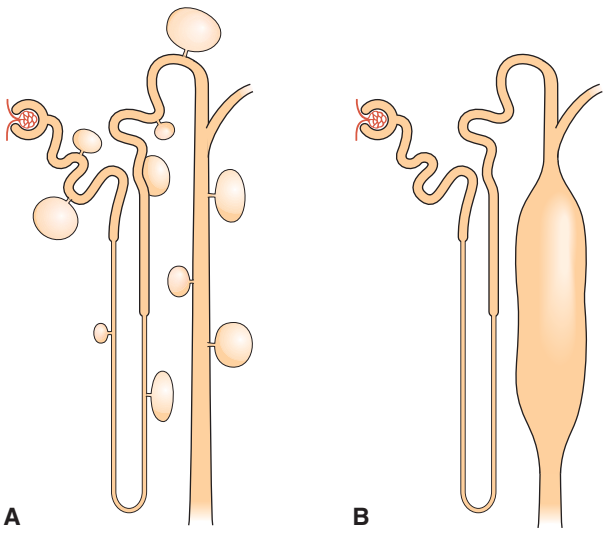


FIGURE 25-9. Mechanism of cyst formation in polycystic kidney disease. **(A)** In autosomal dominant polycystic kidney disease, cystic outpouchings arise in every tubule segment and rapidly close off the nephron of origin. **(B)** By contrast, in autosomal recessive polycystic kidney disease, cysts are derived from collecting tubules, which remain connected to the nephron of origin. (From Wilson P.D. [2004]. Polycystic kidney disease. *New England Journal of Medicine* 350, 155.)

elongated cysts form in the collecting ducts and maintain contact with the nephron of origin (see Fig. 25-9B).

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease, also known as *adult polycystic disease*, is the most common form of renal cystic disease. The disorder, which is inherited as an autosomal trait, results in the formation of destructive fluid-filled cysts in the kidney and other organs.[4,5,26–32] The disease accounts for 10% of all cases of chronic kidney disease that require dialysis or transplantation.

There are two types of ADPKD: type I, which is caused by mutations in the *PKD1* gene and accounts for 85% of cases, and type II, which is caused by mutations in the *PKD2* gene and accounts for most of the remaining 15% of cases.[4,5,26–29] Recent research has shown that the products of these genes, polycystin-1 and polycystin-2 protein, are found in the primary cilia that line the apical surface of the tubular epithelium. These primary cilia are thought to act as sensors of urinary flow and as signal transducers for tubular cell proliferation, differentiation, and apoptosis. Although the two mutations produce almost identical renal and extrarenal disease, disease progression is typically more rapid in people with type I disease.[4]

The link between the genetic defect in the polycystin proteins and the formation of fluid-filled cysts in the kidney has not been fully established. The polycystin molecule has regions of similarity with proteins involved in cell-to-cell matrix adhesion (e.g., domains that bind to components of the extracellular matrix). It also has several domains that bind to receptors that mediate cell proliferation, differentiation, and apoptosis. It is thought that the resultant defect in cell-to-cell matrix interactions may lead to alterations in proliferation, adhesion, differentiation, and matrix production by tubular epithelial cells and in cyst formation. Historically, it was thought that chronic kidney disease resulted from pressure exerted by expanding cysts on the normal surrounding kidney tissue. However, it is now appreciated that cysts arise in less than 2% of nephrons and that factors other than compression by the expanding cysts account for loss of functioning renal tissue.[5] Apoptotic loss of renal tubular cells and accumulation of inflammatory mediators are now thought to contribute to the destruction of normal kidney tissue.[4]

The kidneys are usually enlarged and may achieve enormous sizes (Fig. 25-10). The external contours of the kidneys are distorted by numerous cysts, some as large as 5 cm in diameter, filled with straw-colored fluid.[5] Cysts also may be found in the liver and, less commonly, the pancreas and spleen. Hepatic cysts, which occur in one third of persons with ADPKD, are generally asymptomatic and liver function is normal.[5] Many persons with polycystic disease also develop colonic diverticula. Cardiac abnormalities include mitral valve prolapse and other valvular heart diseases.[28] One of the most devastating extrarenal manifestations is a weakness in the walls of the cerebral arteries that can lead to aneurysm formation. Approximately 10% to 30% of persons with polycystic kidney disease have an associated aneurysm, and subarachnoid hemorrhage is a frequent cause of death.[4]

Clinical Features. The manifestations of ADPKD include pain from the enlarging cysts that may reach debilitating levels,[31] episodes of gross hematuria from bleeding into a cyst, infected cysts from ascending UTIs, and hypertension resulting from compression of intrarenal blood vessels with activation of the renin-angiotensin mechanism.[4,5] Renal colic caused by nephrolithiasis, or kidney stones, occurs in 15% to 20% of patients.[32] The progress

FIGURE 25-10. Gross pathology of polycystic kidneys. (From Centers for Disease Control and Prevention Public Images Library. [Online] Available: http://phil.cdc.gov/phil/details.asp.)

of the disease is slow, and chronic kidney disease is uncommon before 40 years of age.

Ultrasonography usually is the preferred technique for the diagnosis of ADPKD in symptomatic patients and for screening of asymptomatic family members. The ability to detect cysts increases with age; 80% to 90% of affected persons older than 20 years of age have cysts large enough to be detected by ultrasonography.[32] Computed tomography (CT) may be used for detection of small cysts. Genetic linkage studies are now available for diagnosis of ADPKD, but are usually reserved for cases in which radiographic imaging is negative and the need for a definitive diagnosis is essential, such as when screening family members for potential kidney donation.

The treatment of ADPKD is largely supportive and aimed at delaying progression of the disease. Control of hypertension and prevention of ascending UTIs are important. Pain is a common complaint of persons with ADPKD, and a systematic approach is needed to differentiate the etiology of the pain and define an approach for management.[31] Dialysis and kidney transplantation are reserved for those who progress to kidney failure.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease is characterized by cystic dilation of the cortical and medullary collecting tubules[4,5,26] (see Fig. 25-9B). It is rare compared with ADPKD, occurring in 1 to 20,000 live births.[4,26] ARPKD is caused by mutations in the *PKHD1* gene. The gene product fibrocystin is found in the kidney, liver, and pancreas and appears to be involved in the regulation of cell proliferation and adhesion.

Clinical Features. The typical infant with ARPKD presents with bilateral flank masses, accompanied by severe renal failure, signs of impaired lung development, and variable degrees of liver fibrosis and portal hypertension.[4] Potter facies and other defects associated with oligohydramnios may be present. Hypertension is usually noted within the first few weeks of life and is often severe. Approximately 75% of infants die during the perinatal period, often of pulmonary hypoplasia.[5] Exceptional cases of ARPKD manifest in older children and adults.

The treatment of ARPKD is largely supportive. Aggressive ventilatory support is often necessary in the neonatal period because of pulmonary hypoplasia and hypoventilation. Modern neonatal respiratory technology and renal replacement therapy have increased the 10-year survival rate of children surviving beyond the first year of life. Morbidity and mortality in the older child is related to complications of renal failure and liver disease.

Nephronophthisis–Medullary Cystic Disease Complex

The nephronophthisis–medullary cystic disease complex is a group of autosomal recessive and autosomal dominant renal disorders that have their onset in childhood.[4,5] Common characteristics are small and shrunken kidneys and the presence of a variable number of cysts, usually concentrated at the corticomedullary junction. The initial insult involves the distal tubules, with tubular basement membrane disruption followed by chronic and progressive tubular atrophy involving both the medulla and cortex. Although the presence of medullary cysts is important, the cortical and tubular damage is the eventual cause of chronic kidney disease and failure.

As a complex, the disorders account for 10% to 25% of renal failure in childhood.[5] Affected children present first with polyuria, polydipsia, and enuresis (bed-wetting), which reflect impaired ability of the kidneys to concentrate urine. Other manifestations of the disorders include salt wasting, growth retardation, anemia, and progressive renal insufficiency. Some juvenile forms of nephronophthisis have extrarenal complications, including ocular motor abnormalities, retinitis pigmentosa, liver fibrosis, and cerebellar abnormalities. Progressive azotemia and renal failure follow, usually within 5 to 10 years.[4,5]

Simple and Acquired Renal Cysts

Simple cysts are a common acquired disorder of the kidney. The cysts may be single or multiple, unilateral or bilateral, and they usually are less than 1 cm in diameter, although they may grow larger. The cysts usually are confined to the cortex. In rare instances, massive cysts as large as 10 cm in diameter are encountered.[4] Most simple cysts do not produce signs or symptoms or compromise renal function. When symptomatic, they may cause flank pain, hematuria, infection, and hypertension related to ischemia-produced stimulation of the renin-angiotensin system. They are most common in persons older than 50 years. Although the cysts are benign, they may be confused clinically with renal cell carcinoma.

An acquired form of renal cystic disease occurs in persons with chronic kidney disease who have undergone prolonged dialysis treatment.[4] Although the condition is largely asymptomatic, the cysts may bleed, causing hematuria. Tumors, usually adenomas but occasionally adenosarcomas, may develop in the walls of these cysts.

In summary, cystic diseases of the kidney are a group of hereditary and nonhereditary disorders in which there is dilation of tubular structures with cyst formation. Cysts may be single or multiple. Polycystic kidney disease is an inherited form of renal cystic disease; it can be inherited as an autosomal dominant or recessive trait. The autosomal dominant form of the disease (ADPKD) results in the formation of numerous fluid-filled cysts in the tubular structures of both kidneys with the threat of progression to chronic kidney disease. Other manifestations of the disease include hypertension, cardiovascular abnormalities, cerebral aneurysms, and cysts in other organs such as the liver and pancreas. The autosomal recessive form

of polycystic kidney disease (ARPKD) is characterized by cystic transformation of the collecting ducts. It is rare compared with ADPKD and usually presents as severe renal dysfunction during infancy. The nephronophthisis–medullary cystic disease complex is a group of hereditary disorders that usually have their onset during childhood and are characterized by the presence of cysts in the medullary portion of the kidney, renal atrophy, and eventual kidney failure. Single or multiple simple renal cysts most commonly occur in older persons.

Obstructive Disorders

Urinary obstruction can occur in persons of any age and can involve any level of the urinary tract, from the urethra to the renal pelvis (Fig. 25-11). Obstruction may be sudden or insidious, partial or complete, and unilateral or bilateral. The conditions that cause urinary tract obstruction include congenital anomalies, urinary calculi (i.e., stones), pregnancy, benign prostatic hyperplasia, scar tissue resulting from infection and inflammation, tumors, and neurologic disorders such as spinal cord injury. The causes of urinary tract obstructions are summarized in Table 25-2.

Obstructive uropathy is usually classified according to site, degree, and duration of obstruction. Lower urinary tract obstructions are located below the ureterovesical junction and are bilateral in nature. Upper urinary tract obstructions are located above the ureterovesical junction and are usually unilateral. The condition causing the obstruction can cause complete or partial occlusion of urine outflow. When the obstruction is of short duration (i.e., less than a few days), it is said to be acute and is usually caused by conditions such as renal calculi. An obstruction that develops slowly and is longer lasting is said to be chronic and is usually caused by conditions such as congenital ureterovesical abnormalities. Bilateral acute urinary tract obstruction causes acute renal failure. Because many causes of acute obstruction are reversible, prompt recognition is important. When left untreated, an obstructed kidney undergoes atrophy, and in the case of bilateral obstruction, results in chronic kidney disease.

TABLE 25-2 Causes of Urinary Tract Obstruction

Level of Obstruction	Cause
Renal pelvis	Renal calculi
	Papillary necrosis
Ureter	Renal calculi
	Pregnancy
	Tumors that compress the ureter
	Ureteral stricture
	Congenital disorders of the uretero-vesical junction and ureteropelvic junction strictures
Bladder and urethra	Bladder cancer
	Neurogenic bladder
	Bladder stones
	Prostatic hyperplasia or cancer
	Urethral strictures
	Congenital urethral defects

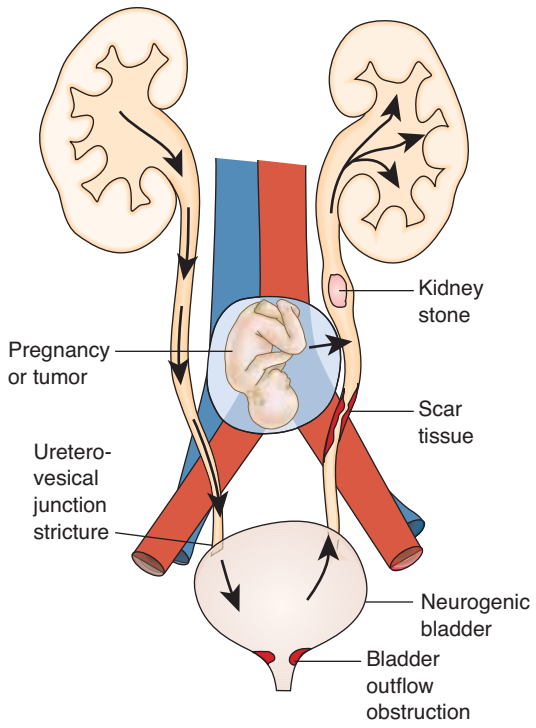


FIGURE 25-11. Locations and causes of urinary tract obstruction.

Mechanisms of Renal Damage

The destructive effects of urinary obstruction on kidney structures are determined by the degree (i.e., partial versus complete, unilateral versus bilateral) and the duration of the obstruction. The two most damaging effects of urinary obstruction are stasis of urine, which predisposes to infection and stone formation, and progressive dilation of the renal collecting ducts and renal tubular structures, which causes destruction and atrophy of renal tissue.

A common complication of urinary tract obstruction is infection. Stagnation of urine predisposes to infection, which may spread throughout the urinary tract. When present, urinary calculi serve as foreign bodies and contribute to the infection. Once established, the infection is difficult to treat. It often is caused by urea-splitting organisms (e.g., *Proteus*, staphylococci) that increase ammonia production and cause the urine to become alkaline.[33] Calcium salts precipitate more readily in stagnant alkaline urine; thus, urinary tract obstructions also predispose to stone formation.

In situations of severe partial or complete obstruction, the impediment to the outflow of urine causes dilation

of the renal pelvis and calyces associated with progressive atrophy of the kidney. Even with complete obstruction, glomerular filtration continues for some time. Because of the continued filtration, the calyces and pelvis of the affected kidney become dilated, often markedly so. The high pressure in the renal pelvis is transmitted back through the collecting ducts of the kidney, compressing renal vasculature and causing renal atrophy. Initially, the functional alterations are largely tubular, manifested primarily by impaired urine-concentrating ability. Only later does the GFR begin to diminish.

Hydronephrosis

Hydronephrosis refers to urine-filled dilation of the renal pelvis and calyces associated with progressive atrophy of the kidney due to obstruction of urine outflow. The degree of hydronephrosis depends on the duration, degree, and level of obstruction. In far-advanced cases, the kidney may be transformed into a thin-walled cystic structure with parenchymal atrophy, total obliteration of the pyramids, and thinning of the cortex (Fig. 25-12). The condition is usually unilateral; bilateral hydronephrosis occurs only when the obstruction is below the level of the ureterovesical junction. When the obstruction affects the outflow of urine from the distal ureter, the increased pressure dilates the ureter, a condition called *hydroureter*. Bilateral hydroureter may develop as a complication of bladder outflow obstruction due to prostatic hyperplasia (see Chapter 39).

Clinical Features

The manifestations of urinary obstruction depend on the site of obstruction, the cause, and the rapidity with which the condition developed. Most of the early symptoms are produced by the underlying pathologic process. Urinary tract obstruction encourages the growth of microorganisms and should be suspected in persons with recurrent urinary tract infections.

FIGURE 25-12. Hydronephrosis. Bilateral urinary tract obstruction has led to conspicuous dilation of the ureters, pelves, and calyces. The kidney on the right shows severe cortical atrophy. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 738]. Philadelphia: Lippincott Williams & Wilkins.)

Complete or partial unilateral hydronephrosis may remain silent for long periods because the unaffected kidney can maintain adequate kidney function. Obstruction may provoke pain due to distention of the collecting system and renal capsule. Acute supravesical obstruction, such as that due to a kidney stone lodged in the ureter, is associated with excruciatingly severe pain. By contrast, more insidious causes of obstruction, such as narrowing of the ureteropelvic junction, may produce little pain but cause total destruction of the kidney.

Complete bilateral obstruction results in oliguria and anuria and renal failure. Acute bilateral obstruction may mimic prerenal failure. With partial bilateral obstruction, the earliest manifestation is an inability to concentrate urine, reflected by polyuria and nocturia. Hypertension is an occasional complication of urinary tract obstruction. It is more common in cases of unilateral obstruction in which renin secretion is enhanced, probably secondary to impaired renal blood flow. In these circumstances, removal of the obstruction often leads to a reduction in blood pressure. When hypertension accompanies bilateral obstruction, it is volume related. The relief of bilateral obstruction leads to a loss of volume and a decrease in blood pressure. In some cases, relieving the obstruction does not correct the hypertension.

Early diagnosis of urinary tract obstruction is important because the condition usually is treatable and a delay in therapy may result in permanent damage to the kidneys. Diagnostic methods vary with the symptoms. Ultrasonography has proved to be the single most useful noninvasive diagnostic modality for urinary obstruction. Radiologic methods, CT scans, and intravenous urography may also be used. Other diagnostic methods, such as urinalysis, are used to determine the extent of renal involvement and the presence of infection.

Treatment of urinary tract obstruction depends on the cause. Urinary stone removal may be necessary, or surgical treatment of structural defects may be indicated. Treatment of complicating urinary tract infections due to urinary stasis is also important.

Renal Calculi

The most common cause of upper urinary tract obstruction is urinary calculi. Although stones can form in any part of the urinary tract, most develop in the kidneys. Renal calculi, also known as *nephrolithiasis* or *kidney stones*, are the third most common disorder of the urinary tract, exceeded only by urinary tract infections and prostate disorders.[34]

Kidney stones are polycrystalline aggregates composed of materials that the kidneys normally excrete in the urine. The etiology of urinary stone formation is complex.[35] It is thought to encompass a number of factors, including increases in blood and urinary levels of stone components and interactions among the components; anatomic changes in urinary tract structures; metabolic and endocrine influences; dietary and intestinal absorption factors; and urinary tract infections.

Kidney Stones

- Kidney stones are polycrystalline structures that form from components of the urine.
- Stones require a nidus to form and a urinary environment that supports continued crystallization of stone components.
- The development of kidney stones is influenced by the concentration of stone components in the urine, the ability of the stone components to complex and form stones, and the presence of substances that inhibit stone formation.

Adding to the mystery of stone formation is the fact that although both kidneys are exposed to the same urinary constituents, kidney stones tend to form in only one kidney. Several factors are used to explain stone formation, including a supersaturated urine, presence of a nucleus for crystal formation, and deficiency of inhibitors of stone formation.[34]

Kidney stone formation requires supersaturated urine and an environment that allows the stone to grow. The risk for stone formation is increased when the urine is supersaturated with stone components (e.g., calcium salts, uric acid, magnesium ammonium phosphate, and cystine). Supersaturation depends on urinary pH, solute concentration, ionic strength, and complexation. The greater the concentration of two ions, the more likely they are to precipitate. Complexation influences the availability of specific ions. For example, oxalate complexes with sodium and decreases the availability of its free ionic form that participates in stone formation.

In addition to supersaturated urine, kidney stone formation requires a nidus or nucleus that facilitates crystal aggregation. In supersaturated urine, stone formation begins with small clusters of crystals such as calcium oxalate. Most small clusters tend to disperse because the internal forces that hold them together are too weak to overcome the random tendency of ions to move apart. Larger ion clusters form nuclei and remain stable because the attraction forces balance surface losses. Once they are stable, nuclei can grow at levels of supersaturation below that needed for their creation. Organic materials, such as mucopolysaccharides derived from the epithelial cells that line the tubules, are also thought to act as nuclei for stone formation by lowering the level of supersaturation required for crystal aggregation.

The fact that many people experience supersaturation of their urine without development of kidney stones is believed to be a result of the presence of natural stone inhibitors, including magnesium, citrate, and the Tamm-Horsfall mucoprotein. To date, the measurement and manipulation of stone inhibitors has not been part of clinical practice, with the exception of citrate.[34–37] Urine citrate reduces supersaturation by binding calcium and inhibiting nucleation and growth of calcium crystals. Citrate is a normal by-product of the citric acid cycle in renal cells. Metabolic stimuli that consume this product (as with metabolic acidosis due to fasting or hypokalemia) reduce the urinary concentration of citrate. Citrate supplementation (potassium citrate) may be used in the treatment of some forms of hypocitraturic kidney stones.

Types of Stones

There are four basic types of kidney stones: calcium stones (i.e., oxalate or phosphate), magnesium ammonium phosphate stones, uric acid stones, and cystine stones.[36–39] The causes and treatment measures for each of these types of renal stones are described in Table 25-3.

TABLE 25-3 Composition, Contributing Factors, and Treatment of Kidney Stones

Type of Stone	Contributing Factors	Treatment
Calcium (oxalate and phosphate)	Hypercalcemia and hypercalciuria	Treatment of underlying conditions
	Immobilization	Increased fluid intake
		Thiazide diuretics
	Hyperparathyroidism	
	Vitamin D intoxication	
	Diffuse bone disease	
	Milk-alkali syndrome	
	Renal tubular acidosis	
	Hyperoxaluria	Dietary restriction of foods high in oxalate
	Intestinal bypass surgery	
Magnesium ammonium phosphate (struvite)	Urea-splitting urinary tract infections	Treatment of urinary tract infection
		Acidification of the urine
		Increased fluid intake
Uric acid (urate)	Formed in acid urine with pH of approximately 5.5	Increased fluid intake
	Gout	Allopurinol for hyperuricosuria
	High-purine diet	Alkalinization of urine
Cystine	Cystinuria (inherited disorder of amino acidmetabolism)	Increased fluid intake
		Alkalinization of urine

Most kidney stones (70% to 80%) are calcium stones—calcium oxalate, calcium phosphate, or a combination of the two materials.[4,5] Calcium stones usually are associated with increased concentrations of calcium in the blood and urine. Excessive bone resorption caused by immobility, bone disease, hyperparathyroidism, and renal tubular acidosis all are contributing conditions. High oxalate concentrations in the blood and urine predispose to formation of calcium oxalate stones.

Magnesium ammonium phosphate stones, also called *struvite stones,* form only in alkaline urine and in the presence of bacteria that possess an enzyme called *urease,* which splits the urea in the urine into ammonia and carbon dioxide. The ammonia that is formed takes up a hydrogen ion to become an ammonium ion, increasing the pH of the urine so that it becomes more alkaline. Because phosphate levels are increased in alkaline urine and because magnesium always is present in the urine, struvite stones form. These stones enlarge as the bacterial count grows, and they can increase in size until they fill an entire renal pelvis (Fig. 25-13). Because of their shape, they often are called *staghorn stones*. They almost always are associated with urinary tract infections and persistently alkaline urine. Because these stones act as a foreign body, treatment of the infection often is difficult. Struvite stones usually are too large to be passed and require lithotripsy or surgical removal.

Uric acid stones develop in conditions of gout and high concentrations of uric acid in the urine. Hyperuricosuria also may contribute to calcium stone formation by acting as a nucleus for calcium oxalate stone formation. Unlike radiopaque calcium stones, uric acid stones are not visible on x-ray films. Uric acid stones form most readily in urine with a pH of 5.1 to 5.9.[37] Thus, these stones can be treated by raising (alkalinizing) the urinary pH to 6.0 to 6.5 with potassium alkali salts.

Cystine stones account for less than 1% of kidney stones overall but represent a significant proportion of childhood calculi.[5] They are seen in cystinuria, which results from a genetic defect in renal transport of cystine. These stones resemble struvite stones except that infection is unlikely to be present.

FIGURE 25-13. Staghorn stones. The kidney shows hydronephrosis and stones that are casts of the dilated calyces. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 738]. Philadelphia: Lippincott Williams & Wilkins.)

Clinical Features

One of the major manifestations of kidney stones is pain. Depending on location, there are two types of pain associated with kidney stones: renal colic and noncolicky renal pain.[34,38,39] *Renal colic* is the term used to describe the colicky pain that accompanies stretching of the collecting system or ureter. The symptoms of renal colic are caused by stones 1 to 5 mm in diameter that can move into the ureter and obstruct flow. Classic ureteral colic is manifested by acute, intermittent, and excruciating pain in the flank and upper outer quadrant of the abdomen on the affected side. The pain may radiate to the lower abdominal quadrant, bladder area, perineum, or scrotum in the man. The skin may be cool and clammy, and nausea and vomiting are common. *Noncolicky pain* is caused by stones that produce distention of the renal calyces or renal pelvis. The pain usually is a dull, deep ache in the flank or back that can vary in intensity from mild to severe. The pain is often exaggerated by drinking large amounts of fluid.

The diagnosis of kidney stones is based on symptomatology and diagnostic tests, which include urinalysis, plain film radiography, intravenous pyelography, and abdominal ultrasonography.[39] Urinalysis provides information related to hematuria, infection, presence of stone-forming crystals, and urine pH. Most stones are radiopaque and readily visible on a plain radiograph of the abdomen. The noncontrast spiral CT scan is the imaging modality of choice in persons with acute renal colic.[34] Intravenous pyelography (IVP) uses an intravenously injected contrast medium that is filtered in the glomeruli to visualize the collecting system of the kidneys and ureters. Abdominal ultrasonography is highly sensitive to hydronephrosis, which may be a manifestation of ureteral obstruction. A new imaging technique called *nuclear scintigraphy* uses bisphosphonate markers as a means of imaging stones.[34] This method has been credited with identifying stones that are too small to be detected by other methods.

Treatment of acute renal colic usually is supportive. Pain relief may be needed during acute phases of obstruction, and antibiotic therapy may be necessary to treat urinary tract infections. Most stones that are less than 5 mm in diameter pass spontaneously. All urine should be strained during an attack in the hope of retrieving the stone for chemical analysis and determination of type. This information, along with a careful

history and laboratory tests, provides the basis for long-term preventive measures.

A major goal of treatment in persons who have passed kidney stones or have had them removed is to prevent their recurrence. Prevention requires investigation into the cause of stone formation using urine tests, blood chemistries, and stone analysis. Underlying disease conditions, such as hyperparathyroidism, are treated. Adequate fluid intake reduces the concentration of stone-forming crystals in the urine and needs to be encouraged. Depending on the type of stone that is formed, dietary changes, medications, or both may be used to alter the concentration of stone-forming elements in the urine (Table 25-3). For example, persons who form calcium oxalate stones may need to decrease their intake of foods that are high in oxalate (e.g., spinach, Swiss chard, cocoa, chocolate, pecans, peanuts). Calcium supplementation with calcium salts such as calcium carbonate and calcium phosphate also may be used to bind oxalate in the intestine and decrease its absorption. Thiazide diuretics lower urinary calcium by increasing tubular reabsorption so that less remains in the urine. Drugs that bind calcium in the gut (e.g., cellulose phosphate) may be used to inhibit calcium absorption and urinary excretion.

Measures to change the pH of the urine also can influence kidney stone formation. In persons who lose the ability to acidify or lower the pH of their urine, there is an increase in the divalent and trivalent forms of urine phosphate that combine with calcium to form calcium phosphate stones. The formation of uric acid stones is increased in acid urine; stone formation can be reduced by raising the pH of urine to 6.0 to 6.5 with potassium alkali (e.g., potassium citrate) salts.

In some cases, stone removal may be necessary. Several methods are available for removing kidney stones: ureteroscopic removal, percutaneous removal, and extracorporeal lithotripsy.[34] All of these procedures eliminate the need for an open surgical procedure, which is another form of treatment. Open stone surgery may be required to remove large calculi or those that are resistant to other forms of removal. A nonsurgical treatment, called *extracorporeal shock-wave lithotripsy,* uses acoustic shock waves to fragment calculi into sandlike particles that are passed in the urine over the next few days. Because of the large amount of stone particles that are generated during the procedure, a ureteral stent (i.e., a tubelike device used to hold the ureter open) may be inserted to ensure adequate urine drainage.

In summary, obstruction of urine flow can occur at any level of the urinary tract. Among the causes of urinary tract obstruction are developmental defects, pregnancy, infection and inflammation, kidney stones, neurologic defects, and prostatic hypertrophy. Obstructive disorders produce stasis of urine, increase the risk for infection and calculi formation, and produce progressive dilation of the renal collecting ducts and renal tubular structures, which causes renal atrophy.

Hydronephrosis refers to urine-filled dilation of the renal pelvis and calyces associated with progressive atrophy of the kidney due to obstruction of urine outflow. Unilateral hydronephrosis may remain silent for long periods because the unaffected kidney can maintain adequate kidney function. With partial bilateral obstruction, the earliest manifestation is an inability to concentrate urine, reflected by polyuria and nocturia. Complete bilateral obstruction results in oliguria and anuria and renal failure.

Kidney stones are a major cause of upper urinary tract obstruction. There are four types of kidney stones: calcium (i.e., oxalate and phosphate) stones, which are associated with increased serum calcium levels; magnesium ammonium phosphate (i.e., struvite) stones, which are associated with urinary tract infections; uric acid stones, which are related to elevated uric acid levels; and cystine stones, which are seen in cystinuria. A major goal of treatment for persons who have passed kidney stones or have had them removed is to identify stone composition and prevent their recurrence. Treatment measures depend on stone type and include adequate fluid intake to prevent urine saturation, dietary modification to decrease intake of stone-forming constituents, treatment of urinary tract infections, measures to change urine pH, and the use of diuretics that decrease the calcium concentration of urine.

Malignant Tumors of the Kidney

There are two major groups of malignant tumors of the kidney: embryonic kidney tumors (i.e., Wilms tumor), which occur during childhood, and renal cell carcinoma, which occurs in adults.

Wilms Tumor

Wilms tumor (nephroblastoma) is one of the most common primary neoplasms of young children. It usually presents between 3 and 5 years of age and is the most common malignant abdominal tumor in children.[5,40] It may occur in one or both kidneys; the incidence of bilateral Wilms tumor is 6% to 7%.

Histologically, the tumor is composed of elements that resemble normal fetal tissue: blastemic, stromal, and epithelial. An important feature of Wilms tumor is its association with other congenital anomalies, including aniridia (absence of the iris), hemihypertrophy (enlargement of one side of the face or body), and other congenital anomalies, usually of the genitourinary system. Several chromosomal abnormalities have been associated with Wilms tumor. One Wilms tumor gene, *WT1,* is located on chromosome 11 and encodes a transcription factor that is critical for normal kidney development.[40]

Wilms tumor usually is a solitary mass that occurs in any part of the kidney. It usually is sharply demarcated and variably encapsulated (Fig. 25-14). The tumors grow to a large size, distorting kidney structure. The tumors

FIGURE 25-14. Wilms tumor. A cross-section of a pale tan neoplasm (*arrow*) attached to a residual portion of the kidney. (From Jennette J.C. [2008]. The kidney. In Rubin R., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 742]. Philadelphia: Lippincott Williams & Wilkins.)

usually are staged using the National Wilms Tumor Study Group classification.[40] Stage I tumors are limited to the kidney and can be excised with the capsular surface intact. Stage II tumors extend into the renal capsule but can be excised. In stage III, extension of the tumor is confined to the abdomen, and in stage IV, hematogenous metastasis most commonly involves the lung. Bilateral kidney involvement occurs in 5% to 10% of cases.

The common presenting signs are a large asymptomatic abdominal mass and hypertension. The tumor is often discovered inadvertently, and it is not uncommon for the mother to discover it while bathing the child. Some children may present with abdominal pain, vomiting, or both. Microscopic and gross hematuria is present in 17% to 25% of children. CT scans are used to confirm the diagnosis.[40]

Treatment involves surgery, chemotherapy, and sometimes radiation therapy. Long-term survival rates have increased to more than 60% for all stages and to 88% to 98% for stages I through III.[40]

Renal Cell Carcinoma

Cancer of the kidney is the 7th leading malignancy among men and the 12th among women, accounting for about 3% of all cancers.[41] Incidence peaks between 55 and 84 years of age.[41] The increased use of imaging procedures such as ultrasonography, CT scanning, and magnetic resonance imaging (MRI) has contributed significantly to early diagnosis and more accurate staging of kidney cancers.[41,42]

Renal cell carcinoma accounts for approximately 90% to 95% of kidney tumors.[42] These tumors are derived from the proximal tubular cells, and hence are located predominantly in the cortex (Fig. 25-15). There are pathologic variants of renal cell carcinoma that reflect differences in cellular pathology, genetic profile, and clinical features ranging from benign to highly malignant.

The cause of renal cell carcinoma remains unclear. Epidemiologic evidence suggests a correlation between heavy smoking and kidney cancer.[41,42] Obesity also is a risk factor, particularly in women. Additional risk factors include occupational exposure to petroleum products, heavy metals, and asbestos.[5] The risk for renal cell carcinoma also is increased in persons with acquired cystic kidney disease associated with chronic renal insufficiency.

Kidney cancer is largely a silent disorder during its early stages, and symptoms usually denote advanced disease. Presenting features include hematuria, flank pain, and presence of a palpable flank mass. Gross or microscopic hematuria, which occurs in more than 50% of cases, is an important clinical clue.[4] It is, however, intermittent and may be microscopic; as a result, the tumor may reach considerable size before it is detected. Ultrasonography and CT scanning are used to confirm the diagnosis. MRI may be used when involvement of the inferior vena cava is suspected.

Surgery (radical nephrectomy with lymph node dissection) is the treatment of choice for all resectable tumors. Nephron-sparing surgery may be done when both kidneys are involved or when the contralateral kidney is threatened by an associated disease such as hypertension or diabetes mellitus. Single-agent and combination chemotherapy have been used with limited success. The 5-year survival rate is 90% if the tumor has not extended beyond the renal capsule, but drops to 30% if metastasis has occurred.[5]

FIGURE 25-15. Gross pathology of a bisected kidney showing large renal cell carcinoma. Much of the kidney has been replaced by gray and yellow tumor tissue. A little remaining renal cortex and pericapsular fat are visible at the bottom of this surgical specimen. (From Centers for Disease Control and Prevention Public Images Library. [Online] Available: http://phil.cdc.gov/phil/details.asp.)

In summary, there are two major groups of renal neoplasms: embryonic kidney tumors (i.e., Wilms tumor) that occur during childhood and adult renal cell carcinomas. Wilms tumor is one of the most common malignant tumors of children. The most common presenting signs are a large abdominal mass and hypertension. Treatment is surgery, chemotherapy, and sometimes radiation therapy. The long-term survival rate for children with Wilms tumor is approximately 90% with an aggressive plan of treatment.

Renal cancer accounts for about 3% of all cancers, with a peak incidence between 55 and 84 years of age. Renal cell carcinoma accounts for 90% to 95% of kidney tumors. These tumors are characterized by a lack of early warning signs, diverse clinical manifestations, and resistance to chemotherapy and radiation therapy. Diagnostic methods include ultrasonography and CT scans. The treatment of choice is surgical resection.

REVIEW EXERCISES

1. A 6-year-old boy is diagnosed with acute glomerulonephritis that developed after a streptococcal throat infection. At this time, the following manifestations are noted: decrease in urine output, increasing lethargy, hyperventilation, and generalized edema. Trace amounts of protein are detected in his urine. Blood analysis reveals the following: pH = 7.35, HCO_3 = 18 mEq/L, hematocrit = 29%, Na = 132 mEq/L, K = 5.6 mEq/L, blood urea nitrogen (BUN) = 62 mg/dL, creatinine = 4.1 mg/dL, and albumin = 2 g/dL.

A. What is the probable cause of this boy's glomerular disease?
B. Use the laboratory values in the Appendix to interpret his laboratory test results. Which values are significant and why?
C. Is he progressing to uremia? How can you tell?

2. A 36-year old man is admitted to the emergency department with a sudden onset of severe, intermittent, cramping pain that makes him feel nauseated. He describes the pain as originating in the left groin and radiating toward the flank. Microscopic examination of his urine reveals the presence of red blood cells. His temperature is normal, and he does not exhibit signs of sepsis.

A. What is the probable cause of this man's pain?
B. What diagnostic measure could be used to confirm the cause of his pain?
C. A plain-film radiograph reveals a 4- to 5-mm kidney stone in the left ureter. What are the chances that this man will pass the stone spontaneously?
D. What type of medications and other treatments should this man receive?
E. Once the stone has been passed, what type of measures can he use to prevent stone recurrence?

REFERENCES

1. National Kidney Foundation. (2009). *The problem of kidney and urologic diseases.* [Online] Available: http://www.kidney.org. Accessed March 8, 2009.
2. Kidney Foundation of Canada. (2009). *Facing the facts.* [Online] Available: http://www.kidney.ca. Accessed March 8, 2009.
3. Chadban S.J., Atkins R.C. (2005). Glomerulonephritis. *Lancet* 365, 1797–1806.
4. Alpers C.E. (2010). The kidney. In Kumar V., Abbas A.K., Fautso N., et al. *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 905–969). Philadelphia: Saunders Elsevier.
5. Jennette J.C. (2008). The kidney. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 694–698, 867–877, 881–884). Philadelphia: Lippincott Williams & Wilkins.
6. Beck L.H., Salant D.J. (2008). Glomerular and tubulointerstitial diseases. *Primary Care Clinics of North America* 35, 265–296.
7. Brady H.R., O'Meara Y.M., Brenner B.M. (2005). Glomerular diseases. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1674–1694). New York: McGraw-Hill.
8. Lau K.K., Wyatt R.J. (2005). Glomerulonephritis. *Adolescent Medicine* 16, 67–85.
9. Vinen C.S., Oliveira D.B.G. (2003). Acute glomerulonephritis. *Postgraduate Medicine Journal* 79, 206–213.
10. Glassock R.J. (2003). The glomerulopathies. In Schrier R.W. (Ed.), *Renal and electrolyte disorders* (6th ed., pp. 623–670). Philadelphia: Lippincott Williams & Wilkins.
11. Hricik D.E., Chung-Park M., Sedor J.R. (1998). Glomerulonephritis. *New England Journal of Medicine* 339, 888–899.
12. Rodriguez-Iturbe B., Musser J.M. (2008). The current state of poststreptococcal glomerulonephritis. *Journal of the American Society of Nephrology* 19, 1855–1864.
13. Orth S.R., Ritz E. (1998). The nephrotic syndrome. *New England Journal of Medicine* 339, 1202–1211.
14. Eddy A.A., Symons J.M. (2003). Nephrotic syndrome in childhood. *Lancet* 362, 629–639.
15. Coresh J., Astor B.C., Greene T., et al. (2003). Prevalence of chronic kidney disease and decreased kidney function in the adult U.S. population: Third National Health and Nutrition Examination Survey. *American Journal of Kidney Disease* 42, 1–12.
16. Donadio J.V., Grande J.P. (2002). IgA nephropathy. *New England Journal of Medicine* 347, 738–748.
17. Baratt J., Feehally J. (2005). IgA nephropathy. *Journal of the American Society of Nephrology* 16, 2088–2097.
18. Weening J.J., D'Agati V.D., Schwartz M.M. (2004). The classification of glomerulonephritis in systemic lupus erythematosus. *Journal of the American Society of Nephrology* 15, 241–250.
19. Gross J.L., De Azevedo M.J., Silverdo P., et al. (2005). Diabetic nephropathy: Diagnosis, prevention, and treatment. *Diabetes Care* 28, 164–188.
20. Remuzza G., Schiepatti A., Ruggenenti P. (2002). Nephropathy in patients with type 2 diabetes. *New England Journal of Medicine* 346, 1145–1151.
21. Jawa A., Kcomt J., Fonseca V.A. (2004). Diabetic nephropathy and retinopathy. *Medical Clinics of North America* 88, 1001–1036.

22. Schena F.P., Gesualdo L. (2005). Pathogenic mechanisms of diabetic nephropathy. *Journal of the American Society of Nephrology* 16(Suppl 1), S30–S33.
23. Ramakrishnan K., Scheid D. (2005). Diagnosis and management of acute pyelonephritis in adults. *American Family Physician* 71, 933–942.
24. Taber S.S., Mueller B.A. (2006). Drug-associated renal dysfunction. *Critical Care Clinics* 22, 357–374.
25. Blowey D.L. (2005). Nephrotoxicity of over-the-counter analgesics, natural medicines, and illicit drugs. *Adolescent Medicine* 16, 31–43.
26. Wilson P.D. (2004). Polycystic kidney disease. *New England Journal of Medicine* 350, 151–164.
27. Sutters M., Germino G.G. (2003). Autosomal dominant polycystic kidney disease: Molecular genetics and pathophysiology. *Journal of Laboratory and Clinical Medicine* 141, 91–110.
28. Igarashi P., Somolo S. (2002). Genetics and pathogenesis of polycystic kidney disease. *Journal of the American Society of Nephrology* 13, 2384–2398.
29. Gantham J.J. (2008). Autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 359(14), 1477–1485.
30. Ong A.C.M., Wheatley D.N. (2003). Polycystic kidney disease: The ciliary connection. *Lancet* 361, 774–776.
31. Bajwa Z.H., Gupta S., Warfield C.A., et al. (2001). Pain management in polycystic kidney disease. *Kidney International* 60, 1631–1644.
32. Asplin J.R., Coe F.L. (2005). Tubular disorders. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1694–1696). New York: McGraw-Hill.
33. Tanagho E.A. (2008). Urinary obstruction and stasis. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., p. 176). New York: McGraw-Hill Medical.
34. Stoller M.L. (2008). Urinary stone disease. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 256–290). New York: McGraw-Hill Medical.
35. Miller N.L., Evan A.P., Lingeman J.E. (2007). Pathogenesis of renal calculi. *Urologic Clinics of North America* 34, 295–313.
36. Moe O.W. (2006). Kidney stones: Pathophysiology and medical management. *Lancet* 367, 333–444.
37. Coe F.L., Evan A., Worcester E. (2005). Kidney stone disease. *Journal of Clinical Investigation* 115, 2598–2608.
38. Pietrow P.E., Karellas M.E. (2006). Medical management of urinary calculi. *American Family Physician* 74, 86–94, 99–100.
39. Portis A.J., Sundram C.P. (2001). Diagnosis and initial management of kidney stones. *American Family Physician* 63, 1329–1338.
40. Jaffe N., Huff V. (2007). Neoplasms of the kidney. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2140–2143). Philadelphia: Elsevier Saunders.
41. Cohen H.T., McGovern F.J. (2005). Renal-cell carcinoma. *New England Journal of Medicine* 353, 2477–2490.
42. Scher H.I., Motzer R.J. (2005). Bladder and renal cell carcinoma. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 541–543). New York: McGraw-Hill.

Acute Renal Failure
Types of Acute Renal Failure
Prerenal Failure
Intrinsic Renal Failure
Postrenal Failure
Diagnosis and Treatment
Chronic Kidney Disease
Definition and Classification
Glomerular Filtration Rate and Other Indicators of Renal Function
Clinical Manifestations
Disorders of Fluid, Electrolyte, and Acid-Base Balance
Disorders of Calcium and Phosphorus Balance and Bone Disease
Disorders of Hematologic Function
Disorders of Cardiovascular Function
Disorders Associated with Accumulation of Nitrogenous Wastes
Disorders of Drug Elimination
Management
Medical Management
Dialysis and Transplantation
Dietary Management
Chronic Kidney Disease in Children and Elderly Persons
Chronic Kidney Disease in Children
Chronic Kidney Disease in Elderly Persons

Chapter 26

Acute Renal Failure and Chronic Kidney Disease

Renal failure is a condition in which the kidneys fail to remove metabolic end products from the blood and regulate the fluid, electrolyte, and pH balance of the extracellular fluids. The underlying cause may be renal disease, systemic disease, or urologic defects of nonrenal origin. Renal failure can occur as an acute or a chronic disorder. Acute renal failure is abrupt in onset and often is reversible if recognized early and treated appropriately. In contrast, chronic kidney disease is the end result of irreparable damage to the kidneys. It develops slowly, usually over the course of a number of years.

Acute Renal Failure

Acute renal failure (ARF), which is a common threat to seriously ill persons, represents a rapid decline in kidney function, resulting in an inability to maintain fluid and electrolyte balance and to excrete nitrogenous wastes.[1–6] Acute renal failure is also called *acute kidney injury*, because even small decrements in kidney function, changes that are insufficient to be recognized as renal failure, are associated with increased morbidity and mortality.[7,8] Despite advances in treatment methods, the mortality rate from ARF has not changed substantially since the 1960s.[1] This probably is because ARF is seen more often in older persons than before, and because it frequently is superimposed on other life-threatening conditions, such as trauma, shock, and sepsis.

The most common indicator of acute renal failure is *azotemia,* an accumulation of nitrogenous wastes (urea nitrogen, uric acid, and creatinine) in the blood and a decrease in the glomerular filtration rate (GFR). As a result, excretion of nitrogenous wastes is reduced and fluid and electrolyte balance cannot be maintained.

Types of Acute Renal Failure

Acute renal failure can be caused by several types of conditions, including a decrease in blood flow without

Acute Renal Failure

- Acute renal failure is caused by conditions that produce an acute shutdown in renal function.
- It can result from decreased blood flow to the kidney (prerenal failure), disorders that disrupt the structures in the kidney (intrinsic or intrarenal failure), or disorders that interfere with the elimination of urine from the kidney (postrenal failure).
- Acute renal failure, although it causes an accumulation of products normally cleared by the kidney, is a potentially reversible process if the factors causing the condition can be corrected.

ischemic injury; ischemic, toxic, or obstructive tubular injury; and obstruction of urinary tract outflow. The causes of ARF commonly are categorized as prerenal, intrinsic, and postrenal[1–6] (Fig. 26-1). Collectively, prerenal and intrinsic causes account for 80% to 95% of ARF cases.[3] Causes of renal failure within these categories are summarized in Chart 26-1.

Prerenal Failure

Prerenal failure, the most common form of ARF, is characterized by a marked decrease in renal blood flow. It is reversible if the cause of the decreased renal blood flow can be identified and corrected before kidney damage occurs.

Normally, the kidneys receive 22% of the cardiac output.[9] This large blood supply is required to remove metabolic wastes and regulate body fluids and electrolytes.

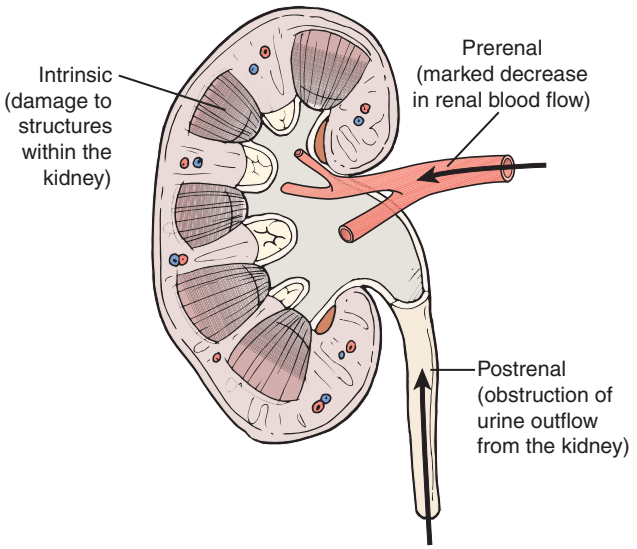


FIGURE 26-1. Types of acute renal failure.

CHART 26-1 Causes of Acute Renal Failure

Prerenal

Hypovolemia
- Hemorrhage
- Dehydration
- Excessive loss of gastrointestinal tract fluids
- Excessive loss of fluid due to burn injury

Decreased vascular filling
- Anaphylactic shock
- Septic shock

Heart failure and cardiogenic shock

Decreased renal perfusion due to sepsis, vasoactive mediators, drugs, diagnostic agents

Intrinsic or intrarenal

Acute tubular necrosis
- Prolonged renal ischemia
- Exposure to nephrotoxic drugs, heavy metals, and organic solvents
- Intratubular obstruction resulting from hemoglobinuria, myoglobinuria, myeloma light chains, or uric acid casts
- Acute renal disease (acute glomerulonephritis, pyelonephritis)

Postrenal

Bilateral ureteral obstruction

Bladder outlet obstruction

Fortunately, the normal kidney can tolerate relatively large reductions in blood flow before renal damage occurs. As renal blood flow falls, the GFR decreases, the amount of sodium and other substances that are filtered by the glomeruli is reduced, and the blood flow needed for the energy-dependent mechanisms that reabsorb these substances is reduced (see Chapter 24). As the GFR and urine output approach zero, oxygen consumption by the kidney approximates that required to keep renal tubular cells alive. When blood flow falls below this level, which is about 25% of normal, ischemic changes occur.[9] Because of their high metabolic rate, the tubular epithelial cells are most vulnerable to ischemic injury. Improperly treated, prolonged renal hypoperfusion can lead to ischemic tubular necrosis with significant morbidity and mortality.

Causes of prerenal failure include profound depletion of vascular volume (e.g., hemorrhage, loss of extracellular fluid volume), impaired perfusion due to heart failure and cardiogenic shock, and decreased vascular filling because of increased vascular capacity (e.g., anaphylaxis or sepsis). Elderly persons are particularly at risk because of their predisposition to hypovolemia and their high prevalence of renal vascular disorders.

Some vasoactive mediators, drugs, and diagnostic agents stimulate intense intrarenal vasoconstriction and can induce glomerular hypoperfusion and prerenal failure. Examples include endotoxins, radiocontrast agents such as those used for cardiac catheterization, cyclosporine (an immunosuppressant drug that is used to prevent transplant

rejection), amphotericin B (an antifungal agent), epinephrine, and high doses of dopamine.[3] Many of these agents also cause acute tubular necrosis (discussed later). In addition, several commonly used classes of drugs can impair renal adaptive mechanisms and can convert compensated renal hypoperfusion into prerenal failure. Angiotensin II is a potent renal vasoconstrictor that preferentially constricts the efferent arterioles of the kidney as a means of preserving the GFR in situations of arterial hypotension or volume depletion. The angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce the effects of angiotensin II on renal blood flow. They also reduce intraglomerular pressure and may have a renal protective effect in persons with hypertension or type 2 diabetes. However, when combined with diuretics, they may cause prerenal failure in persons with decreased blood flow due to large-vessel or small-vessel kidney disease. Prostaglandins have a vasodilatory effect on renal blood vessels. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce renal blood flow through inhibition of prostaglandin synthesis. In some persons with diminished renal perfusion, NSAIDs can precipitate prerenal failure.

Prerenal failure is manifested by a sharp decrease in urine output and a disproportionate elevation of blood urea nitrogen (BUN) in relation to serum creatinine levels. The kidney normally responds to a decrease in the GFR with a decrease in urine output. Thus, an early sign of prerenal failure is a sharp decrease in urine output. A low fractional excretion of sodium (<1%) suggests that oliguria is due to decreased renal perfusion and that the nephrons are responding appropriately by decreasing the excretion of filtered sodium in an attempt to preserve vascular volume. BUN levels also depend on the GFR. A low GFR allows more time for small particles such as urea to be reabsorbed into the blood. Creatinine, which is larger and nondiffusible, remains in the tubular fluid, and the total amount of creatinine that is filtered, although small, is excreted in the urine. Consequently, there also is a disproportionate elevation in the ratio of BUN to serum creatinine, from a normal value of 10:1 to a ratio greater than 20:1.[1]

Intrinsic Renal Failure

Intrinsic, or intrarenal, renal failure results from conditions that cause injury to structures within the kidney. The major causes of intrinsic failure are ischemia associated with prerenal failure, injury to the tubular structures of the nephron, and intratubular obstruction. Acute glomerulonephritis and acute pyelonephritis also are intrinsic causes of ARF. Injury to the tubular structures of the nephron (acute tubular necrosis) is the most common cause and often is ischemic or toxic in origin.

Acute Tubular Necrosis. Acute tubular necrosis (ATN) is characterized by the destruction of tubular epithelial cells with acute suppression of renal function (Fig. 26-2). ATN can be caused by a number of conditions, including acute tubular damage due to ischemia, sepsis, nephrotoxic effects of drugs, tubular obstruction, and toxins from a

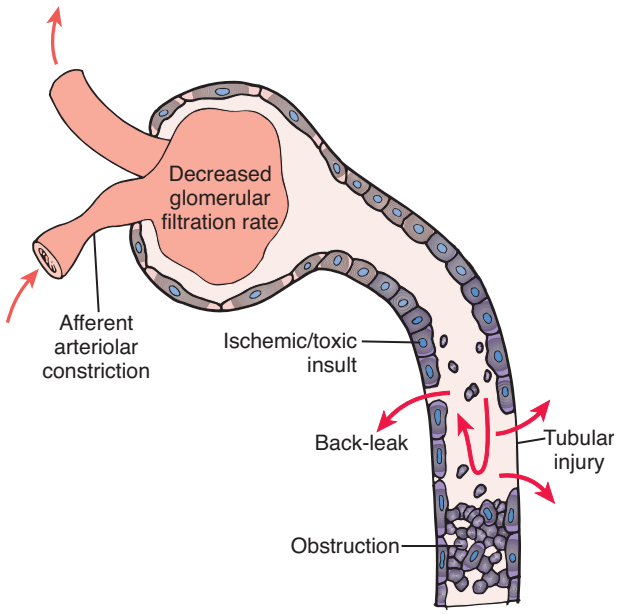


FIGURE 26-2. Pathogenesis of acute tubular necrosis (ATN). Sloughing and necrosis of tubular epithelial cells lead to obstruction and increased intraluminal pressure, which reduce glomerular filtration. Afferent arteriolar vasoconstriction caused in part by tubuloglomerular feedback mechanisms results in decreased glomerular capillary filtration pressure. Tubular injury and increased intraluminal pressure cause fluid to move from the tubular lumen into the interstitium (back-leak). (Modified from Rubin E., Farber J.L. [Eds.]. [1999]. *Pathology* [3rd ed., p. 901]. Philadelphia: Lippincott-Raven.)

massive infection.[3–5,10] Tubular epithelial cells are particularly sensitive to ischemia and also are vulnerable to toxins. The tubular injury that occurs in ATN frequently is reversible. The process depends on recovery of the injured cells, removal of the necrotic cells and intratubular casts, and regeneration of tubular cells to restore the normal continuity of the tubular epithelium.[5,11]

ATN occurs most frequently in persons who have major surgery, severe hypovolemia, or overwhelming sepsis, trauma, or burns.[3] Sepsis produces ischemia by provoking a combination of systemic vasodilation and intrarenal hypoperfusion. In addition, sepsis results in the generation of toxins that sensitize renal tubular cells to the damaging effects of ischemia. ATN complicating trauma and burns frequently is multifactorial in origin, resulting from the combined effects of hypovolemia, myoglobinuria, and other toxins released from damaged tissue. In contrast to prerenal failure, the GFR does not improve with the restoration of renal blood flow in ARF caused by ischemic ATN.

Nephrotoxic ATN complicates the administration of or exposure to many structurally diverse drugs and other nephrotoxic agents. These agents cause tubular injury by inducing varying combinations of renal vasoconstriction, direct tubular damage, or intratubular obstruction. The kidney is particularly vulnerable to nephrotoxic injury because of its rich blood supply and ability to concentrate toxins to high levels in the medullary portion of the

kidney. In addition, the kidney is an important site for metabolic processes that transform relatively harmless agents into toxic metabolites. Pharmacologic agents that are directly toxic to the renal tubule include antimicrobials such as aminoglycosides (e.g., gentamicin), cancer chemotherapeutic agents such as cisplatin and ifosfamide, and radiocontrast agents.[3,5] Several factors contribute to aminoglycoside nephrotoxicity, including a decrease in the GFR, preexisting renal disease, hypovolemia, and concurrent administration of other drugs that have a nephrotoxic effect. Cisplatin accumulates in proximal tubule cells, inducing mitochondrial injury and inhibition of adenosine triphosphatase (ATPase) activity and solute transport. Radiocontrast media–induced nephrotoxicity is thought to result from direct tubular toxicity and renal ischemia.[12] The risk for renal damage caused by radiocontrast media is greatest in elderly persons and those with preexisting kidney disease, volume depletion, diabetes mellitus, and recent exposure to other nephrotoxic agents.

The presence of multiple myeloma light chains, excess uric acid, myoglobin, or hemoglobin in the urine is the most frequent cause of ATN due to intratubular obstruction. Both myeloma cast nephropathy (Chapter 11) and acute urate nephropathy (Chapter 8) usually are seen in the setting of widespread malignancy or massive tumor destruction by therapeutic agents.[3] Hemoglobinuria results from blood transfusion reactions and other hemolytic crises. Skeletal and cardiac muscles contain myoglobin, which corresponds to hemoglobin in function, serving as an oxygen reservoir in the muscle fibers. Myoglobin normally is not found in the serum or urine. It has a low molecular weight; if it escapes into the circulation, it is rapidly filtered in the glomerulus. A life-threatening condition known as *rhabdomyolysis* occurs when increasing myoglobinuria levels cause myoglobin to precipitate in the renal tubules, leading to obstruction and damage to surrounding tubular cells. Myoglobinuria most commonly results from muscle trauma, but may result from extreme exertion, hyperthermia, sepsis, prolonged seizures, potassium or phosphate depletion, and alcoholism or drug abuse. Both myoglobin and hemoglobin discolor the urine, which may range from the color of tea to red, brown, or black.

The clinical course of ATN can be divided into three phases: the onset or initiating phase, the maintenance phase, and the recovery or reparative phase. The *onset* or *initiating phase,* which lasts hours or days, is the time from the onset of the precipitating event (e.g., ischemic phase of prerenal failure or toxin exposure) until tubular injury occurs.

The *maintenance phase* of ATN is characterized by a marked decrease in the GFR, causing sudden retention of endogenous metabolites, such as urea, potassium, sulfate, and creatinine, that normally are cleared by the kidneys. The urine output usually is lowest at this point. Fluid retention gives rise to edema, water intoxication, and pulmonary congestion. If the period of oliguria is prolonged, hypertension frequently develops and with it signs of uremia. When untreated, the neurologic manifestations of uremia progress from neuromuscular irritability to seizures, somnolence, coma, and death. Hyperkalemia usually is asymptomatic until the serum potassium level rises above 6 to 6.5 mEq/L (6 to 6.5 mmol/L), at which point characteristic electrocardiographic changes and symptoms of muscle weakness are seen.

Formerly, most patients with ATN were oliguric. During the past several decades, a nonoliguric form of ATN has become increasingly prevalent. Persons with nonoliguric failure have higher levels of glomerular filtration and excrete more nitrogenous waste, water, and electrolytes in their urine than persons with acute oliguric renal failure. Abnormalities in blood chemistry levels usually are milder and cause fewer complications. The decrease in oliguric ATN probably reflects new approaches to the treatment of poor cardiac performance and circulatory failure that focus on vigorous plasma volume expansion and the selective use of dopamine and other drugs to improve renal blood flow (see Chapter 20). Dopamine has renal vasodilator properties and inhibits sodium reabsorption in the proximal tubule, thereby decreasing the work demands of the nephron.

The *recovery phase* is the period during which repair of renal tissue takes place. Its onset usually is heralded by a gradual increase in urine output and a fall in serum creatinine, indicating that the nephrons have recovered to the point at which urine excretion is possible. Diuresis often occurs before renal function has fully returned to normal. Consequently, BUN and serum creatinine, potassium, and phosphate levels may remain elevated or continue to rise even though urine output is increased. In some cases, the diuresis may result from impaired nephron function and may cause excessive loss of water and electrolytes. Eventually, renal tubular function is restored with improvement in concentrating ability. At about the same time, the BUN and creatinine begin to return to normal. In some cases, mild to moderate kidney damage persists.

Postrenal Failure

Postrenal failure results from obstruction of urine outflow from the kidneys. The obstruction can occur in the ureter (i.e., calculi and strictures), bladder (i.e., tumors or neurogenic bladder), or urethra (i.e., prostatic hyperplasia). Prostatic hyperplasia is the most common underlying problem. Because both ureters must be occluded to produce renal failure, obstruction of the bladder rarely causes ARF unless one of the kidneys already is damaged or a person has only one kidney. The treatment of acute postrenal failure consists of treating the underlying cause of obstruction so that urine flow can be reestablished before permanent nephron damage occurs.

Diagnosis and Treatment

Given the high morbidity and mortality rates associated with ARF, attention should be focused on prevention and early diagnosis. This includes assessment measures to identify persons at risk for development of ARF, including those with preexisting renal insufficiency and diabetes. These persons are particularly at risk for development of

ARF due to nephrotoxic drugs (e.g., aminoglycosides and radiocontrast agents) or drugs such as the NSAIDs that alter intrarenal hemodynamics. Elderly persons are susceptible to all forms of ARF because of the effects of aging on renal reserve.

Careful observation of urine output is essential for persons at risk for development of ARF. Urine tests that measure urine osmolality, urinary sodium concentration, and fractional excretion of sodium help differentiate prerenal azotemia, in which the reabsorptive capacity of the tubular cells is maintained, from tubular necrosis, in which these functions are lost. One of the earliest manifestations of tubular damage is the inability to concentrate the urine. Further diagnostic information that can be obtained from the urinalysis includes evidence of proteinuria, hemoglobinuria, myoglobinuria, and casts or crystals in the urine. Blood tests for BUN and creatinine provide information regarding the ability to remove nitrogenous wastes from the blood. It also is important to exclude urinary obstruction.

A major concern in the treatment of ARF is identifying and correcting the cause (e.g., improving renal perfusion, discontinuing nephrotoxic drugs). Fluids are carefully regulated in an effort to maintain normal fluid volume and electrolyte concentrations. Adequate caloric intake is needed to prevent the breakdown of body proteins, which increases nitrogenous wastes.[5,8,10] Parenteral hyperalimentation may be used for this purpose. Because secondary infections are a major cause of death in persons with ARF, constant effort is needed to prevent and treat such infections.

Hemodialysis or continuous renal replacement therapy (CRRT) may be indicated when nitrogenous wastes and the water and electrolyte balance cannot be kept under control by other means.[5,10] Venovenous or arteriovenous CRRT has emerged as a method for treating ARF in patients too hemodynamically unstable to tolerate hemodialysis. An associated advantage of CRRT is the ability to administer nutritional support. The disadvantages are the need for prolonged anticoagulation therapy and continuous sophisticated monitoring.

In summary, acute renal failure (ARF) is an acute, potentially reversible suppression of kidney function. The disorder, which is a common threat to seriously ill persons in intensive care units, is characterized by a decrease in GFR, accumulation of nitrogenous wastes in the blood, and alterations in body fluids and electrolytes. ARF is classified as prerenal, intrinsic, and postrenal in origin. Prerenal failure is caused by decreased blood flow to the kidneys, intrinsic failure by disorders within the kidney itself, and postrenal failure by obstruction to urine output. Acute tubular necrosis, due to ischemia, sepsis, or nephrotoxic agents, is a common cause of acute intrarenal failure. Acute tabular necrosis (ATN) typically progresses through three phases: the initiation phase, during which tubular injury is induced; the maintenance phase, during which the GFR falls, nitrogenous wastes accumulate, and urine output decreases; and the recovery or reparative phase, during which the GFR, urine output, and blood levels of nitrogenous wastes return to normal.

Because of the high morbidity and mortality rates associated with ARF, identification of persons at risk is important to clinical decision making. Acute renal failure often is reversible, making early identification and correction of the underlying cause (e.g., improving renal perfusion, discontinuing nephrotoxic drugs) important. Treatment includes the judicious administration of fluids and hemodialysis or continuous renal replacement therapy.

Chronic Kidney Disease

Chronic kidney disease (CKD) is increasingly being recognized as a global health problem affecting people of all ages, races, and economic groups. The prevalence and incidence of the disease continues to rise, reflecting the growing elderly population and the increasing numbers of people with diabetes and hypertension. In the United States alone, 9.6% of noninstitutionalized adults are estimated to have CKD.[13] Statistics from Canada, Europe, Australia, and Asia confirm the high prevalence of CKD.[13,14]

Definition and Classification

Chronic kidney disease is a pathophysiologic process with multiple etiologies that results in the permanent loss of nephrons and a decline in function that frequently lead to kidney failure. Chronic kidney disease is commonly classified using the internationally accepted Kidney Disease Outcome Quality Initiative (KDOQI) staging system of the National Kidney Foundation (NKF).[15,16] The KDOQI definition and classification uses the GFR to classify CKD into five stages, beginning with kidney damage with normal or elevated GFR, progressing to CKD and, potentially, to kidney failure (Table 26-1). It is anticipated that early detection of kidney damage along with implementation of aggressive measures to decrease its progression can delay or prevent the onset of kidney failure.

GFR is used as it is much more sensitive than serum creatinine. Kidney damage that is present but undetected due to a normal GFR is classified as stage 1. Individuals with a mild decrease in GFR of 60 to 89 mL/minute/1.73 m^2 (corrected for body surface area) without kidney damage are classified as stage 2.[15] Decreased GFR without recognized markers of kidney damage can occur in infants and older adults and is usually considered to be "normal for age." Other causes of chronically decreased GFR without kidney damage in adults include removal of one kidney, extracellular fluid volume depletion, and systemic illnesses associated with reduced kidney perfusion, such as heart failure and cirrhosis.[15] Even at this stage, there is often a characteristic loss of renal reserve.

Chronic kidney disease, or stages 3 and 4 kidney disease, are defined as either kidney damage or a GFR of 30 to 59 mL/minute/1.73 m^2 for 3 months or longer.[15] CKD can result from a number of conditions that cause

TABLE 26-1 Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR, glomerular filtration rate.
Adapted from National Kidney Foundation. (2002). K/DOQI *clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification*. [Online.] Available: www.kidney.org/professionals/kdoqi/guidelines_ckd/toc/htm. Accessed April 16, 2009.

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

permanent loss of nephrons, including diabetes, hypertension, glomerulonephritis, systemic lupus erythematosus, and polycystic kidney disease.[15,17]

The KDOQI guidelines define stage 5 CKD or *kidney failure* "as either (1) a GFR of less than 15 mL/min/1.73 m², usually accompanied by most of the signs and symptoms of uremia, or (2) a need to start renal replacement therapy (dialysis or transplantation)."[15] These guidelines point out that kidney failure is not synonymous with end-stage renal disease (ESRD), which is an administrative term in the United States that indicates a person is being treated with dialysis and transplantation, a condition that qualifies persons to receive health care through the Medicare ESRD program.

Regardless of cause, CKD represents a loss of functioning kidney nephrons with progressive deterioration of glomerular filtration, tubular reabsorptive capacity, and endocrine functions of the kidneys. All forms of CKD are characterized by a reduction in the GFR, reflecting a corresponding reduction in the number of functional nephrons (Fig. 26-3).[17] The rate of nephron destruction differs from case to case, ranging from several months to many years. Typically, the signs and symptoms of CKD occur gradually and do not become evident until the disease is far advanced. This is because of the amazing compensatory ability of the kidneys. As

Chronic Kidney Disease

- Chronic kidney disease (CKD) represents the progressive decline in kidney function due to the permanent loss of nephrons.
- CKD can result from a number of conditions, including diabetes, hypertension, glomerulonephritis, and other kidney diseases.
- The glomerular filtration rate (GFR) is considered the best measure of kidney function.
- The National Kidney Foundation (NKF) Practice Guidelines divide CKD into five stages based on GFR, beginning with minimal loss of renal function (stage 1) and progressing to kidney failure (stage 5).
- The Practice Guidelines are intended to encourage the early diagnosis of CKD so that measures to delay or prevent its progression are instituted.

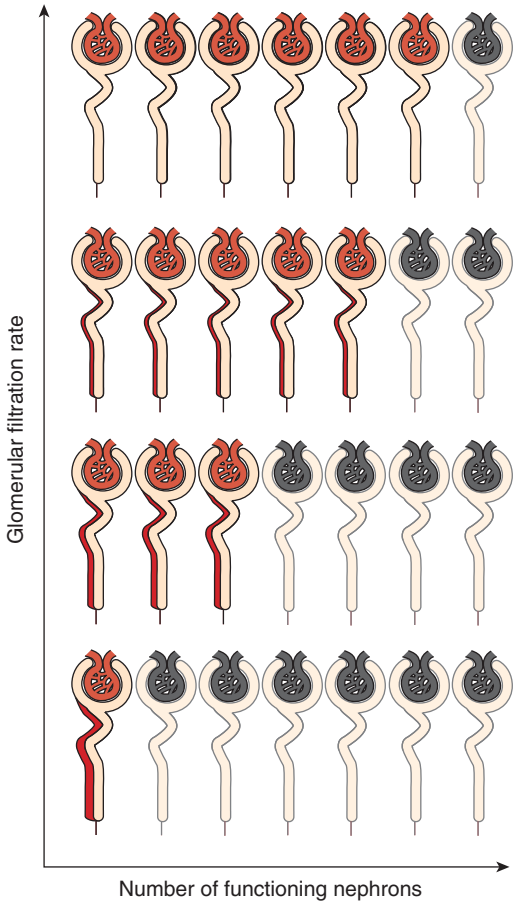


FIGURE 26-3. Relation of renal function and nephron mass. Each kidney contains about 1 million tiny nephrons. A proportional relation exists between the number of nephrons affected by a disease process and the resulting glomerular filtration rate.

kidney structures are destroyed, the remaining nephrons undergo structural and functional hypertrophy, each increasing its function as a means of compensating for those that have been lost. In the process, each of the remaining nephrons must filter more solute particles from the blood. It is only when the few remaining nephrons are destroyed that the manifestations of kidney failure become evident.

Glomerular Filtration Rate and Other Indicators of Renal Function

The GFR is considered the best measure of overall function of the kidney. The normal GFR, which varies with age, sex, and body size, is approximately 120 to 130 mL/minute/1.73 m^2 for normal young healthy adults.[15] A GFR below 60 mL/minute/1.73 m^2 represents a loss of one half or more of the level of normal adult kidney function.[18] In clinical practice, GFR is usually estimated using the serum creatinine concentration. Creatinine, a by-product of muscle metabolism, is freely filtered in the glomerulus and is not reabsorbed in the renal tubules. It is produced at a relatively constant rate by muscles in the body, and essentially all the creatinine that is filtered in the glomerulus is lost in the urine rather than being reabsorbed into the blood. Thus, serum creatinine can be used as an indirect method for assessing the GFR and the extent of kidney damage that has occurred in CKD.

Although the GFR can be obtained from measurements of creatinine clearance using timed (e.g., 24-hour) urine collection methods, the levels gathered are reportedly no more reliable than the estimated levels obtained by using serum creatinine levels.[15] Because GFR varies with age, sex, ethnicity, and body size, the Modification of Diet in Renal Diseases (MDRD) equation that takes these factors into account is often used for estimating the GFR based on serum creatinine levels[15,17,19] (available online at http://www.kidney.org/professionals/Kdoqi/gfr.cfm).

Proteinuria serves as a key adjunctive tool for measuring nephron injury and repair. Urine normally contains small amounts of protein. However, a persistent increase in protein excretion usually is a sign of kidney damage. The type of protein (e.g., low–molecular-weight globulins or albumin) depends on the type of kidney disease.[20] Increased excretion of low–molecular-weight globulins is a marker of tubulointerstitial disease, and excretion of albumin is a marker of CKD, resulting from hypertension or diabetes mellitus. For the diagnosis of CKD in adults and postpuberal children with diabetes, measurement of urinary albumin is preferred.[21] In most cases, urine dipstick tests are acceptable for detecting albuminuria. If the urine dipstick test is positive (1+ or greater), albuminuria is usually confirmed by quantitative measurement of the albumin-to-creatinine ratio in a spot (untimed) urine specimen.[20,21] Microalbuminuria, which is an early sign of diabetic kidney disease, refers to albumin excretion that is above the normal range but below the range normally detected by tests of total protein excretion in the urine. Populations at risk for CKD (i.e., those with diabetes mellitus, hypertension, or family history of kidney disease) should be screened for microalbuminuria, at least annually, as part of their health examination.[21]

Other markers of kidney disease include abnormalities in urine sediment (red and white blood cells) and abnormal findings on imaging studies.[16,17,20] Ultrasonography is particularly useful for detecting a number of kidney disorders, including urinary tract obstructions, infections, stones, and polycystic kidney disease. Other tests such as red blood cell indices, serum albumin levels, plasma electrolytes, and blood urea nitrogen are used to follow the progress of the disorder.

Clinical Manifestations

The manifestations of CKD include altered fluid, electrolyte, and acid-base balance; disorders of mineral metabolism and bone disease; anemia and coagulation disorders; cardiovascular complications; and disorders associated with an accumulation of nitrogenous wastes and impaired drug elimination[16,18,22] (Fig. 26-4). The underlying mechanisms for many of these manifestations are often interrelated. The point at which these disorders make their appearance and the severity of the manifestations are determined largely by coexisting disease conditions and the extent to which kidney function has been reduced. Many of them make their appearance before the GFR has reached the kidney failure stage.

Disorders of Fluid, Electrolyte, and Acid-Base Balance

The kidneys function in the regulation of extracellular fluid volume.[16] They do this by either eliminating or conserving sodium and water. CKD can produce dehydration or fluid overload, depending on the pathologic process of the kidney disease. In addition to volume regulation, the ability of the kidneys to concentrate the urine is diminished. An early symptom of kidney damage is *isosthenuria* or polyuria with urine that is almost isotonic with plasma (i.e., specific gravity of 1.008 to 1.012) and varies little from voiding to voiding.

As renal function declines further, the ability to regulate sodium excretion is reduced. The kidneys normally tolerate large variations in sodium intake while maintaining normal serum sodium levels. In CKD, they lose the ability to regulate sodium excretion. There is impaired ability to adjust to a sudden reduction in sodium intake and poor tolerance of an acute sodium overload. Volume depletion with an accompanying decrease in the GFR can occur with a restricted sodium intake or excess sodium loss caused by diarrhea or vomiting. Salt wasting is a common problem in advanced kidney failure because of impaired tubular reabsorption of sodium. Increasing sodium intake in persons with kidney failure often improves the GFR and whatever renal function remains. In patients with associated hypertension, the possibility of increasing blood pressure or producing congestive heart failure often excludes supplemental sodium intake.

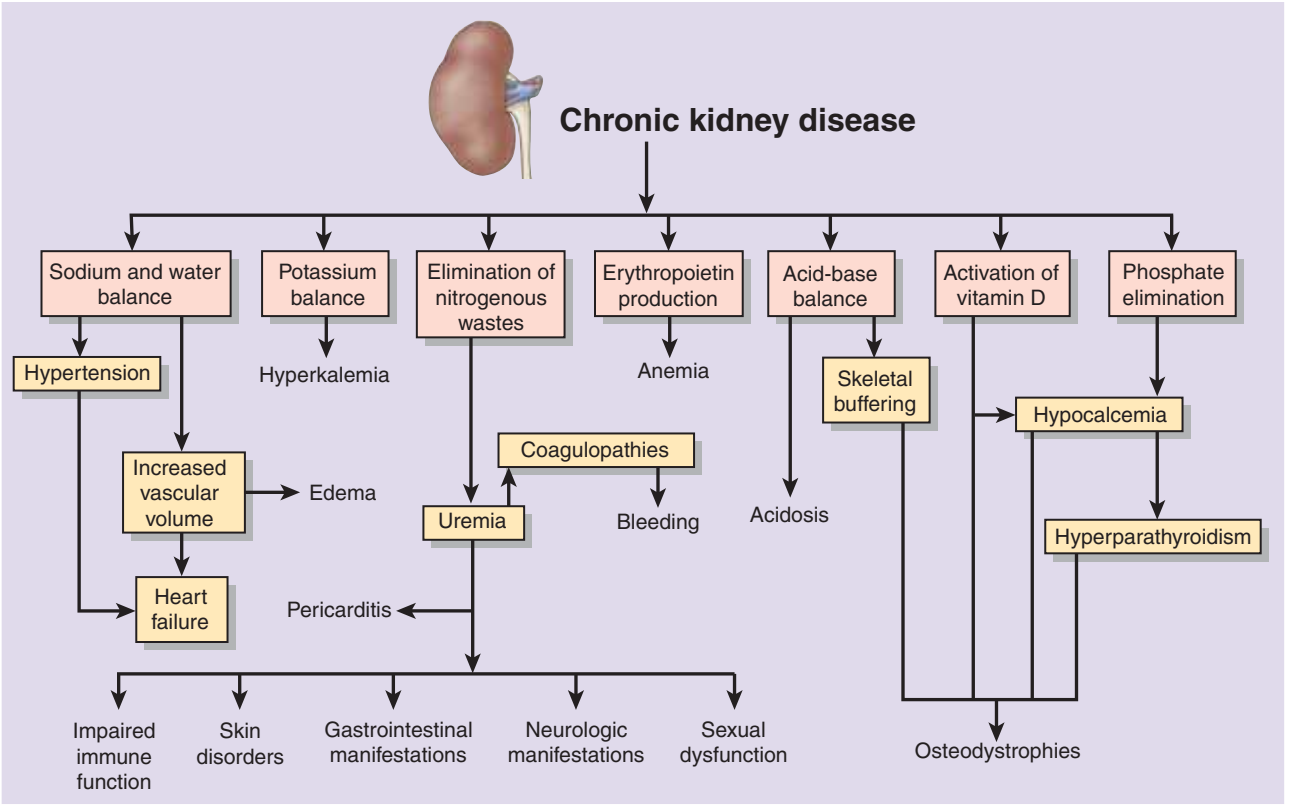


FIGURE 26-4. Mechanisms and manifestations of chronic kidney disease.

Approximately 90% of potassium excretion is through the kidneys. In CKD, potassium excretion by each nephron increases as the kidneys adapt to a decrease in the GFR. In addition, excretion in the gastrointestinal tract is increased. As a result, hyperkalemia usually does not develop until kidney function is severely compromised.[16] Because of this adaptive mechanism, it usually is not necessary to restrict potassium intake until the GFR has dropped below 5 to 10 mL/minute/1.73 m^2.[21] In persons with kidney failure, hyperkalemia often results from failure to follow dietary potassium restrictions; constipation; acute acidosis that causes the release of intracellular potassium into the extracellular fluid; trauma or infection that causes release of potassium from body tissues; or exposure to medications that contain potassium, prevent its entry into cells, or block its secretion in distal nephrons.

The kidneys also regulate the pH of the blood by eliminating hydrogen ions produced in metabolic processes and regenerating bicarbonate.[16] This is achieved through hydrogen ion secretion, sodium and bicarbonate reabsorption, and the production of ammonia, which acts as a buffer for titratable acids (see Chapter 8). With a decline in kidney function, these mechanisms become impaired and metabolic acidosis may occur when the person is challenged with an excessive acid load or loses excessive alkali, as in diarrhea. The acidosis that occurs in persons with kidney failure seems to stabilize as the disease progresses, probably as a result of the tremendous buffering capacity of bone. However, this buffering action is thought to increase bone resorption and contribute to the skeletal disorders that occur in persons with CKD.

Disorders of Calcium and Phosphorous Balance and Bone Disease

Abnormalities in calcium and phosphorous metabolism occur early in the course of CKD due to impaired phosphate elimination and vitamin D activation.[17,22–25] The regulation of serum phosphate levels requires a daily urinary excretion of an amount equal to that ingested in the diet. With deteriorating renal function, phosphate excretion is impaired, causing serum phosphate levels to rise. As a result, serum calcium levels, which are inversely regulated in relation to serum phosphate levels, fall. The drop in serum calcium, in turn, stimulates parathyroid hormone (PTH) release, with a resultant increase in calcium resorption from bone. Although serum calcium levels are maintained through increased PTH function, this adjustment is accomplished at the expense of the skeletal system and other body organs.

The kidneys regulate vitamin D activity by converting the inactive form of vitamin D (25[OH] vitamin D_3) to calcitriol (1,25[OH] vitamin D_3), the active form of vitamin D.[23–25] Reduced levels of 1,25[OH] vitamin D_3 impair the absorption of calcium from the intestine. Calcitriol also has a direct suppressive effect on PTH production; therefore, reduced levels of calcitriol produce an increase in PTH Levels. Most persons with CKD develop secondary hyperparathyroidism, the result of chronic

stimulation of the parathyroid glands. Vitamin D also regulates osteoblast differentiation, thereby affecting bone replacement.

The term *renal osteodystrophy* is used to describe the skeletal complications of CKD.[23–25] The skeletal changes that occur with CKD have been divided into two major types of disorders: high–bone-turnover and low–bone-turnover osteodystrophy. Some persons may have predominantly one type of bone disorder, whereas others may have a mixed type of bone disease. Inherent to both of these conditions is abnormal reabsorption and defective remodeling of bone (see Chapter 44). Mild forms of defective bone metabolism may be observed in early stages of CKD (stage 2), and they become more severe as kidney function deteriorates.

High–bone-turnover osteodystrophy, sometimes referred to as *osteitis fibrosa,* is characterized by increased bone resorption and formation, with bone resorption predominating. The disorder is associated with secondary hyperparathyroidism; altered vitamin D metabolism, along with resistance to the action of vitamin D; and impaired regulation of locally produced growth factors and inhibitors. There is an increase in both osteoblast and osteoclast numbers and activity. Although the osteoblasts produce excessive amounts of bone matrix, mineralization fails to keep pace, and there is a decrease in bone density and formation of porous and coarse-fibered bone. Cortical bone is affected more severely than cancellous bone. Bone marrow fibrosis is another component of osteitis fibrosa; it occurs in areas of increased bone cell activity. In advanced stages of the disorder, cysts may develop in the bone, a condition called *osteitis fibrosa cystica*.

Low–bone-turnover osteodystrophy is characterized by decreased numbers of osteoblasts and low or reduced numbers of osteoclasts, a low rate of bone turnover, and an accumulation of unmineralized bone matrix. There are two forms of low–bone-turnover osteodystrophy: osteomalacia and adynamic osteodystrophy. *Osteomalacia* is characterized by a slow rate of bone formation and defects in bone mineralization, which may be caused by vitamin D deficiency, excess aluminum deposition, or metabolic acidosis. Metabolic acidosis is thought to have a direct effect on both osteoblastic and osteoclastic activity, as well as on the mineralization process, by decreasing the availability of trivalent phosphate. Until the 1980s, the osteomalacia seen in CKD resulted mainly from aluminum intoxication. During the 1970s and 1980s, it was discovered that accumulation of aluminum from water used in dialysis and aluminum salts used as phosphate binders caused osteomalacia and adynamic bone disease. This discovery led to a change in the composition of dialysis solutions and the substitution of calcium carbonate for aluminum salts as phosphate binders. As a result, the prevalence of osteomalacia in persons with CKD has declined.

The second type of low–bone-turnover osteodystrophy, *adynamic osteodystrophy,* is characterized by a low number of osteoblasts, with the osteoclast number being normal or reduced. It is now recognized as being as common as high–bone-turnover osteodystrophy and is especially common among persons with diabetes. Adynamic bone disease is characterized by reduced bone volume and mineralization that may result, in part, from excessive suppression of PTH production with calcitriol.

Regardless of the cause of skeletal abnormalities in CKD, bone disease can lead to bone pain and muscle weakness. In the lower extremities, proximal muscle can give rise to gait abnormalities and make it difficult to get out of a chair or climb stairs. Spontaneous bone fractures can occur that are slow to heal. When the calcium–phosphate product (serum calcium [mg/dL] × serum phosphate [mg/dL]) rises above 60 to 70, metastatic calcifications are commonly seen in blood vessels, soft tissues, lungs, and myocardium.

Early treatment of hyperphosphatemia and hypocalcemia is important to prevent or slow the development of skeletal complications. Milk products and other foods high in phosphorus content are restricted in the diet. Phosphate-binding antacids (aluminum salts, calcium carbonate, or calcium acetate) may be prescribed to decrease absorption of phosphate from the gastrointestinal tract. Aluminum-containing antacids can contribute to the development of osteodystrophy, whereas calcium-containing phosphate binders can lead to hypercalcemia, thus worsening soft tissue calcification, especially in persons receiving vitamin D therapy. Phosphate-binding agents that do not contain calcium or aluminum (e.g., sevelamer, lanthanum) are now available.[23–25] Pharmacologic forms of activated vitamin D often are used to increase serum calcium levels and, at least partially, reverse the secondary hyperparathyroidism and osteitis fibrosis that occur with CKD. Secondary hyperparathyroidism may also be treated by activating the calcium-sensing receptor on the parathyroid gland (see Chapter 8). The calcimimetic agent cinacalcet, the first representative of a new class of drugs that act through the calcium-sensing receptor, has been approved for treatment of secondary hyperparathyroidism in CKD.[25] However, because adynamic bone disease is often a consequence of overzealous treatment of secondary hyperthyroidism, these agents require careful use.

Disorders of Hematologic Function

Anemia is a common complication of CKD. It tends to develop early in the course of the disease process, often interfering with quality of life.[26] Approximately 8 million people in the United States have stage 3 kidney disease (GFR of 30 to 60 mL/minute/1.73 m^2) and almost half of these persons are anemic.[27] Current KDOQI guidelines recommend monitoring of hemoglobin at least once a year in persons with CKD, with more frequent monitoring in the later stages when anemia treatment is necessary.

The anemia of CKD is due to several factors, including chronic blood loss, hemolysis, bone marrow suppression due to retained uremic factors, and decreased red cell production due to impaired production of erythropoietin and iron deficiency. The kidneys are the primary site for the production of the hormone *erythropoietin,* which controls red blood cell production.[26–28] In renal failure, erythropoietin production usually is insufficient to stimulate adequate red blood cell production by the bone marrow.

Among the causes of iron deficiency in persons with CKD are anorexia and dietary restrictions that limit intake and the blood loss that occurs during dialysis.

When untreated, anemia causes or contributes to weakness, fatigue, depression, insomnia, and decreased cognitive function. There also is an increasing concern regarding the physiologic effects of anemia on cardiovascular function.[28] The anemia of renal failure produces a decrease in blood viscosity and a compensatory increase in heart rate. The decreased blood viscosity also exacerbates peripheral vasodilation and contributes to decreased vascular resistance. Cardiac output increases in a compensatory fashion to maintain tissue perfusion. Anemia also limits myocardial oxygen supply, particularly in persons with coronary heart disease, predisposing to angina pectoris and other ischemic events.

A remarkable advance in the treatment of anemia in CKD was realized when recombinant human erythropoietin (rhEPO) became available.[16,26,27] The K/DOQI guidelines recommend maintaining a target hemoglobin level of at least 11 to 12 g/dL but find that evidence is insufficient to support routinely maintaining hemoglobin levels of 13 g/dL or greater. Because iron deficiency is common among persons with CKD, iron supplementation often is needed.[16,26] Iron can be given orally or intravenously. Intravenous iron is used for treatment of persons who are not able to maintain adequate iron status with oral iron. Although adverse reactions have been reported, intravenous preparations are generally safe and well tolerated.[27]

Bleeding disorders manifested by persons with CKD include epistaxis, menorrhagia, gastrointestinal bleeding, and bruising of the skin and subcutaneous tissues. Although platelet production often is normal in CKD, platelet function is impaired.[29] Coagulative function improves with dialysis but does not completely normalize, suggesting that uremia contributes to the problem. Persons with CKD also have greater susceptibility to thrombotic disorders, particularly if their underlying disease was characterized by a nephrotic presentation.

Disorders of Cardiovascular Function

Cardiovascular disease continues to be a major cause of death in persons with CKD. In fact, persons with CKD are more likely to die of cardiovascular disease than kidney failure.[30] Coexisting conditions that have been identified as contributing to the burden of cardiovascular disease include hypertension, diabetes mellitus, anemia, endothelial dysfunction, and vascular calcifications. Dyslipidemia is often an additional risk factor for cardiovascular disease in persons with CKD. The most common lipid abnormalities are hypertriglyceridemia, reduced high-density lipoprotein (HDL) levels, and increased concentrations of lipoprotein (a) (see Chapter 18).[31]

Hypertension commonly is an early manifestation of CKD. The mechanisms that produce hypertension in CKD are multifactorial; they include an increased vascular volume, elevation of peripheral vascular resistance, decreased levels of renal vasodilator prostaglandins, and increased activity of the renin-angiotensin-aldosterone system. Early identification and aggressive treatment of hypertension has been shown to slow the progression of renal impairment in many types of kidney disease.[16,22,30] Treatment involves salt and water restriction and the use of antihypertensive medications to control blood pressure. Many persons with CKD need to take several antihypertensive medications to control blood pressure (see Chapter 18).

The spectrum of cardiovascular disease due to CKD includes left ventricular hypertrophy, ischemic heart disease, and congestive heart failure.[16,22,32] People with CKD tend to have an increased prevalence of left ventricular dysfunction, with both depressed left ventricular ejection fraction, as in systolic dysfunction, and impaired ventricular filling, as in diastolic failure (see Chapter 19). Multiple factors lead to development of left ventricular dysfunction, including extracellular fluid overload, shunting of blood through an arteriovenous fistula for dialysis, and anemia. Anemia, in particular, has been correlated with the presence of left ventricular hypertrophy. These abnormalities, coupled with the hypertension that often is present, cause increased myocardial work and oxygen demand, with eventual development of heart failure.

Pericarditis occurs in approximately 20% of persons receiving chronic dialysis.[33] It can result from metabolic toxins associated with the uremic state or from dialysis. The manifestations of uremic pericarditis resemble those of viral pericarditis, with all its potential complications, including cardiac tamponade (see Chapter 19). The presenting signs include mild to severe chest pain with respiratory accentuation and a pericardial friction rub. Fever is variable in the absence of infection and is more common in dialysis than uremic pericarditis.

Disorders Associated with Accumulation of Nitrogenous Wastes

The accumulation of nitrogenous wastes in the blood, or *azotemia,* is often an early sign of kidney failure, occurring before other signs and symptoms become evident. Urea is one of the first nitrogenous wastes to accumulate in the blood, and the BUN level becomes increasingly elevated as CKD progresses. The normal concentration of urea in the blood is 8 to 20 mg/dL (2.9 to 7.1 mmol/L). In kidney failure, this level may rise to as high as 800 mg/dL (288 mmol/L).

Uremia, which literally means "urine in the blood," is the term used to describe the manifestations of kidney failure that are due to the accumulation of organic waste products in the blood.[34] Hypertension due to volume overload and anemia due to reduced production of erythropoietin were once regarded as signs of uremia; however, since their causes have been discovered, they are no longer considered as such.[34] The uremic state is characterized by signs and symptoms of altered neuromuscular function (e.g., fatigue, peripheral neuropathy, restless leg syndrome, sleep disturbances, uremic encephalopathy); gastrointestinal disturbances such as anorexia and nausea; white blood cell and immune dysfunction; amenorrhea and sexual dysfunction; and dermatologic manifestations such as pruritus. The onset of uremia in persons with CKD varies; some symptoms may be present to a lesser degree in persons with a GFR that is barely below 50% of normal.[34]

However, symptoms such as weakness and fatigue are often nonspecific and difficult to identify.

Neuromuscular Manifestations. Many persons with CKD have alterations in peripheral and central nervous system function.[17,22,35] Peripheral neuropathy, or involvement of the peripheral nerves, affects the lower limbs more frequently than the upper limbs. It is symmetric, affects both sensory and motor function, and is associated with atrophy and demyelination of nerve fibers, possibly due to uremic toxins. Restless leg syndrome is a manifestation of peripheral nerve involvement and can be seen in as many as two thirds of persons on dialysis. This syndrome is characterized by creeping, prickling, and itching sensations that typically are more intense at rest. Temporary relief is obtained by moving the legs. A burning sensation of the feet, which may be followed by muscle weakness and atrophy, is a manifestation of uremia.

The central nervous system disturbances in uremia are similar to those caused by other metabolic and toxic disorders. Sometimes referred to as *uremic encephalopathy,* the condition is poorly understood and may result, at least in part, from an excess of toxic organic acids that alter neural function. Electrolyte abnormalities, such as sodium shifts, also may contribute. The manifestations are more closely related to the progress of the uremic state than to the level of the metabolic end products. Reductions in alertness and awareness are the earliest and most significant indications of uremic encephalopathy. These often are followed by an inability to fix attention, loss of recent memory, and perceptual errors in identifying persons and objects. Delirium and coma occur late in the disease course; seizures are the preterminal event.

Disorders of motor function commonly accompany the neurologic manifestations of uremic encephalopathy. During the early stages, there often is difficulty in performing fine movements of the extremities; the gait becomes unsteady and clumsy with tremulousness of movement. Asterixis (dorsiflexion movements of the hands and feet) typically occurs as the disease progresses. It can be elicited by having the person hyperextend his or her arms at the elbow and wrist with the fingers spread apart. If asterixis is present, this position causes side-to-side flapping movements of the fingers.

Gastrointestinal Manifestations. Anorexia, nausea, and vomiting are common in persons with uremia, along with a metallic taste in the mouth that further depresses the appetite.[17,22] Early-morning nausea is common. Ulceration and bleeding of the gastrointestinal mucosa may develop, and hiccups are common. A possible cause of nausea and vomiting is the decomposition of urea by intestinal flora, resulting in a high concentration of ammonia. Nausea and vomiting often improve with restriction of dietary protein and after initiation of dialysis, and disappear after kidney transplantation.

Infection and Disorders of Immune Function. Infection is a common complication of CKD. Immunologic abnormalities decrease the efficiency of the immune response to infection.[22] All aspects of inflammation and immune function may be affected adversely by the high levels of urea and metabolic wastes, including a decreased granulocyte count, impaired humoral and cell-mediated immunity, and defective phagocyte function. The acute inflammatory response and delayed-type hypersensitivity response are impaired. Although persons with CKD have normal humoral responses to vaccines, a more aggressive immunization program may be needed. Skin and mucosal barriers to infection also may be defective. In persons who are maintained on dialysis, vascular access devices are common portals of entry for pathogens. Many persons with CKD fail to mount a fever with infection, making a diagnosis of infection more difficult.

Sexual Function. Alterations in sexual function and reproductive ability are common in CKD. The cause probably is multifactorial and may result from high levels of uremic toxins, neuropathy, altered endocrine function, psychological factors, and medications (e.g., antihypertensive drugs).

Impotence occurs in as many as 56% of male patients on dialysis.[36] Derangements of the pituitary and gonadal hormones, such as decreases in testosterone levels and increases in prolactin and luteinizing hormone levels, are common and cause erectile difficulties and decreased spermatocyte counts. Loss of libido may result from chronic anemia and decreased testosterone levels.

Impaired sexual function in women is manifested by abnormal levels of progesterone, luteinizing hormone, and prolactin. Hypofertility, menstrual abnormalities, decreased vaginal lubrication, and various orgasmic problems have been described. Amenorrhea is common among women who are on dialysis therapy.[17]

Skin Integrity. Skin disorders are common in persons with CKD.[17] The skin and mucous membranes often are dry, and subcutaneous bruising is common. Skin dryness is caused by a reduction in perspiration owing to the decreased size of sweat glands and the diminished activity of oil glands. Pruritus is common; it results from the high serum phosphate levels and the development of phosphate crystals that occur with hyperparathyroidism. Severe scratching and repeated needle sticks, especially with hemodialysis, break the skin integrity and increase the risk for infection. In the advanced stages of untreated kidney failure, urea crystals may precipitate on the skin as a result of the high urea concentration in body fluids. The fingernails may become thin and brittle, with a dark band just behind the leading edge of the nail followed by a white band. This appearance is known as *Terry nails.*

Disorders of Drug Elimination

The kidneys are responsible for the elimination of many drugs and their metabolites. CKD and its treatment can interfere with the absorption, distribution, and elimination of drugs.[37] The administration of large quantities of phosphate-binding antacids to control hyperphosphatemia and hypocalcemia in patients with advanced renal failure interferes with the absorption of some drugs. Many drugs are bound to plasma proteins, such as

albumin, for transport in the body; the unbound portion of the drug is available to act at the various receptor sites and is free to be metabolized. A decrease in plasma proteins, particularly albumin, that occurs in many persons with CKD results in less protein-bound drug and greater amounts of free drug.

In the process of metabolism, some drugs form intermediate metabolites that are toxic if not eliminated. Some pathways of drug metabolism, such as hydrolysis, are slowed with uremia. In persons with diabetes, for example, insulin requirements may be reduced as renal function deteriorates. Decreased elimination by the kidneys allows drugs or their metabolites to accumulate in the body and requires that drug dosages be adjusted accordingly. Some drugs contain unwanted nitrogen, sodium, potassium, and magnesium and must be avoided in patients with CKD. Penicillin, for example, contains potassium. Nitrofurantoin and ammonium chloride add to the body's nitrogen pool. Many antacids contain magnesium. Because of problems with drug dosing and elimination, persons with CKD should be cautioned against the use of over-the-counter remedies.

Management

Chronic kidney disease is treated by conservative management to prevent or slow the rate of nephron destruction and, when necessary, by renal replacement therapy with dialysis or transplantation.

Medical Management

Conservative treatment can often delay the progression of CKD.[17,38] It includes measures to retard deterioration of renal function and assist the body in managing the effects of impaired function. Urinary tract infections should be treated promptly and medication with renal damaging potential should be avoided. It should be noted that these strategies are complementary to the treatment of the original cause of the renal disorder, which is of the utmost importance and needs to be continually addressed.

Blood pressure control is important, as is control of blood glucose in persons with diabetes mellitus. Intensive glycemic control in persons with diabetes helps to prevent the development of microalbuminuria and retards the progression of diabetic nephropathy (see Chapter 33). In addition to reduction in cardiovascular risk, antihypertensive therapy in persons with CKD aims to slow the progression of nephron loss by lowering intraglomerular hypertension and hypertrophy.[17] Elevated blood pressure also increases proteinuria due to transmission of the elevated pressure to the glomeruli. This is the basis for the treatment guideline establishing 125/75 mm Hg as the target blood pressure for persons with CKD[15] (see Chapter 18). The ACE inhibitors and ARBs, which have a unique effect on the glomerular microcirculation (i.e., dilation of the efferent arteriole), are increasingly being used in the treatment of hypertension and proteinuria, particularly in persons with diabetes.[17]

It has become apparent that smoking has a negative impact on kidney function, and it is one of the most remedial risk factors for CKD.[39] The mechanisms of smoking-induced renal damage appear to include both acute hemodynamic effects (i.e., increased blood pressure, intraglomerular pressure, and urinary albumin excretion) and chronic effects (endothelial cell dysfunction).[39] Smoking is particularly nephrotoxic in elderly persons with hypertension and in those with diabetes. Importantly, the adverse effects of smoking appear to be independent of the underlying kidney disease.

Dialysis and Transplantation

Dialysis or renal replacement therapy is indicated when advanced uremia or serious electrolyte imbalances are present. The choice between dialysis and transplantation is dictated by age, related health problems, donor availability, and personal preference. Although transplantation often is the preferred treatment, dialysis plays a critical role as a treatment method for kidney failure. It is life sustaining for persons who are not candidates for transplantation or who are awaiting transplantation. There are two broad categories of dialysis: hemodialysis and peritoneal dialysis.

Hemodialysis. The basic principles of hemodialysis have remained unchanged over the years, although new technology has improved the efficiency and speed of dialysis.[40,41] A hemodialysis system, or artificial kidney, consists of three parts: a blood delivery system, a dialyzer, and a dialysis fluid delivery system. The dialyzer is usually a hollow cylinder composed of bundles of capillary tubes through which blood circulates, while the dialysate travels on the outside of the tubes.[40] The walls of the capillary tubes in the dialysis chamber are made up of a semipermeable membrane material that allows all molecules except blood cells and plasma proteins to move freely in both directions—from the blood into the dialyzing solution and from the dialyzing solution into the blood. The direction of flow is determined by the concentration of the substances contained in the two solutions. The waste products and excess electrolytes in the blood normally diffuse into the dialyzing solution. If there is a need to replace or add substances, such as bicarbonate, to the blood, these can be added to the dialyzing solution (Fig. 26-5).

During dialysis, blood moves from an artery through the tubing and blood chamber in the dialysis machine and then back into the body through a vein. Access to the vascular system is accomplished through an external arteriovenous shunt (i.e., tubing implanted into an artery and a vein) or, more commonly, through an internal arteriovenous fistula (i.e., anastomosis of a vein to an artery, usually in the forearm). Heparin is used to prevent clotting during the dialysis treatment; it can be administered continuously or intermittently. Problems that may occur during dialysis, depending on the rates of blood flow and solute removal, include hypotension, nausea, vomiting, muscle cramps, headache, chest pain, and disequilibrium syndrome. Most persons are dialyzed three times each

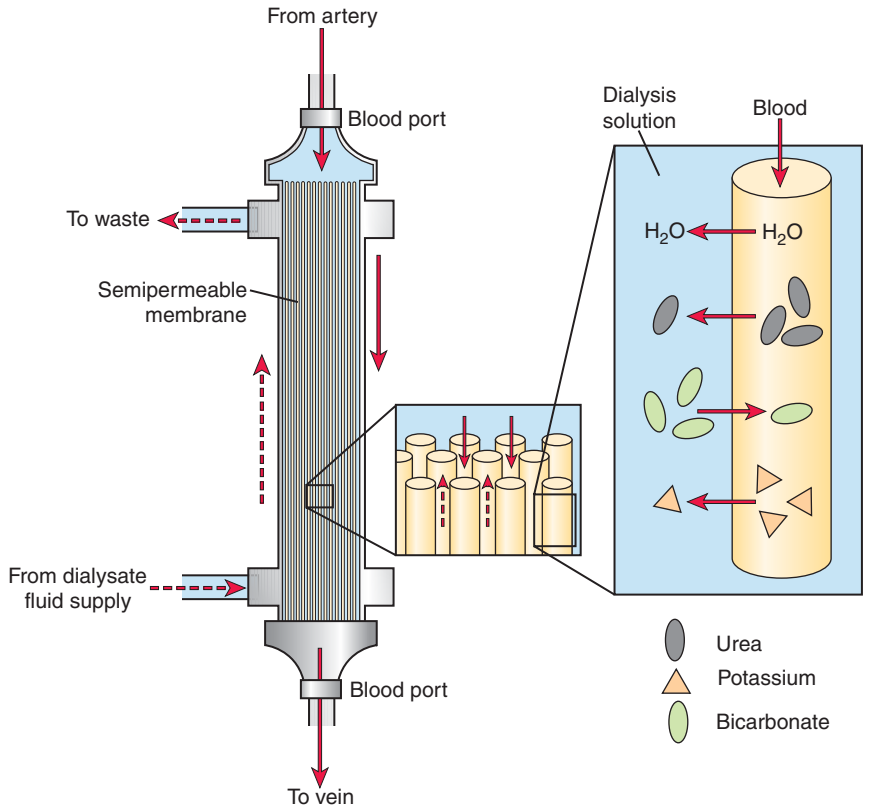


FIGURE 26-5. Schematic diagram of a hemodialysis system. The blood compartment and dialysis solution compartment are separated by a semipermeable membrane. This membrane is porous enough to allow all the constituents, except the plasma proteins and blood cells, to diffuse between the two compartments.

week for 3 to 4 hours. Many dialysis centers provide the option for patients to learn how to perform hemodialysis at home.

Peritoneal Dialysis. The same principles of diffusion, osmosis, and ultrafiltration that apply to hemodialysis apply to peritoneal dialysis.[40] The thin serous membrane of the peritoneal cavity serves as the dialyzing membrane. A Silastic catheter is surgically implanted in the peritoneal cavity below the umbilicus to provide access. The catheter is tunneled through subcutaneous tissue and exits on the side of the abdomen (Fig. 26-6). The dialysis process involves instilling a sterile dialyzing solution (usually 1 to 3 L) through the catheter over a period of approximately 10 minutes. The solution then is allowed to remain, or *dwell,* in the peritoneal cavity for a prescribed amount of time, during which the metabolic end products and extracellular fluid diffuse into the dialysis solution. At the end of the dwell time, the dialysis fluid is drained out of the peritoneal cavity by gravity into a sterile bag. The osmotic effects of glucose in the dialysis solution account for water removal.

Peritoneal dialysis can be performed at home or in a dialysis center and can be carried out by continuous ambulatory peritoneal dialysis (CAPD), continuous cyclic peritoneal dialysis (CCPD), or nocturnal intermittent peritoneal dialysis (NIPD)—all with variations in the number of exchanges and dwell times.[40] Individual preference, manual ability, lifestyle, knowledge of the procedure, and physiologic response to treatment are used to determine the type of dialysis that is used. The most common method is CAPD, a self-care procedure in which the person exchanges the dialysate four to six times a day. In CCPD, exchanges usually are performed at night, with the person connected to an automatic cycler. In the morning, the person, with the last exchange remaining in the abdomen, is disconnected from the cycler and goes about

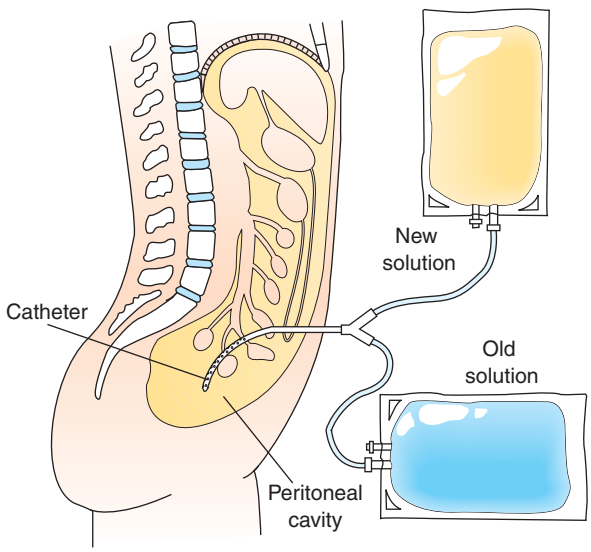


FIGURE 26-6. Peritoneal dialysis. A semipermeable membrane, richly supplied with small blood vessels, lines the peritoneal cavity. With dialysate dwelling in the peritoneal cavity, waste products diffuse from the network of blood vessels into the dialysate.

his or her usual activities. In NIPD, the person is given approximately 10 hours of automatic cycling each night, with the abdomen left dry during the day.

Potential problems with peritoneal dialysis include infection, catheter malfunction, dehydration caused by excessive fluid removal, hyperglycemia, and hernia. The most serious complication is infection, which can occur at the catheter exit site, in the subcutaneous tunnel, or in the peritoneal cavity (i.e., peritonitis).

Transplantation. Greatly improved success rates have made kidney transplantation the treatment of choice for many patients with CKD. The availability of donor organs continues to limit the number of transplantations performed each year. Donor organs are obtained from cadavers and living related donors (e.g., parent, sibling). Transplants from living unrelated donors (e.g., spouse) have been used in cases of suitable ABO blood type and tissue compatibility. The success of transplantation depends primarily on the degree of histocompatibility, adequate organ preservation, and immunologic management.[42] Maintenance immunosuppressive therapy plays an essential role in controlling T- and B-cell activation.

Dietary Management

A major component in the treatment of CKD is dietary management.[43] The goal of dietary treatment is to provide optimum nutrition while maintaining tolerable levels of metabolic wastes. The specific diet prescription depends on the type and severity of renal disease and on the dialysis modality. Because of the severe restrictions placed on food and fluid intake, these diets may be complicated and unappetizing. After kidney transplantation, some dietary restrictions still may be necessary, even when renal function is normal, to control the adverse effects from immunosuppressive medication.

Restriction of dietary proteins may decrease the progress of renal impairment in persons with advanced renal disease. Proteins are broken down to form nitrogenous wastes, and reducing the amount of protein in the diet lowers the BUN and reduces symptoms. Moreover, a high-protein diet is high in phosphates and inorganic acids. Considerable controversy exists over the degree of restriction needed. If the diet is too low in protein, protein malnutrition can occur, with a loss of strength, muscle mass, and body weight.

With CKD, adequate calories in the form of carbohydrates and fat are required to meet energy needs. This is particularly important when the protein content of the diet is severely restricted. If sufficient calories are not available, the limited protein in the diet goes into energy production, or body tissue itself is used for energy purposes.

Sodium and fluid restrictions depend on the kidneys' ability to excrete sodium and water and must be individually determined. Renal disease of glomerular origin is more likely to contribute to sodium retention, whereas tubular dysfunction causes salt wasting. Fluid intake in excess of what the kidneys can excrete causes circulatory overload, edema, and water intoxication. Thirst is a common problem among patients on hemodialysis, often resulting in large weight gains between treatments. Inadequate intake, on the other hand, causes volume depletion and hypotension and can cause further decreases in the already compromised GFR. It is common practice to allow a daily fluid intake of 500 to 800 mL, which is equal to insensible water loss plus a quantity equal to the 24-hour urine output.

When the GFR falls to extremely low levels in kidney failure or during hemodialysis therapy, dietary restriction of potassium becomes mandatory. Using salt substitutes that contain potassium or ingesting fruits, fruit juice, chocolate, potatoes, or other high-potassium foods can cause hyperkalemia. Most persons on CAPD do not need to limit potassium intake and often may even need to increase intake.

Persons with CKD are usually encouraged to limit their dietary phosphorus as a means of preventing secondary hyperparathyroidism, renal osteodystrophy, and metastatic calcification. Unfortunately, many processed and convenience foods contain considerable amounts of phosphorus additives. The most notable products using phosphorus additives are restructured meats (e.g., chicken nuggets, hot dogs), processed and spreadable cheeses, instant products (e.g., puddings, sauces), refrigerated bakery products, and beverages.[44] These phosphorus additives are highly absorbable. In a typical diet of grains, meats, and dairy products, only about 60% of phosphorus is absorbed, whereas phosphorus additives (e.g., polyphosphates, pyrophosphates) are almost 100% absorbed.[44] Identifying these newer phosphorus-containing foods is often challenging because manufacturers are no longer required to list the phosphorus content on food labels.

In summary, chronic kidney disease (CKD) results from the destructive effects of many forms of renal disease. Regardless of the cause, the consequences of nephron destruction in CKD are alterations in the filtration, reabsorption, and endocrine functions of the kidneys. Chronic disease is defined as either diagnosed kidney damage or a GFR of less than 60 mL/minute/1.73 m^2 for 3 months or more, and kidney failure as a GFR of less than 15 mL/minute/1.73 m^2, usually accompanied by most of the signs and symptoms of uremia or a need to start renal replacement therapy.

The manifestations of CKD reflect alterations in fluid, electrolyte, and acid-base balance; anemia and coagulopathies; cardiovascular complications; disorders of calcium and phosphate metabolism and skeletal disorders; and impaired elimination of drugs that are excreted by the kidney. It also results in an accumulation of nitrogenous wastes and signs and symptoms of the uremic state, such as neuromuscular disorders, gastrointestinal disturbances, immune disorders, sexual dysfunction, and discomforting skin changes.

The treatment measures for CKD can be divided into two types: conservative treatment measures and renal replacement therapy. Conservative treatment consists of measures to prevent or retard deterioration in remaining

renal function and assist the body in compensating for the existing impairment. Interventions that have been shown to retard the progression of CKD include blood pressure normalization and control of blood glucose in persons with diabetes. Recombinant human erythropoietin is used to treat the profound anemia that occurs in persons with CKD. Activated vitamin D can be used to increase calcium absorption and control secondary hyperparathyroidism. Renal replacement therapy (dialysis or kidney transplantation) is indicated when advanced uremia and serious electrolyte problems are present.

Chronic Kidney Disease in Children and Elderly Persons

Although the spectrum of CKD among children and elderly persons is similar to that of adults, several unique issues affecting these groups warrant further discussion.

Chronic Kidney Disease in Children

The true incidence of CKD in infants and children is unknown. Available data suggest that 1% to 2% of persons with CKD are in the pediatric age range.[45] The causes of CKD in children include congenital malformations, inherited disorders, acquired diseases, and metabolic syndromes. The underlying cause correlates closely with the age of the child.[46] In children younger than 5 years of age, CKD is commonly the result of congenital malformations, such as renal dysplasia or obstructive uropathy. After 5 years of age, acquired diseases (e.g., glomerulonephritis) and inherited disorders (e.g., familial juvenile nephronophthisis) predominate. CKD related to metabolic disorders, such as hyperoxaluria, and inherited disorders, such as polycystic kidney disease, may present throughout childhood.

The stages for progression of CKD in children are similar to those for adults: mild reduction of GFR to 60 to 89 mL/minute/1.73 m^2; moderate reduction of GFR to 30 to 59 mL/minute/1.73 m^2; severe reduction of GFR to 15 to 29 mL/minute/1.73 m^2; and kidney failure with a GFR of less than 15 mL/minute/1.73 m^2, or a need for renal replacement therapy.[47] Because the GFR is much lower in infancy and undergoes gradual changes in relation to body size during the first 2 years of age, these values apply only to children older than 2 years of age.[47]

The manifestations of CKD in children are quite varied and depend on the underlying disease condition. Features of CKD that are marked during childhood include severe growth impairment, developmental delay, delay in sexual maturation, bone abnormalities, and development of psychosocial problems. Critical growth periods occur during the first 2 years of life and during adolescence. Physical growth and cognitive development occur at a slower rate as consequences of CKD, especially among children with congenital kidney disease.[48] Puberty usually occurs at a later age in children with CKD, partly because of endocrine abnormalities. Renal osteodystrophies are more common and extensive in children than in adults. The most common condition seen in children is high–bone-turnover osteodystrophy caused by secondary hyperparathyroidism. Some hereditary renal diseases, such as medullary cystic disease, have patterns of skeletal involvement that further complicate the problems of renal osteodystrophy. Clinical manifestations of renal osteodystrophy include muscle weakness, bone pain, and fractures with minor trauma.[46] In growing children, rachitic bone changes, varus and valgus deformities of long bones, and slipped capital femoral epiphysis may be seen (see Chapter 43).

Factors related to impaired growth include deficient nutrition, anemia, renal osteodystrophy, chronic acidosis, and cases of nephrotic syndrome that require high-dose corticosteroid therapy. Nutrition is believed to be the most important determinant of growth during infancy. During childhood, growth hormone is important, and gonadotropic hormones become important during puberty. Parental heights provide a means of assessing growth potential (see Chapter 32). For many children, catch-up growth is important because a growth deficit frequently is established during the first months of life. Recombinant human growth hormone therapy has been used to improve growth in children with CKD.[49] Success of treatment depends on the level of bone maturation at the initiation of therapy.

All forms of renal replacement therapy can be safely and reliably used for children. Age is a defining factor in dialysis modality selection. The majority of North American children are treated with CCPD or NIPD, which leaves the child and family free of dialysis demands during waking hours, with the exchanges being performed automatically during sleep by the machine. Renal transplantation is considered the best alternative for children.[45,50] Early transplantation in young children is regarded as the best way to promote physical growth, improve cognitive function, and foster psychosocial development. Immunosuppressive therapy in children is similar to that used in adults. All of these immunosuppressive agents have side effects, including increased risk for infection. Corticosteroids, which have been the mainstay of chronic immunosuppressive therapy for decades, carry the risk for hypertension, orthopedic complications (especially aseptic necrosis), cataracts, and growth retardation.

Chronic Kidney Disease in Elderly Persons

Since the mid-1980s, there have been increasing numbers of elderly persons accepted to renal replacement therapy programs.[51,52] Data from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that almost 75% of people 75 years of age or older have a GFR less than 90 mL/minute/1.73 m^2 and almost 25% may have a GFR less than 60 mL/minute/1.73 m^2.[51] However, the true prevalence or outcomes of CKD in the elderly have not been systematically studied. Also, the

presentation and course of CKD may be altered because of age-related changes in the kidneys and concurrent medical conditions.

Normal aging is associated with a decline in the GFR and subsequently with reduced homeostatic regulation under stressful conditions.[52] This reduction in GFR makes elderly persons more susceptible to the detrimental effects of nephrotoxic drugs, such as radiographic contrast compounds. The reduction in GFR related to aging is not accompanied by a parallel rise in the serum creatinine level because the serum creatinine level, which results from muscle metabolism, is significantly reduced in elderly persons because of diminished muscle mass and other age-related changes. The KDOQI guidelines suggest that the same criteria for establishing the presence of CKD in younger adults (i.e., GFR <60 mL/minute/1.73 m^2) should be used for the elderly. Evaluation of elderly persons with a GFR of 60 to 89 mL/minute/1.73 m^2 should include age-adjusted measurements of creatinine clearance, along with assessment of CKD risks, measurement of blood pressure, albumin-to-creatinine ratio in a "spot" urine specimen, and examination of the urine sediment for red and white blood cells.[51]

The prevalence of chronic disease affecting the cerebrovascular, cardiovascular, and skeletal systems is higher in this age group.[53] Because of concurrent disease, the presenting symptoms of kidney disease in elderly persons may be less typical than those observed in younger adults. For example, congestive heart failure and hypertension may be the dominant clinical features with the onset of acute glomerulonephritis, whereas oliguria and discolored urine more often are the first signs in younger adults. The course of CKD may be more complicated in older patients with numerous chronic diseases.

Treatment of the elderly with CKD is usually based on the severity of kidney function impairment and stratification of risk for progression to renal failure and cardiovascular disease.[52] Persons with low risk may require only modification of dosages of medications excreted by the kidney, monitoring of blood pressure, avoidance of drugs and procedures that increase the risk of ARF, and lifestyle modification to reduce the risk of cardiovascular disease.

Elderly persons with more severe impairment of kidney function may require renal replacement therapy. Treatment options for CKD in elderly patients include hemodialysis, peritoneal dialysis, transplantation, and acceptance of death from uremia. Neither hemodialysis nor peritoneal dialysis has proved to be superior in the elderly. The mode of renal replacement therapy should be individualized, taking into account underlying medical and psychosocial factors. Age alone should not preclude renal transplantation.[52,53] With increasing experience, many transplantation centers have increased the age for acceptance on transplant waiting lists. Reluctance to provide transplantation as an alternative may have been due, at least in part, to the scarcity of available organs and the view that younger persons are more likely to benefit for a longer time. The general reduction in T-lymphocyte function that occurs with aging has been suggested as a beneficial effect that increases transplant graft survival.

In summary, available data suggest that 1% to 2% of patients with CKD are in the pediatric age range. The causes of CKD include congenital malformations (e.g., renal dysplasia and obstructive uropathy), inherited disorders (e.g., polycystic kidney disease), acquired diseases (e.g., glomerulonephritis), and metabolic syndromes (e.g., hyperoxaluria). Problems associated with CKD in children include growth impairment, delay in sexual maturation, and more extensive bone abnormalities than in adults. Although all forms of renal replacement therapy can be safely and reliably used in children, CCPD, NIPD, or transplantation optimizes growth and development.

Since the mid-1980s, there have been increasing numbers of elderly persons accepted for renal replacement therapy programs. Normal aging is associated with a decline in the GFR, which makes elderly persons more susceptible to the detrimental effects of nephrotoxic drugs and other conditions that compromise renal function. Current guidelines for diagnosis of CKD and stratification of risk for progression to kidney failure are the same as for younger adults. Treatment options for chronic renal failure in elderly patients are also similar to those for younger adults.

REVIEW EXERCISES

1. A 55-year-old man with diabetes and coronary heart disease, who had undergone cardiac catheterization with the use of a radiocontrast agent 2 days ago, is admitted to the emergency department with a flulike syndrome including chills, nausea, vomiting, abdominal pain, fatigue, and pulmonary congestion. His serum creatinine is elevated, and he has protein in his urine. He is admitted to the intensive care unit with a tentative diagnosis of acute renal failure due to radiocontrast nephropathy.

A. Radiocontrast agents are thought to exert their effects through decreased renal perfusion and through direct toxic effects on renal tubular structures. Explain how each of these phenomena contributes to the development of acute renal failure.

B. Explain the elevated serum creatinine, proteinuria, and presence of pulmonary congestion.

2. A 35-year-old, 70-kg white man with diabetes mellitus is seen in the diabetic clinic for his 6-month check-up. His serum creatinine, which was slightly elevated at his last visit, is now 1.6 mg/dL.

A. Use the following website to estimate his GFR: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

B. Would he be classified as having chronic kidney disease? If so, what stage? What might be done to delay or prevent further deterioration of his kidney function?

3. Chronic kidney disease is accompanied by hyperphosphatemia, hypocalcemia, impaired activation of vitamin D, hyperparathyroidism, and skeletal complications.

A. Explain the impaired activation of vitamin D and its consequences on calcium and phosphate homeostasis, parathyroid function, and mineralization of bone in persons with CKD.
B. Explain the possible complications of the administration of activated forms of vitamin D on parathyroid function and calcium and phosphate homeostasis.

REFERENCES

1. Singri N., Ahya S.N., Levin M.L. (2003). Acute renal failure. *Journal of the American Medical Association* 289, 747–751.
2. Brady H.R., Clarkson M.R., Liebman W. (2004). Acute renal failure. In Brenner B.M. (Ed.), *Brenner and Rector's the kidney online* (7th ed.). Philadelphia: Elsevier Saunders.
3. Thadhani R., Pascual M., Bonventre J.V. (1996). Acute renal failure. *New England Journal of Medicine* 334, 1448–1460.
4. Lameire N., Van Biesen W., Vanholder R. (2005). Acute renal failure. *Lancet* 365, 417–430.
5. Schrier R.W., Wang W., Pooler B., et al. (2004). Acute renal failure: Definitions, diagnosis, pathogenesis, and therapy. *Journal of Clinical Investigation* 114, 5–14.
6. Mitra A., Zolty E., Wang W., et al. (2005). Clinical acute renal failure. *Comprehensive Therapy* 31, 262–269.
7. Khalil P., Murty P., Palevsky P.M. (2008). The patient with acute renal injury. *Primary Care Clinics in Office Practice* 35, 239–264.
8. Abuelo J.G. (2007). Normotensive ischemic acute renal failure. *New England Journal of Medicine* 357(8), 797–805.
9. Guyton A., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 309–326). Philadelphia: Elsevier Saunders.
10. Gill N., Nally J.V., Fatica R.A. (2005). Renal failure secondary to acute tubular necrosis. *Chest* 128, 2847–2863.
11. Alpers C.E. (2010). The kidney. In Kumar V., Abbas A.K., Fausto N. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 935–938). Philadelphia: Saunders Elsevier.
12. McCullough P.A., Soman S.S. (2005). Contrast-induced nephropathy. *Critical Care Clinics* 21, 261–280.
13. Levey A.S., Atkins R., Coresh J., et al. (2007). Chronic kidney disease as a global health problem: Approaches and initiative—A position statement from Kidney Disease Improving Global Outcomes. *Kidney International* [Online] Available: http://www.kidney-international.org. Accessed March 15, 2009.
14. Levin A., Hemmelgarn B., Culleton B., et al. (2008). Guidelines for management of chronic kidney disease. *CMAJ* 179(11), 1154–1162.
15. National Kidney Foundation. (2002). *K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification.* [Online] Available: http://www.kidney.org/Professionals/kdoqi/. Accessed June 12, 2010.
16. Levey A.S., Eckardt K.-W., Tsukamato Y. (2005). Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving global outcomes (KDIGO). *Kidney International* 67, 2089–2100.
17. Skorecki K., Green J., Brenner B.M. (2005). Chronic renal failure. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1653–1663). New York: McGraw-Hill.
18. Levey A.S., Coresh J., Balk E., et al. (2003). National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Annals of Internal Medicine* 139, 137–147.
19. Stevens L.A., Coresh J., Greene T., et al. (2006). Assessing kidney function: Measured and estimated glomerular filtration rate. *New England Journal of Medicine* 354, 2473–2483.
20. Johnson C.A., Levey A.S., Coresh J., et al. (2004). Clinical practice guidelines for chronic kidney disease in adults: Part II. Glomerular filtration rate, proteinuria, and other markers. *American Family Physician* 70, 1091–1097.
21. Eknoyan G., Hostetter T., Barkis G.L., et al. (2003). Proteinuria and other markers of chronic kidney disease: A position statement of the National Kidney Foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). *American Journal of Kidney Diseases* 42, 617–622.
22. Thomas R., Kanso A., Sedor J.R. (2008). Chronic kidney disease and its complications. *Primary Care Clinics in Office Practice* 35, 329–344.
23. Eknoyan G., Levin N.W. (2003). Bone metabolism and disease in chronic kidney disease. *American Journal of Kidney Diseases* 42(Suppl 3), S1–S201.
24. Goodman W.G. (2005). Calcium and phosphorous metabolism in patients who have chronic kidney disease. *Medical Clinics of North America* 89, 631–647.
25. Martin K.J., Olgaard K., Colburn J.W., et al. (2004). Diagnosis, assessment, and treatment of bone turnover abnormalities in renal osteodystrophy. *American Journal of Kidney Diseases* 43, 558–565.
26. *KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target.* [Online] Available: http://www.kidney.org/professionals/kdoqi/guidelines_anemiaUP/guide1.htm. Accessed April 10, 2009.
27. Hsu C.Y., McCulloch C.E., Curhan G.C. (2000). Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the Third National Health and Nutrition Examination Survey. *Journal of the American Society of Nephrology* 13, 504–510.
28. Pendse S., Singh A.K. (2005). Complications of chronic renal kidney disease: Anemia, mineral metabolism, and cardiovascular disease. *Medical Clinics of North America* 89, 549–561.
29. Boccardo P., Remuzzi G., Galbusera M. (2004). Platelet dysfunction in renal failure. *Seminars in Thrombosis and Hemostasis* 30, 579–589.
30. Schiffrin E.L., Lipman M.L., Mann J.F.E. (2007). Chronic kidney disease: Effects on cardiovascular function. *Circulation* 116, 85–97.
31. Tsimihodimos V., Dounousi E., Siamopoulos K.C. (2008). Dyslipidemia in chronic kidney disease: An approach to pathogenesis and treatment. *American Journal of Nephrology* 28, 958–973.
32. Curtis B.M., Parfey P.S. (2005). Congestive heart failure in chronic kidney disease: Disease specific mechanisms of systolic and diastolic heart failure and management. *Cardiovascular Clinics* 23, 275–284.
33. Gunukula S., Spodick D.H. (2001). Pericardial disease in renal failure. *Seminars in Nephrology* 21, 52–56.
34. Meyer T.W., Hostetter T.H. (2007). Uremia. *New England Journal of Medicine* 357(13), 1316–1325.
35. Brouns R., De Deyn P.P. (2004). Neurological complications in renal failure: A review. *Clinical Neurology and Neurosurgery* 107, 1–16.
36. Foulks C.J., Cushner H.M. (1986). Sexual dysfunction in the male dialysis patient: Pathogenesis, evaluation, and therapy. *American Journal of Kidney Diseases* 8, 211–212.

37. Quan D.J., Aweeks F.T. (2005). Dosing of drugs in renal failure. In Koda-Kimble M.A., Young L.Y., Kradjan W.A., et al. (Eds.), *Applied therapeutics: The clinical use of drugs* (8th ed., pp. 34-1–34-26). Philadelphia: Lippincott Williams & Wilkins.
38. Jabor B.L., Madias N.E. (2005). Progression of chronic kidney disease: Can it be prevented or arrested? *American Journal of Medicine* 118, 1323–1330.
39. Orth S.R. (2004). Effects of smoking on systemic and intrarenal hemodynamics: Influence on renal function. *Journal of the American Society of Nephrology* 15(Suppl 1), S58–S63.
40. Singh A.K., Brenner B. (2005). Dialysis in treatment of renal failure. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1663–1667). New York: McGraw-Hill.
41. Daelemans R.A., D'Haese P.C., BeBroe M.E. (2001). Dialysis. *Seminars in Nephrology* 21, 204–212.
42. Carpenter C.B., Milford E.L., Sayegh M.H. (2005). Transplantation in treatment of renal failure. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1668–1674). New York: McGraw-Hill.
43. National Kidney Foundation. (2000). *Clinical practice guidelines for nutrition in chronic renal failure*. [Online] Available: www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_nut.html. Accessed January 19, 2007.
44. Karalis M. (2005). Hidden phosphorus in popular beverages: Part 1; at breakfast: Part II, and enhanced meats: Part IV. *Journal of Renal Nutrition* 15(2, 3, 4), e1–e6, e1–e6, e1–e4.
45. Chan J.C.M., Williams D.M., Roth K.S. (2002). Kidney failure in infants and children. *Pediatrics in Review* 23(2), 47–60.
46. Vogt B.A., Avner E.D. (2004). Renal failure. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 1767–1775). Philadelphia: Elsevier Saunders.
47. Hogg R.J., Furth S., Lemley K.V., et al. (2003). National Kidney Foundation's kidney disease outcomes quality initiative clinical practice guidelines for chronic kidney disease in children and adolescents: Evaluation, classification, and stratification. *Pediatrics* 111, 1416–1423.
48. Hanna J.D., Krieg R.J., Scheinman J.I., et al. (1996). Effects of uremia on growth in children. *Seminars in Nephrology* 16, 230–241.
49. Haffner D., Schaffer F., Nissel R., et al. (Study Group for Growth Hormone Treatment in Chronic Renal Failure). (2000). Effect of growth hormone treatment on the adult height of children with chronic renal failure. *New England Journal of Medicine* 343, 923–930.
50. Urizar R.E. (2007). Renal transplantation. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2214–2219). Philadelphia: Saunders Elsevier.
51. National Kidney Foundation. (2002). *Decreased kidney function in the elderly. KDOQI guidelines*. [Online] Available: http://www.kidney.org/PROFESSIONALS/kdoqi/guidelines_ckd/p9_approach.htm. Accessed June 21, 2010.
52. Tedla F.M., Friedman E.A. (2008). The trend toward geriatric nephrology. *Primary Care Clinics in Office Practice* 35, 515–530.
53. Hansberry M.R., Whittier W.L., Krause M.W. (2005). The elderly patient with chronic kidney disease. *Advances in Chronic Kidney Disease* 12(1), 71–77.

Control of Urine Elimination
Bladder Structure
Neural Control of Bladder Function
Spinal Cord Centers
Brain Stem and Higher Cortical Centers
Micturition and Maintenance of Continence
Evaluation of Bladder Function
Disorders of Bladder Structure and Function
Lower Urinary Tract Obstruction and Stasis
Compensatory and Decompensatory Changes
Neurogenic Bladder Disorders
Spastic Bladder: Failure to Store Urine
Flaccid Bladder: Failure to Empty Urine
Nonrelaxing External Sphincter
Treatment
Urinary Incontinence
Types and Causes of Incontinence
Diagnosis and Treatment
Special Needs of Elderly Persons
Urinary Tract Infections
Etiologic Factors
Host–Agent Interactions
Obstruction and Reflux
Catheter-Induced Infection
Clinical Features
Diagnosis and Treatment
Infections in Special Populations
Urinary Tract Infections in Women
Urinary Tract Infections in Children
Urinary Tract Infections in the Elderly
Cancer of the Bladder
Etiology and Pathogenesis
Manifestations
Diagnosis and Treatment

Chapter 27

Disorders of the Bladder and Lower Urinary Tract

Although the kidneys control the formation of urine and regulate the composition of body fluids, it is the bladder that stores urine and controls its elimination from the body. Alterations in the storage and expulsion functions of the bladder can result in incontinence, with its accompanying social and hygienic problems, or obstruction of urinary flow, which has deleterious effects on ureteral and, ultimately, renal function. The discussion in this chapter focuses on normal control of urine elimination and disorders of bladder function, urinary tract infections, and cancer of the bladder.

Control of Urine Elimination

The bladder, also known as the *urinary vesicle,* is a freely movable organ located retroperitoneally on the pelvic floor, just posterior to the pubic symphysis. It consists of two main components: the body in which urine collects, and the neck, which is a funnel-shaped extension of the body that connects with the urethra.[1–4] In the male, the urethra continues anteriorly through the penis, with the prostate gland surrounding the neck of the bladder where it empties into the urethra. In the female, the bladder is located anterior to the vagina and uterus.

Urine passes from the kidneys to the bladder through the ureters. The interior of the bladder has openings for both the ureters and the urethra. The smooth triangular area that is bounded by these three openings is called the *trigone* (Fig. 27-1). There are no valves at the ureteral openings, but as the pressure of the urine in the bladder rises, the ends of the ureters are compressed against the bladder wall to prevent the backflow of urine.

Bladder Structure

The bladder is composed of four layers. The first is an outer serosal layer, which covers the upper surface of the bladder and is continuous with the peritoneum. The second is a network of smooth muscle fibers called the *detrusor muscle.*

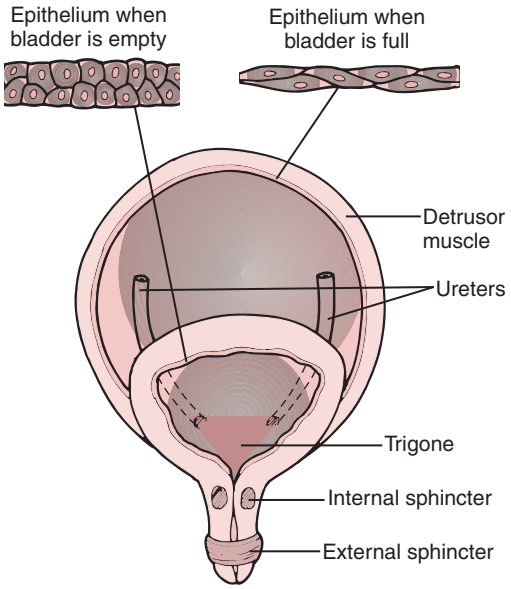


FIGURE 27-1. Diagram of the bladder, showing the detrusor muscle, ureters, trigone area, and urethral orifice. Note the flattening of epithelial cells when the bladder is full and the wall is stretched.

Bladder Function

- The functions of the bladder are storage and emptying of urine.
- The control of the storage and emptying functions of the bladder involves both involuntary (autonomic nervous system) and voluntary (somatic nervous system) control.
- The parasympathetic nervous system promotes bladder emptying. It produces contraction of the smooth muscle of the bladder wall and relaxation of the internal sphincter.
- The sympathetic nervous system promotes bladder filling. It produces relaxation of the smooth muscle of the bladder wall and contraction of the internal sphincter.
- The striated muscles in the external sphincter and pelvic floor, which are innervated by the somatic nervous system, provide for the voluntary control of urination and maintenance of continence.

The third is a submucosal layer of loose connective tissue, and the fourth is an inner mucosal lining of transitional epithelium (urothelium). This epithelium is essentially impermeable to salts and water. The tonicity and composition of the urine often is quite different from that of the blood, and the epithelial lining of the bladder acts as an effective barrier to prevent the passage of water and other urine elements between the bladder and the blood. The epithelial lining of the bladder is six or more layers thick in the empty bladder. However, when the bladder is distended, as few as two or three layers are seen. This change reflects the ability of these cells to flatten and unfold to accommodate the increased surface area of a distended bladder (see Fig. 27-1).

The detrusor muscle is the muscle of micturition (passage of urine). When it contracts, urine is expelled from the bladder. Muscles in the bladder neck, sometimes referred to as the *internal urethral sphincter,* are a continuation of the detrusor muscle. They run down obliquely behind the proximal urethra, forming the posterior urethra in males and the entire urethra in females. When the bladder is relaxed, these circular muscle fibers are closed and act as a sphincter. When the detrusor muscle contracts, the sphincter is pulled open as the shape of the bladder changes. In the female, the urethra (2.5 to 3.5 cm) is shorter than in the male (16.5 to 18.5 cm), and usually affords less resistance to urine outflow.

Another muscle important to bladder function is the *external sphincter,* a circular muscle composed of striated muscle fibers that surrounds the urethra distal to the base of the bladder. The external sphincter operates as a reserve mechanism to stop micturition when it is occurring and to maintain continence in the face of unusually high bladder pressure. The skeletal muscle of the pelvic floor also contributes to the support of the bladder and the maintenance of continence.

Neural Control of Bladder Function

Normal bladder function requires the coordinated interaction between the sensory and motor components of the involuntary autonomic and voluntary somatic nervous systems. The motor component of the neural reflex that causes bladder emptying is controlled by the parasympathetic nervous system, whereas the relaxation and storage function of the bladder is controlled by the sympathetic nervous system. The somatic nervous system provides for the voluntary control of the external sphincter and pelvic floor muscles. These functions are controlled by three neurologic centers: the spinal cord reflex centers, the micturition center in the pons, and cortical and subcortical centers.

Spinal Cord Centers

The centers for reflex control of bladder function are located in the sacral (S1 through S4) and thoracolumbar (T11 through L2) segments of the spinal cord[2–5] (Fig. 27-2). The parasympathetic lower motor neurons (LMNs) for the detrusor muscle of the bladder are located in the sacral segments of the spinal cord; their axons travel to the bladder by way of the *pelvic nerve*. LMNs for the external sphincter also are located in the sacral segments of the spinal cord. These LMNs receive their control from the motor cortex through the corticospinal tract and send impulses to the external sphincter through the *pudendal*

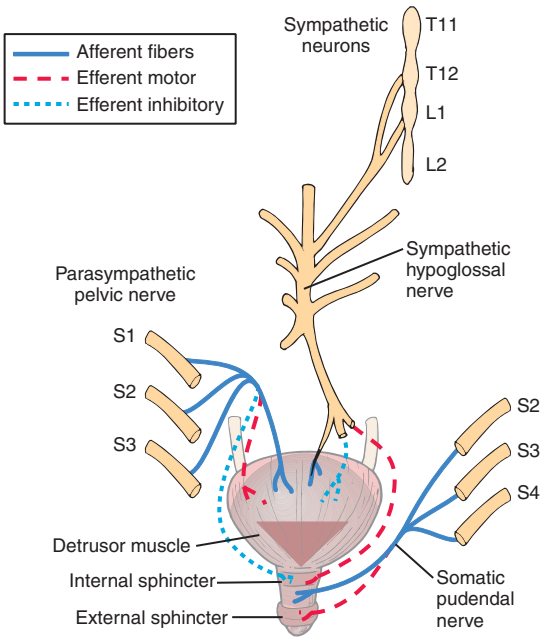


FIGURE 27-2. Nerve supply to the bladder and the urethra.

nerve. The bladder neck and trigone area of the bladder, because of their different embryonic origins, receive sympathetic outflow from the thoracolumbar (T11 to L2) segments of the spinal cord. In the male, the seminal vesicles, ampulla, and vas deferens also receive sympathetic innervation from the thoracolumbar segments of the cord.

The afferent input from the bladder and urethra is carried to the central nervous system (CNS) by fibers that travel with the parasympathetic (pelvic), somatic (pudendal), and sympathetic (hypogastric) nerves. The pelvic nerve carries sensory fibers from the stretch receptors in the bladder wall, the pudendal nerve carries sensory fibers from the external sphincter and pelvic muscles, and the hypogastric nerve carries sensory fibers from the trigone area.[2]

Brain Stem and Higher Cortical Centers

Pontine Micturition Center. The immediate coordination of the normal micturition reflex occurs in the micturition center in the pons, facilitated by descending input from the forebrain and ascending input from the reflex centers in the spinal cord[5] (Fig. 27-3). This center

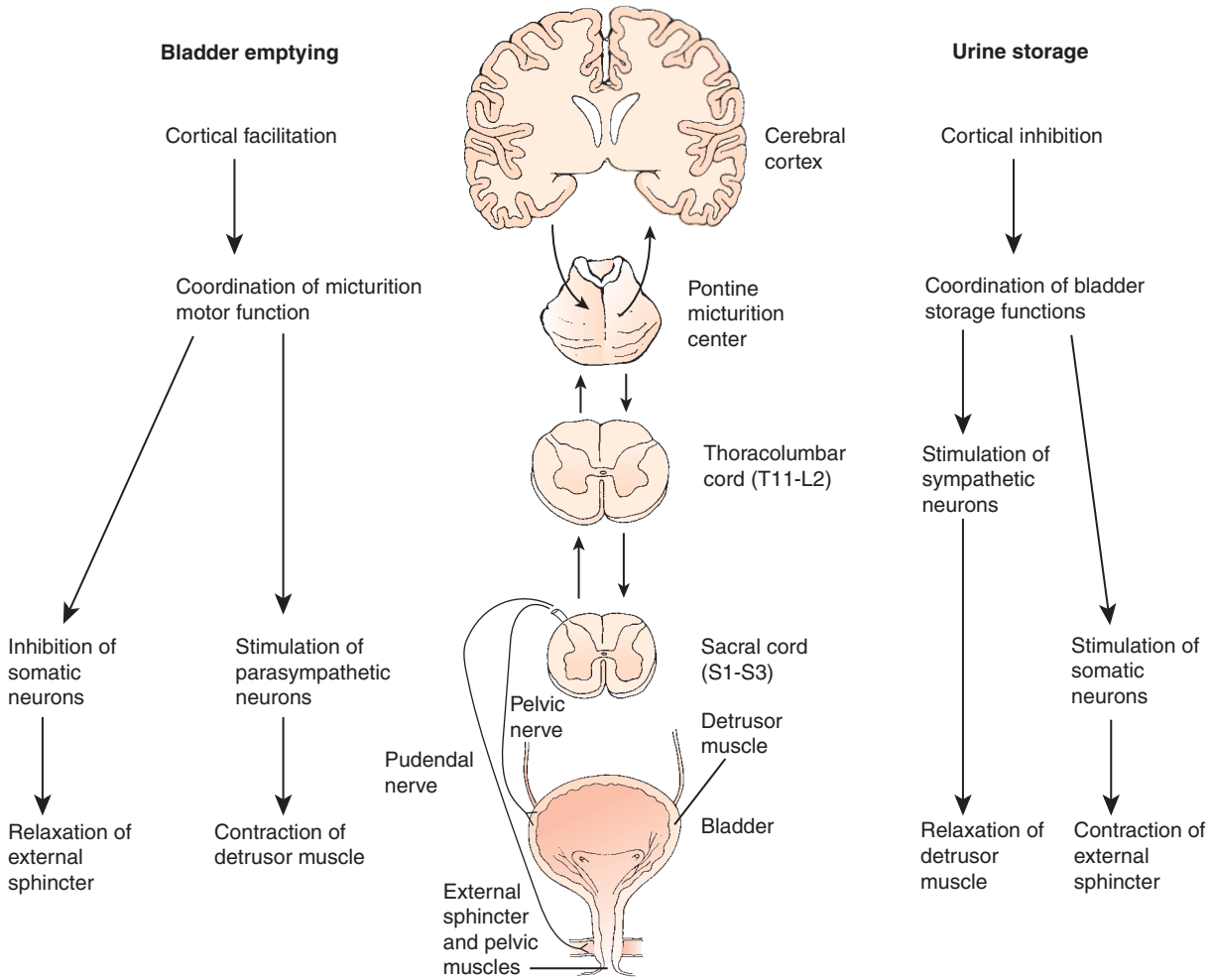


FIGURE 27-3. Pathways and central nervous system centers involved in the control of bladder emptying (*left*) and storage (*right*) functions. Efferent pathways for micturition (*left*) and urine storage (*right*) also are shown.

is thought to coordinate the activity of the detrusor muscle and the external sphincter. As bladder filling occurs, ascending spinal afferents relay this information to the micturition center, which also receives important descending information from the forebrain concerning behavioral cues for bladder emptying and urine storage. Descending pathways from the pontine micturition center produce coordinated inhibition or relaxation of the external sphincter. Disruption of pontine control of micturition, as in spinal cord injury, results in uninhibited spinal reflex–controlled contraction of the bladder without relaxation of the external sphincter, a condition known as *detrusor–sphincter dyssynergia*.

Cortical and Subcortical Centers. Cortical brain centers enable inhibition of the micturition center in the pons and conscious control of urination. Neural influences from the subcortical centers in the basal ganglia modulate the contractile response. They modify and delay the detrusor contractile response during filling and then modulate the expulsive activity of the bladder to facilitate complete emptying.

Neuromediator Control of Micturition. The autonomic nervous system (ANS) and its neuromediators play a central role in micturition. Parasympathetic innervation of the bladder is mediated by the neurotransmitter acetylcholine. Two types of cholinergic receptors, nicotinic and muscarinic, affect various aspects of micturition. *Nicotinic* (N) receptors are found in the synapses between the preganglionic and postganglionic neurons of the sympathetic and the parasympathetic system, as well as in the neuromuscular endplates of the striated muscle fibers of the external sphincter and pelvic muscles. *Muscarinic* (M) receptors are found in the postganglionic parasympathetic endings of the detrusor muscle. Several subtypes of M receptors have been identified. Both M_2 and M_3 receptors appear to mediate detrusor muscle activity, with the M_3 subtype mediating direct activation of detrusor muscle contraction. The M_2 subtype appears to act indirectly by inhibiting sympathetically mediated detrusor muscle relaxation.[4–7] The identification of muscarinic receptor subtypes has facilitated the development of medications that selectively target bladder structures while minimizing undesired side effects.

Although sympathetic innervation is not essential to the act of micturition, it allows the bladder to store a large volume without the involuntary escape of urine—a mechanism that is consistent with the fight-or-flight function subserved by the sympathetic nervous system. The bladder is supplied with α_1- and β_2-adrenergic receptors. The β_2-adrenergic receptors are found in the detrusor muscle; they produce relaxation of the detrusor muscle, increasing the bladder volume at which the micturition reflex is triggered. The α_1-adrenergic receptors are found in the trigone area, including the intramural ureteral musculature, bladder neck, and internal sphincter. The activation of α_1-adrenergic receptors produces contraction of these muscles. Sympathetic activity ceases when the micturition reflex is activated. During male ejaculation, which is mediated by the sympathetic nervous system, the musculature of the trigone area and that of the bladder neck and prostatic urethra contract and prevent the backflow of seminal fluid into the bladder.

Because of their effects on bladder function, drugs that selectively activate or block ANS outflow or receptor activity can alter urine elimination. Table 27-1 describes the action of drug groups that impair bladder function or can be used in the treatment of micturition disorders. For example, many of the nonprescription cold preparations contain α-adrenergic agonists and antihistamine agents that have anticholinergic properties. These drugs can cause urinary retention. Many of the antidepressant and antipsychotic drugs also have anticholinergic actions that influence urination.

TABLE 27-1 Action of Drug Groups on Bladder Function

Function	Drug Groups	Mechanism of Action
Detrusor Muscle		
Increased tone and contraction	Cholinergic drugs	Stimulate parasympathetic receptors that cause detrusor contraction
Inhibition of detrusor muscle relaxation during filling	β_2-Adrenergic blockers	Block β_2 receptors that produce detrusor muscle relaxation
Decreased tone	Anticholinergic drugs and drugs with an anticholinergic action	Block the muscarinic receptors that cause detrusor muscle contraction
	Calcium channel blockers	May interfere with influx of calcium to support contraction of detrusor smooth muscle
Internal Bladder Sphincter		
Increased tone	α_1-Adrenergic agonists	Activate α_1 receptors that produce contraction of the smooth muscle of the internal sphincter
Decreased tone	α_1-Adrenergic blockers	Block contraction of the smooth muscle of the internal sphincter
External Sphincter		
Decreased tone	Skeletal muscle relaxants	Decrease the tone of the external sphincter by acting at the level of the spinal cord or by interfering with release of calcium in the muscle fibers

Micturition and Maintenance of Continence

To maintain continence, or retention of urine, the bladder must function as a low-pressure storage system, with the pressure in the bladder being lower than that in the urethra. To ensure that this condition is met, the increase in intravesical pressure that accompanies bladder filling is almost imperceptible. For example, an increase in bladder volume from 10 to 400 mL may be accompanied by only a 5-cm H_2O increase in pressure. Abnormal sustained elevations in intravesical pressures (>40 to 50 cm H_2O) often are associated with vesicoureteral reflux (i.e., backflow of urine from the bladder into the ureter) and the development of ureteral dilation. Although the pressure in the bladder is maintained at low levels, sphincter pressure remains high (45 to 65 cm H_2O) as a means of preventing loss of urine as the bladder fills.

Micturition, or the act of bladder emptying, involves both sensory and motor functions associated with bladder emptying. When the bladder is distended to 150 to 250 mL in the adult, the sensation of fullness is transmitted to the spinal cord and then to the cerebral cortex, allowing for conscious inhibition of the micturition reflex.[3] During the act of micturition, the detrusor muscle of the bladder fundus and bladder neck contract down on the urine, the ureteral orifices are forced shut, the bladder neck is widened and shortened as it is pulled up by the globular muscles in the bladder fundus, the resistance of the internal sphincter in the bladder neck is decreased, and the external sphincter relaxes as urine moves out of the bladder.

Evaluation of Bladder Function

Bladder function can be assessed by a number of methods.[8] Reports or observations of frequency, hesitancy, straining to void, and a weak or interrupted stream are suggestive of outflow obstruction. Palpation and percussion provide information about bladder distention.

Postvoid residual (PVR) urine volume provides information about bladder emptying. It can be estimated by abdominal palpation and percussion. Catheterization and ultrasonography can be used to obtain specific measurements of PVR. A PVR value of less than 50 mL is considered adequate bladder emptying, and more than 200 mL indicates inadequate bladder emptying.

Pelvic examination is used in women to assess perineal skin condition, perivaginal muscle tone, genital atrophy, pelvic prolapse (e.g., cystocele, rectocele, uterine prolapse), pelvic mass, or other conditions that may impair bladder function. Bimanual examination (i.e., pelvic and abdominal palpation) can be used to assess PVR volume. Rectal examination is used to test for perineal sensation, sphincter tone, fecal impaction, and rectal mass. It is used to assess the contour of the prostate in men.

Urine tests provide information about kidney function and urinary tract infections. The presence of bacteriuria or pyuria suggests urinary tract infection and the possibility of urinary tract obstruction. Blood tests (i.e., blood urea nitrogen and creatinine) provide information about renal function.

Bladder structures can be visualized indirectly by taking x-ray films of the abdomen and by using excretory urography, which involves the use of a radiopaque dye, computed tomographic (CT) scanning, magnetic resonance imaging (MRI), or ultrasonography. Cystoscopy enables direct visualization of the urethra, bladder, and ureteral orifices. The ultrasound bladder scan provides a noninvasive method for estimating bladder volume. Urodynamic studies are used to study bladder function and voiding problems.

In summary, the bladder, also known as the *urinary vesicle,* is a freely movable organ located retroperitoneally on the pelvic floor, just posterior to the pubic symphysis. It consists of two main components: the body in which urine collects, and the neck, which is a funnel-shaped extension of the body that connects with the urethra. The bladder is composed of four layers: an outer serosal layer, which covers the upper surface and is continuous with the peritoneum; a layer of smooth muscle called the *detrusor muscle*; a submucosal layer of loose connective tissue; and an inner mucosal lining of transitional epithelium that is essentially impermeable to salts and water.

Micturition or passing urine is a function of the autonomic nervous system, subject to facilitation or inhibition from higher neurologic centers. The parasympathetic nervous system controls the function of the detrusor muscle and internal sphincter; its cell bodies are located in S1 through S3 of the spinal cord and communicate with the bladder through the pelvic nerve. Sympathetic control originates at the thoracolumbar level (T11 through L2) of the spinal cord and produces relaxation of the detrusor muscle and contraction of the internal sphincter. Skeletal muscle found in the external sphincter and the pelvic muscles that support the bladder are supplied by the pudendal nerve, which exits the spinal cord at the sacral level (S2 through S4) of the spinal cord. The pontine micturition center coordinates the action of the detrusor muscle and the external sphincter, whereas cortical centers permit conscious control of micturition.

Bladder function can be evaluated using a variety of methods including physical examination, urine tests, radiologic studies, and urodynamic studies that measure bladder, urethral, and abdominal pressures; urine flow characteristics; and skeletal muscle activity of the external urethral sphincter.

Disorders of Bladder Structure and Function

Disorders of bladder structure and function include urinary obstruction with retention or stasis of urine and urinary incontinence with involuntary loss of urine. Although the two conditions have almost opposite effects on urination, they can have similar causes.

Lower Urinary Tract Obstruction and Stasis

In lower urinary tract obstruction and stasis, urine is produced normally by the kidneys but is retained in the bladder. Obstructions can be classified according to their location (bladder neck, urethra, or external urethral meatus), cause (congenital or acquired), degree (partial or complete), and duration (acute or chronic).[9] Because it has the potential to produce vesicoureteral reflux and cause kidney damage, lower urinary tract obstruction and stasis is a serious disorder.

The common sites of congenital obstructions are the external meatus (i.e., meatal stenosis) in boys and just inside the external urinary meatus in girls. Another congenital cause of urinary stasis is the damage to sacral nerves that is seen in spina bifida and meningomyelocele. The acquired causes of lower urinary tract obstruction and stasis are numerous. In males, the most important cause of urinary obstruction is external compression of the urethra caused by enlargement of the prostate gland.[9,10] Gonorrhea and other sexually transmitted infections contribute to the incidence of infection-produced urethral strictures. Bladder tumors and secondary invasion of the bladder by tumors arising in structures that surround the bladder and urethra can compress the bladder neck or urethra and cause obstruction. Obstructive disorders in women include conditions related to relaxation of the pelvic support structures, such as cystocele and rectocele. Because of the proximity of the involved structures, severe constipation and fecal impaction can compress the urethra and produce urethral obstruction. This can be a particular problem in elderly persons.

Compensatory and Decompensatory Changes

The body compensates for the obstruction of urine outflow with mechanisms designed to prevent urine retention. These mechanisms can be divided into two stages: a compensatory stage and a decompensatory stage.[9] The degree to which these changes occur and their effect on bladder structure and urinary function depend on the extent of the obstruction, the rapidity with which it occurs, and the presence of other contributing factors, such as neurologic impairment and infection.

During the early stage of obstruction, the bladder begins to hypertrophy and becomes hypersensitive to afferent stimuli arising from stretch receptors in the bladder wall. The ability to suppress urination is diminished, and bladder contraction can become so strong that it virtually produces bladder spasm. There is urgency, sometimes to the point of incontinence, and frequency during the day and at night.

With continuation and progression of the obstruction, compensatory changes begin to occur. There is further hypertrophy of the bladder muscle, the thickness of the bladder wall may double, and the pressure generated by detrusor contraction can increase from a normal 20 to 40 cm H_2O to 50 to 100 cm H_2O to overcome the resistance from the obstruction. As the force needed to expel urine from the bladder increases, compensatory mechanisms may become ineffective, causing muscle fatigue before complete emptying can be accomplished. After a few minutes, voiding can again be initiated and completed, accounting for the frequency of urination.

The inner bladder surface forms smooth folds. With continued outflow obstruction, this smooth surface is replaced with coarsely woven structures (i.e., hypertrophied smooth muscle fibers) called *trabeculae*. Small pockets of mucosal tissue, called *cellules,* commonly develop between the trabecular ridges. These pockets form diverticula when they extend between the actual fibers of the bladder muscle (Fig. 27-4). Because the diverticula have no muscle, they are unable to contract and expel their urine into the bladder, and secondary infections caused by stasis are common. Along with hypertrophy of the bladder wall, there is hypertrophy of the trigone area and the interureteric ridge, which is located between the two ureters. This causes backpressure on the ureters, the development of hydroureters, and, eventually, kidney damage. Stasis of urine also predisposes to urinary tract infections.

When compensatory mechanisms no longer are effective, signs of decompensation begin to appear. The period of detrusor muscle contraction becomes too short to expel the urine completely, and residual urine remains in the bladder. At this point, the symptoms of obstruction—frequency of urination, hesitancy, need to strain to initiate urination, a weak and small stream, and termination

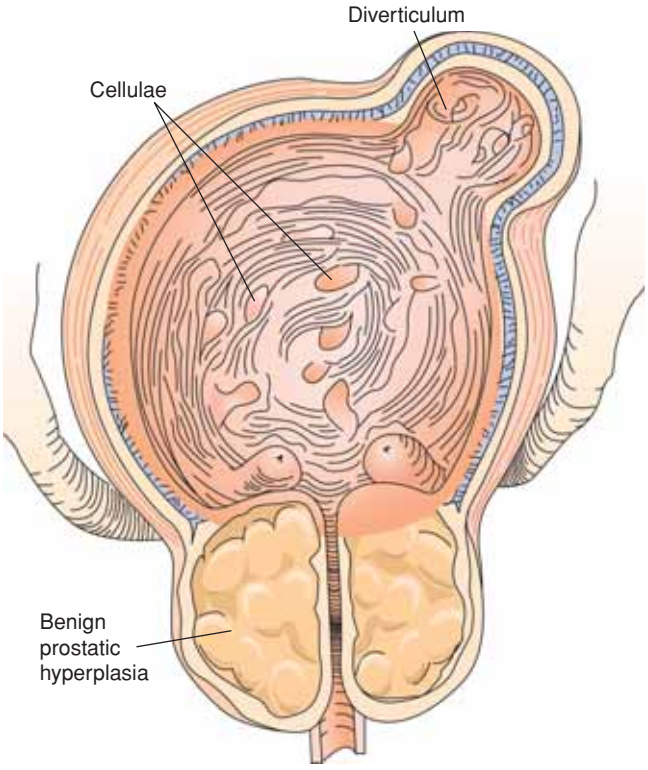


FIGURE 27-4. Destructive changes of the bladder wall with development of diverticulum caused by benign prostatic hyperplasia.

CHART 27-1 Signs of Outflow Obstruction and Urine Retention

Bladder distention
Hesitancy
Straining when initiating urination
Small and weak stream
Frequency of urination
Feeling of incomplete bladder emptying
Overflow incontinence

of the stream before the bladder is completely emptied—become pronounced. With progressive decompensation, the bladder may become severely overstretched, with a residual urine volume of 1000 to 3000 mL.[9] At this point, it loses its power of contraction and overflow incontinence occurs. The signs of outflow obstruction and urine retention are summarized in Chart 27-1.

The immediate treatment of lower urinary tract obstruction and stasis is directed toward relief of bladder distention. This usually is accomplished through urinary catheterization. Long-term treatment is directed toward correcting the problem causing the obstruction.

Neurogenic Bladder Disorders

The urinary bladder is unique in that it is probably the only autonomically innervated visceral organ that is under CNS control. The neural control of bladder function can be interrupted at any level. It can be interrupted at the level of the peripheral nerves that connect the bladder to the reflex micturition center in the sacral cord, the ascending and descending tracts in the spinal cord, the pontine micturition center, or the cortical centers that are involved in voluntary control of micturition[5,11,12] (see Fig. 27-3).

Neurogenic disorders of bladder function commonly are manifested in one of two ways: failure to store urine (spastic bladder dysfunction) or failure to empty (flaccid bladder dysfunction). Spastic bladder dysfunction usually results from neural lesions located above the level of the sacral micturition reflexes, whereas flaccid bladder dysfunction results from lesions at the level of the sacral micturition reflexes or the peripheral nerves that innervate the bladder. In addition to disorders of detrusor muscle function, disruption of micturition occurs when the neurologic control of external sphincter function is disrupted. Some disorders, such as stroke and Parkinson disease, may affect both the storage and emptying functions of the bladder. Table 27-2 describes the characteristics of neurogenic bladder according to the level of the lesion.

Spastic Bladder: Failure to Store Urine

Failure to store urine results from conditions that cause reflex bladder spasm and a decrease in bladder volume. It commonly is caused by conditions that produce partial or extensive neural damage above the micturition reflex center in the sacral cord (see Fig. 27-3). As a result, bladder function is regulated by segmental reflexes, without control from higher brain centers. The degree of bladder spasticity and dysfunction depends on the level and extent of neural dysfunction. Usually, both the ANS neurons controlling bladder function and the somatic neurons controlling the function of the striated muscles in the external sphincter are affected. In some cases, there is a detrusor–sphincter dyssynergia with uncoordinated contraction and relaxation of the detrusor and external sphincter muscles. The most common causes of spastic

TABLE 27-2 Types and Characteristics of Neurogenic Bladder

Level of Lesion	Change in Bladder Function	Common Causes
Sensory cortex, motor cortex, or corticospinal tract	Loss of ability to perceive bladder filling; low-volume, physiologically normal micturition that occurs suddenly and is difficult to inhibit	Stroke and advanced age
Basal ganglia or extrapyramidal tract	Detrusor contractions are elicited suddenly without warning and are difficult to control; bladder contraction is shorter than normal and does not produce full bladder emptying	Parkinson disease
Pontine micturition center or communicating tracts in the spinal cord	Storage reflexes are provoked during filling, and external sphincter responses are heightened; uninhibited bladder contractions occur at a lower volume than normal and do not continue until the bladder is emptied; antagonistic activity occurs between the detrusor muscle and the external sphincter	Spinal cord injury
Sacral cord or nerve roots	Areflexic bladder fills but does not contract; loss of external sphincter tone occurs when the lesion affects the α-adrenergic motor neurons or pudendal nerve	Injury to sacral cord or spinal roots
Pelvic nerve	Increased filling and impaired sphincter control cause increased intravesicular pressure	Radical pelvic surgery
Autonomic peripheral sensory pathways	Bladder overfilling occurs owing to a loss of ability to perceive bladder filling	Diabetic neuropathies, multiple sclerosis

bladder dysfunction are spinal cord lesions such as spinal cord injury, herniated intervertebral disk, vascular lesions, tumors, and myelitis (inflammation of the spinal cord).

Bladder Dysfunction Caused by Spinal Cord Injury. One of the most common types of spinal cord lesions is spinal cord injury (see Chapter 36). The immediate and early effects of spinal cord injury on bladder function are quite different from those that follow recovery from the initial injury. During the period immediately after spinal cord injury, a state of spinal shock develops, during which all the reflexes, including the micturition reflex, are depressed. During this stage, the bladder becomes atonic and cannot contract. Catheterization is necessary to prevent injury to urinary structures associated with overdistention of the bladder. Depression of reflexes lasts from a few weeks to 6 months (usually 2 to 3 months), after which the spinal reflexes return and become hyperactive.

After the acute stage of spinal cord injury, the micturition response changes from a long-tract reflex to a segmental reflex. Because the sacral reflex arc remains intact, stimuli generated by bladder stretch receptors during filling produce frequent spontaneous contractions of the detrusor muscle. This creates a small, hyperactive bladder subject to high-pressure and short-duration uninhibited bladder contractions. Voiding is interrupted, involuntary, or incomplete. Dilation of the internal sphincter and spasticity of the external sphincter and perineal muscles innervated by upper motor neurons occur, producing resistance to bladder emptying. Hypertrophy of the trigone develops, often leading to vesicoureteral reflux and risk for renal damage.

Spastic bladder due to spinal cord injuries at the cervical level is often accompanied by a condition known as *autonomic hyperreflexia* (see Chapter 36). Because the injury interrupts CNS control of sympathetic reflexes in the spinal cord, severe hypertension, bradycardia, and sweating can be triggered by insertion of a catheter or mild overdistention of the bladder.

Neurogenic Bladder Disorders

- Neurogenic disorders of the bladder commonly are manifested by a spastic bladder dysfunction, in which there is failure to store urine, or as flaccid bladder dysfunction, in which bladder emptying is impaired.
- Spastic bladder dysfunction results from neural lesions above the level of the sacral cord that allow neurons in the micturition center to function reflexively without control from higher central nervous system centers.
- Flaccid bladder dysfunction results from neural disorders affecting the motor neurons in the sacral cord or peripheral nerves that control detrusor muscle contraction and bladder emptying.

Uninhibited Neurogenic Bladder. A mild form of reflex neurogenic bladder, sometimes called *uninhibited bladder,* can develop after a stroke, during the early stages of multiple sclerosis, or as a result of lesions located in the inhibitory centers of the cortex or the pyramidal tract. With this type of disorder, the sacral reflex arc and sensation are retained, the urine stream is normal, and there is no residual urine. Bladder capacity is diminished, however, because of increased detrusor muscle tone and spasticity.

Detrusor–Sphincter Dyssynergia. Depending on the level of the lesion, the coordinated activity of the detrusor muscle and the external sphincter may be affected. Lesions that affect the micturition center in the pons or impair communication between the micturition center and spinal cord centers interrupt the coordinated activity of the detrusor muscle and the external sphincter. This is called *detrusor–sphincter dyssynergia*. Instead of relaxing during micturition, the external sphincter becomes more constricted. This condition can lead to elevated intravesical pressures, vesicoureteral reflux, and kidney damage.

Treatment. Among the methods used to treat spastic bladder and detrusor–sphincter dyssynergia are the administration of anticholinergic medications to decrease bladder hyperactivity and urinary catheterization to produce bladder emptying. A sphincterotomy (surgical resection of the external sphincter) or implantable urethral stent may be used to decrease outflow resistance in a person who cannot be managed with medications and catheterization procedures. An alternative to surgical resection of the external sphincter is the injection of botulinum toxin type A (BTX-A) to produce paralysis of the striated muscles in the external sphincter. The effects of the injection last from 3 to 9 months, after which the injection must be repeated.[12]

Flaccid Bladder: Failure to Empty Urine

Failure to empty the bladder can be due to flaccid bladder dysfunction, peripheral neuropathies that interrupt afferent or efferent communication between the bladder and the spinal cord, or conditions that prevent relaxation of the external sphincter (see Fig. 27-3).

Flaccid Bladder Dysfunction. Detrusor muscle areflexia, or flaccid neurogenic bladder, occurs when there is injury to the micturition center of the sacral cord, the cauda equina, or the sacral nerves that supply the bladder. Atony of the detrusor muscle and loss of the perception of bladder fullness permit the overstretching of the detrusor muscle that contributes to weak and ineffective bladder contractions. External sphincter tone and perineal muscle tone are diminished. Voluntary urination does not occur, but fairly efficient emptying usually can be achieved by increasing the intra-abdominal pressure or applying manual suprapubic pressure. Among the causes of flaccid neurogenic bladder are trauma, tumors, and congenital anomalies (e.g., spina bifida, meningomyelocele).

Bladder Dysfunction Caused by Peripheral Neuropathies. In addition to CNS lesions and conditions that disrupt bladder function, disorders of the peripheral (pelvic, pudendal, and hypogastric) nerves that supply the muscles of micturition can occur. These neuropathies can selectively interrupt sensory or motor pathways for the bladder or involve both pathways.

Bladder atony with dysfunction is a frequent complication of diabetes mellitus.[13,14] The disorder initially affects the sensory axons of the urinary bladder without involvement of the pudendal nerve. This leads to large residual volumes after micturition, sometimes complicated by infection. There frequently is a need for straining, accompanied by hesitation, weakness of the stream, dribbling, and a sensation of incomplete bladder emptying.[14] The most common complications are vesicoureteral reflux and ascending urinary tract infection. Because persons with diabetes are already at risk for development of kidney disease, urinary stasis and reflux can have serious effects on renal function (see Chapter 33). Treatment consists of client education, including the need for frequent voiding (e.g., every 3 to 4 hours while awake); use of abdominal compression to effect more complete bladder emptying; and intermittent catheterization when necessary.

Nonrelaxing External Sphincter

Another condition that affects micturition and bladder function is the nonrelaxing external sphincter. This condition usually is related to a delay in maturation, developmental regression, psychomotor disorders, or locally irritative lesions. Inadequate relaxation of the external sphincter can be the result of anxiety or depression. Any local irritation can produce spasms of the sphincter through afferent sensory input from the pudendal nerve, including vaginitis, perineal inflammation, and inflammation or irritation of the urethra. In men, chronic prostatitis contributes to impaired relaxation of the external sphincter.

Treatment

The goals of treatment for neurogenic bladder disorders focus on preventing bladder overdistention, urinary tract infections, and potentially life-threatening kidney damage and reducing the undesirable social and psychological effects of the disorder. The methods used in treatment of neurogenic bladder disorders are individualized based on the type of neurologic lesion that is involved; information obtained through the health history, including fluid intake; report or observation of voiding patterns; presence of other health problems; urodynamic studies when indicated; and the ability of the person to participate in the treatment. Treatment methods include catheterization, bladder training, pharmacologic manipulation of bladder function, and surgery.

Catheterization involves the insertion of a small-diameter latex or silicone tube into the bladder through the urethra. The catheter may be inserted on a one-time basis to relieve temporary bladder distention, left indwelling (i.e., retention catheter), or inserted intermittently.

The methods used for bladder retraining depend on the type of lesion causing the disorder.[15] In spastic neurogenic bladder, methods designed to trigger the sacral micturition reflex (e.g., tapping the suprapubic or genital region) are used; in flaccid neurogenic bladder, manual methods (applying pressure to the suprapubic area) that increase intravesical pressure are used. Biofeedback methods have been useful for teaching some aspects of bladder control. They involve the use of electromyography (EMG) or cystometry as a feedback signal for training a person to control the function of the external sphincter or raise intravesical pressure enough to overcome outflow resistance. Methods used to supplement bladder retraining include monitoring fluid intake to prevent urinary tract infections and control urine volume and osmolality, developing scheduled times for urination, and using body positions that facilitate micturition. Adequate fluid intake also is needed to prevent urinary tract infections, the irritating effects of which increase bladder irritability and the risk for urinary incontinence and renal damage. Fluid intake must be balanced to prevent bladder overdistention from occurring during the night.

Pharmacologic manipulation includes the use of drugs to alter the contractile properties of the bladder, decrease the outflow resistance of the internal sphincter, and relax the external sphincter. Antimuscarinic drugs decrease detrusor muscle tone and increase bladder capacity in persons with spastic bladder dysfunction.[5] Cholinergic drugs that stimulate parasympathetic receptors provide increased bladder tonus and may prove helpful in the symptomatic treatment of milder forms of flaccid neurogenic bladder. Muscle relaxants may be used to decrease the tone of the external sphincter. A nasal spray preparation of desmopressin (DDAVP), a synthetic antidiuretic hormone, can be used to reduce urine output in persons with nighttime frequency due to spastic bladder symptoms.

Among the surgical procedures used in the management of neurogenic bladder are sphincterectomy, reconstruction of the sphincter, nerve resection of the sacral reflex nerves that cause spasticity or the pudendal nerve that controls the external sphincter, and urinary diversion. Urinary diversion can be done by creating an ileal or a colon loop into which the ureters are anastomosed; the distal end of the loop is brought out and attached to the abdominal wall. Extensive research is being conducted on methods of restoring voluntary control of the storage and evacuation functions of the bladder through the use of implanted electrodes.

Urinary Incontinence

Urinary incontinence represents the involuntary loss or leakage of urine. Incontinence can be caused by a number of conditions and is a common problem, particularly in older adults, with women being affected twice as often as men.[16–21] It can occur without the person's knowledge; at other times, the person may be aware of the condition but be unable to prevent it.

TABLE 27-3 Types and Characteristics of Urinary Incontinence

Type	Characteristics
Stress	Involuntary loss of urine associated with activities, such as coughing, that increase intra-abdominal pressure
Overactive bladder/ urge incontinence	Urgency and frequency associated with hyperactivity of the detrusor muscle; may or may not involve involuntary loss of urine
Overflow	Involuntary loss of urine when intravesicular pressure exceeds maximal urethral pressure in the absence of detrusor activity

Types and Causes of Incontinence

The Urinary Incontinence Guideline Panel has identified four main types of incontinence: stress incontinence, urge incontinence, overflow incontinence, and mixed incontinence, which is a combination of stress incontinence and urge incontinence.[16] Recently, the term *urge incontinence* has been expanded to include *overactive bladder* (i.e., overactive bladder/urge incontinence). Table 27-3 summarizes the characteristics of stress incontinence, overactive bladder/urge incontinence, and overflow incontinence.

Stress Incontinence. Stress incontinence is the involuntary loss of urine that occurs when, in the absence of detrusor muscle action, the intravesical pressure exceeds the maximum urethral closure pressure.[22] Except during the act of micturition, intraurethral pressure is normally greater than intravesical pressure. The pressure difference between the bladder and urethra is known as the *urethral closure pressure*. If intra-abdominal pressure increases as it does during actions such as a cough, laugh, or sneeze, and if this pressure is not equally transmitted to the urethra, then incontinence occurs. Among the proposed causes of stress incontinence are changes in the anatomic relationship between the bladder and the urethra, so that increases in intra-abdominal pressure are unevenly distributed to urethra.[17–22] Diminution of muscle tone associated with normal aging, childbirth, or surgical procedures can cause weakness of the pelvic floor muscles and can decrease the urethral closure pressure and result in stress incontinence by changing the relationship between the bladder base and the posterior urethral junction. Any activity that causes downward pressure on the bladder is sufficient to allow the urine to escape involuntarily.

Another cause of stress incontinence is intrinsic urethral deficiency, which may result from congenital sphincter weakness, as occurs with meningomyelocele. It also may be acquired as a result of trauma, irradiation, or sacral cord lesions. Stress incontinence in men may result from trauma or surgery to the bladder outlet, as occurs with prostatectomy.[21] Neurologic dysfunction, as occurs with impaired sympathetic innervation of the bladder neck, impaired pelvic nerve innervation to the intrinsic sphincter, or impaired pudendal nerve innervation to the external sphincter, may also be a contributing factor.

Incontinence

- Incontinence represents the involuntary loss of urine due to increased bladder pressures (overactive bladder with urge incontinence or overflow incontinence) or decreased ability of the vesicourethral sphincter to prevent the escape of urine (stress incontinence).
- Stress incontinence is caused by the decreased ability of the vesicourethral sphincter to prevent the escape of urine during activities, such as lifting and coughing, that raise bladder pressure above the sphincter closing pressure.
- Overactive bladder/urge incontinence is caused by neurogenic or myogenic disorders that result in hyperactive bladder contractions.
- Overflow incontinence results from overfilling of the bladder with escape of urine.

Overactive Bladder/Urge Incontinence. The Urinary Incontinence Guideline Panel has defined urge incontinence as the involuntary loss of urine associated with a strong desire to void (urgency).[16] The International Continence Society defines overactive bladder as the presence of involuntary bladder contractions during filling and while the person is trying to inhibit micturition.[23] Nocturia often occurs and is associated with sleep disruption. Although overactive bladder often is associated with urge incontinence, it can occur without incontinence. Despite recent media coverage of overactive bladder and advances in treatment, many people continue to suffer in silence, probably because they are embarrassed or think it is an inevitable consequence of aging.

The symptoms of overactive bladder, which are caused by involuntary bladder contractions during filling, may occur alone or in any combination, and they constitute overactive bladder when they occur in the absence of other pathologic processes.[7,23–25] Regardless of the primary cause of overactive bladder, two types of mechanisms are thought to contribute to its symptomatology: those involving CNS and neural control of bladder sensation and emptying (neurogenic) and those involving the smooth muscle of the bladder itself (myogenic).[7,23,24]

The *neurogenic* theory for overactive bladder postulates that the CNS functions as an on–off switching circuit for voluntary control of bladder function. Therefore, damage to the CNS inhibitory pathways may trigger bladder overactivity owing to uncontrolled voiding reflexes. Neurogenic causes of overactive bladder include stroke,

Parkinson disease, and multiple sclerosis. Other neurogenic causes of overactive bladder include increased sensitization of the afferent nerves that sense bladder filling or increased sensitivity to efferent nerves that produce bladder emptying.

The *myogenic* causes of overactive bladder are thought to result from changes in the properties of the smooth muscle of the bladder itself. One example is overactive bladder associated with bladder outlet obstruction. It is hypothesized that the sustained increase in intravesical pressure that occurs with the outlet obstruction causes a partial destruction of the nerve endings that control bladder excitability.[7,23,24] This partial denervation results in increased excitability of the individual muscle cells. The result is urgency and frequency of urination due to spontaneous bladder contractions resulting from detrusor muscle hyperexcitability. Disorders of detrusor muscle structure and excitability also can occur as the result of the aging process or disease conditions such as diabetes mellitus. Overactive bladder symptoms usually are exaggerated by incomplete bladder emptying, a common accompaniment of overactive bladder.

Overflow Incontinence. Overflow incontinence is an involuntary loss of urine that occurs when intravesical pressure exceeds the maximal urethral pressure because of bladder distention in the absence of detrusor activity. It can occur with retention of urine owing to nervous system lesions or obstruction of the bladder neck. With this type of incontinence, the bladder is distended, and small amounts of urine are passed, particularly at night. In men, one of the most common causes of obstructive incontinence is enlargement of the prostate gland. Another cause that commonly is overlooked is fecal impaction (i.e., dry, hard feces in the rectum). When a large bolus of stool forms in the rectum, it can push against the urethra and block the flow of urine.

The Standardization Subcommittee of the International Continence Committee recommends that the term *overflow incontinence* should no longer be used, indicating that the term is confusing and lacking definition.[26] Instead, it suggests that more specific terms such as *reduced urethral function* or *overactivity/low bladder compliance* be used.

Other Causes of Incontinence. Other causes of incontinence include decreased bladder compliance or distensibility. This abnormal bladder condition may result from radiation therapy, radical pelvic surgery, or interstitial cystitis. Many persons with this disorder have severe urgency related to bladder hypersensitivity that results in loss of bladder elasticity, such that any small increase in bladder volume or detrusor function causes a sharp rise in bladder pressure and severe urgency.

Incontinence may occur as a transient and correctable phenomenon, or it may not be totally correctable and may occur with various degrees of frequency. Among the transient causes of urinary incontinence are recurrent urinary tract infections; medications that alter bladder function or perception of bladder filling and the need to urinate; diuretics and conditions that increase bladder filling; stool impaction; restricted mobility; and confusional states.

Incontinence also may be caused by factors outside the lower urinary tract, such as the inability to locate, reach, or receive assistance in reaching an appropriate place to void. This may be a particular problem for elderly persons, who may have problems with mobility and manual dexterity or find themselves in unfamiliar surroundings. It occurs when a person cannot find or reach the bathroom or manipulate clothing quickly enough. Failing vision may contribute to the problem. Embarrassment in front of other persons at having to use the bathroom, particularly if the timing seems inappropriate, may cause a person to delay emptying the bladder and may lead to incontinence. Treatment with drugs such as diuretics may cause the bladder to fill more rapidly than usual, making it difficult to reach the bathroom in time if there are problems with mobility or if a bathroom is not readily available. Night sedation may cause a person to sleep through the signal that normally would waken a person so that he or she could get up and empty the bladder and avoid wetting the bed.

Diagnosis and Treatment

Urinary incontinence is not a single disease but a symptom with many possible causes. As a symptom, it requires full investigation to establish its cause.[16,17,27,28] This usually is accomplished through a careful history, physical examination, blood tests, and urinalysis. A voiding record (i.e., diary) may be used to determine the frequency, timing, and amount of voiding, as well as other factors associated with the incontinence. Because many drugs affect bladder function, a full drug history is essential. Estimation of the PVR volume is recommended for all persons with incontinence.

Treatment or management depends on the type of incontinence, accompanying health problems, and the person's age. It includes behavioral methods; exercises to strengthen the pelvic floor muscles; pharmacologic measures; surgical interventions; and, when urine flow cannot be controlled, noncatheter devices to obstruct urine flow or collect urine as it is passed.[27–29] Indwelling catheters, although a solution to the problem of urinary incontinence, usually are considered only after all other treatment methods have failed. In some types of incontinence, such as that associated with spinal cord injury or meningomyelocele, self-catheterization may provide the best means for controlling urine elimination (see Chapter 36).

Behavioral methods include fluid management, timed/prompted voiding, bladder retraining, and toileting assistance. Bladder retraining and biofeedback techniques seek to reestablish cortical control over bladder function by having the person ignore urgency and respond only to cortical signals during waking hours. Exercises of the pelvic muscles or Kegel exercises involve repetitive contraction and relaxation of the pelvic floor muscles and are an essential component of patient-dependent behavioral interventions.[29]

Pharmacologic treatment is aimed at using drugs to alter the physiologic mechanisms that contribute to the

neurogenic or myogenic causes of incontinence (see Table 27-1).[30,31] They include the use of drugs that increase sphincter tone in stress incontinence, decrease hyperexcitability of the detrusor muscle in overactive bladder/urge incontinence, or relieve outflow obstruction in overflow incontinence.

Surgical intervention may be considered when other treatment methods have proved ineffective. Three types of surgical procedures are used: procedures that increase outlet resistance, decrease detrusor muscle instability, or remove outflow obstruction to reduce overflow incontinence and detrusor muscle instability. The principal objective of surgical treatment of stress incontinence is to increase outlet resistance through restoration of the proper suspension and support of the vesicourethral segment of the urethra. A minimally invasive procedure for the treatment of stress incontinence due to internal sphincter weakness is the periurethral injection of a bulking agent.[20]

Surgically implanted artificial sphincters are available for use in treatment of incontinence due to severe sphincter damage.[20] These devices consist of an inflatable cuff that surrounds the proximal urethra. The cuff is connected by tubing to an implanted fluid reservoir and an inflation bulb. Pressing the bulb, which is placed in the scrotum in men, inflates the cuff. It is emptied in a similar manner.

Special Needs of Elderly Persons

Urinary incontinence is a common problem in elderly persons, both male and female.[21,29,32–35] Incontinence increases social isolation, frequently leads to institutionalization of elderly persons, and predisposes to infections and skin breakdown. Many factors contribute to incontinence in elderly persons, a number of which can be altered. The overall capacity of the bladder is reduced, as is the urethral closing pressure. Detrusor muscle function also tends to decline with aging; thus, there is a trend toward a reduction in the strength of bladder contraction and impairment in emptying that leads to larger PVR volumes.[2,34,35] It has been proposed that many of these changes are due to degenerative detrusor muscle changes rather than neurologic changes, as was once thought. The combination of involuntary detrusor contraction (detrusor hyperactivity) leading to urge incontinence along with impaired contractile function leads to incomplete bladder emptying. Urge incontinence is the most frequent type of incontinence in elderly men. In about 50% of these men, detrusor overactivity is found; the urge to urinate comes on suddenly, without warning, accompanied by an uncontrolled detrusor contraction causing incontinence.[33]

Furthermore, advancing age often results in restricted mobility, an increasing number of medications being taken, comorbid illness, infection, and stool impaction, all of which can precipitate urinary incontinence.[35] More than half of normal elderly persons experience nocturia. Many elderly persons have difficulty getting to the toilet in time. This can be caused by arthritis that makes walking or removing clothing difficult or by failing vision that makes trips to the bathroom precarious, especially in new and unfamiliar surroundings.

Medication prescribed for other health problems may prevent a healthy bladder from functioning normally.[29,34] Potent, fast-acting diuretics are known for their ability to cause urge incontinence. Impaired thirst or limited access to fluids predisposes to constipation with urethral obstruction and overflow incontinence and to concentrated and infected urine, which increases bladder excitability. Drugs such as hypnotics, tranquilizers, and sedatives can interfere with the conscious inhibition of voiding, leading to urge incontinence. Diuretics, particularly in elderly persons, increase the flow of urine and may contribute to incontinence, particularly in persons with diminished bladder capacity and in those who have difficulty reaching the toilet.

Diagnosis and Treatment. As with urinary incontinence in younger persons, incontinence in elderly persons requires a thorough history and physical examination to determine the cause of the problem. A voiding history is important. A voiding diary provides a means for the person to provide objective information about the number of bathroom visits, the number of protective pads used, and even the volume of urine voided. A medication history is also important because medications can affect bladder function.[35]

There are many nonurologic conditions that predispose to urinary incontinence. The transient and often treatable causes of urinary incontinence in elderly persons may best be remembered with the acronym DIAPPERS, in which the *D* stands for dementia/dementias, *I* for infection (urinary or vaginal), *A* for atrophic vaginitis, *P* for pharmaceutical agents, *P* for psychological causes, *E* for endocrine conditions (diabetes), *R* for restricted mobility, and *S* for stool impaction.[28] These eight transient causes of incontinence should be identified and treated before other treatment options are considered.

Treatment may involve changes in the physical environment so that the older person can reach the bathroom more easily or remove clothing more quickly. Habit training with regularly scheduled toileting—usually every 2 to 4 hours—often is effective. Many elderly persons who void on a regular schedule can gradually increase the interval between toileting while improving their ability to suppress bladder instability. The treatment plan may require dietary changes to prevent constipation or a plan to promote adequate fluid intake to ensure adequate bladder filling and prevent urinary stasis and symptomatic urinary tract infections.

In summary, disorders of bladder function include urinary obstruction with retention or stasis of urine and urinary incontinence with involuntary loss of urine. Although the two conditions have almost opposite effects on urination, they can have similar causes. Both can result from structural changes in the bladder, urethra, or surrounding organs or from impairment of neurologic control of bladder function.

In lower urinary tract obstruction, urine is produced normally by the kidneys but is retained in the bladder. Obstructions can be classified according to their location (bladder neck, urethra, or external urethral meatus), cause (congenital or acquired), degree (partial or complete), and duration (acute or chronic). The acquired causes of lower urinary tract obstruction include sexually transmitted infections, enlargement of the prostate gland in men, and tumors of the bladder or surrounding structures. Urethral obstruction causes bladder irritability, detrusor muscle hypertrophy, formation of trabeculae and diverticula, vesicoureteral reflux, development of hydroureter, and eventual renal failure.

Neurogenic bladder is caused by interruption in the innervation of the bladder. It can result in spastic bladder dysfunction caused by failure of the bladder to fill or flaccid bladder dysfunction caused by failure of the bladder to empty. Spastic bladder dysfunction usually results from neural lesions that are above the level of the sacral micturition reflex center; flaccid bladder dysfunction results from lesions at the level of the sacral micturition reflexes or peripheral innervation of the bladder. A third type of neurogenic disorder involves a nonrelaxing external sphincter.

Urinary incontinence is the involuntary loss of urine in amounts sufficient to be a problem. It may manifest as stress incontinence, in which the loss of urine occurs as a result of coughing, sneezing, laughing, or lifting; overactive bladder/urge incontinence, characterized by urgency, frequency, and nocturia associated with hyperactive bladder contractions; or overflow incontinence, which results when intravesical pressure exceeds the maximal urethral pressure because of bladder distention. Other causes of incontinence include a small, contracted bladder or external environmental conditions that make it difficult to access proper toileting facilities. Diagnosis usually is accomplished through a careful history (including a voiding record and full drug history), physical examination, blood tests and urinalysis, and, in some cases, urodynamic studies. Treatment methods include correction of the underlying cause, such as obstruction due to prostatic hyperplasia; pharmacologic methods to improve bladder and external sphincter tone; behavioral methods that focus on bladder and habit training; exercises to improve pelvic muscle function; and the use of catheters and urine collection devices.

Urinary incontinence is a common problem in elderly persons. Many factors, including health problems, medications, and changes in bladder structure and function, contribute to incontinence in elderly persons. The acronym DIAPPERS—*D* (dementia), *I* (infection), *A* (atrophic vaginitis), *P* (pharmaceutical agents), *P* (psychological factors), *E* (endocrine conditions), *R* (restricted mobility), and *S* (stool impaction)—emphasizes the transient and often treatable causes of incontinence in the elderly.

Urinary Tract Infections

Urinary tract infections (UTIs) include several distinct entities, including asymptomatic bacteriuria, symptomatic lower UTIs such as cystitis, and upper UTIs such as pyelonephritis. Because of their ability to cause renal damage, upper UTIs are considered more serious than lower UTIs. Acute pyelonephritis (discussed in Chapter 25) represents an infection of the renal parenchyma and renal pelvis. The discussion in this chapter focuses on lower urinary tract infections.

Urinary Tract Infections

- Urinary tract (UT) infections involve host–agent interactions that pit the defenses of the host against the virulence of the infectious agent.
- Infection is facilitated by host conditions that disrupt washout of the agent from the UT through urine flow, change the protective properties of the mucin lining of the UT, disrupt the protective function of the normal bacterial flora, or impair the function of the immune system.
- Virulence of the agent is derived from its ability to gain access to and thrive in the UT environment, adhere to the tissues of the lower or upper UT, evade the destructive effects of the host's immune system, and develop resistance to antimicrobial agents.

Etiologic Factors

The term *uncomplicated* refers to the absence of known predisposing factors that affect the microbiology, incidence, and recurrence rates of UTI. Most uncomplicated lower UTIs are caused by *Escherichia coli*.[36–39] Other uropathic pathogens include *Staphylococcus saprophyticus* in uncomplicated UTIs and both non–*E. coli* gram-negative rods (*Proteus mirabilis*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa*) and gram-positive cocci (*Staphylococcus aureus*) in complicated UTIs.[39] Most upper and lower UTIs are caused by bacteria that enter through the urethra. Although the distal portion of the urethra often contains pathogens, the urine formed in the kidneys and found in the bladder normally is sterile or free of bacteria. This is because of the *washout phenomenon*, in which urine from the bladder normally washes bacteria out of the urethra.

There is an increased risk for UTIs in persons with urinary obstruction and reflux, in people with neurogenic disorders that impair bladder emptying, in women who are sexually active, in postmenopausal women, in men with diseases of the prostate, and in elderly persons. Instrumentation and urinary catheterization are the most common predisposing factors for nosocomial UTIs. UTIs occur more commonly in women with diabetes than in women without the disease. People with diabetes are also at increased risk for complications associated with UTIs, including pyelonephritis, and they are more susceptible to fungal infections (particularly *Candida* species) and

infections with gram-negative pathogens other than *E. coli,* both of which are accompanied by increased severity and unusual manifestations.[40]

Host–Agent Interactions

Because certain people tend to be predisposed to development of UTIs, considerable interest has been focused on host–pathogen interactions and factors that increase the risk for UTI.

Host Defenses. In the development of a UTI, host defenses are matched against the virulence of the pathogen. The host defenses of the bladder have several components, including the washout phenomenon, in which bacteria are removed from the bladder and urethra during voiding; the protective mucin layer that lines the bladder and protects against bacterial invasion; and local immune responses.[37] Immune mechanisms, particularly secretory immunoglobulin (Ig) A, appear to provide an important antibacterial defense. Phagocytic blood cells further assist in the removal of bacteria from the urinary tract.

There has been a growing appreciation of the protective function of the bladder's mucin layer.[37] It is thought that the epithelial cells that line the bladder synthesize protective substances that subsequently become incorporated into the mucin layer that adheres to the bladder wall. One theory proposes that the mucin layer acts by binding water, which then constitutes a protective barrier between the bacteria and the bladder epithelium. Elderly and postmenopausal women produce less mucin than younger women, suggesting that estrogen may play a role in mucin production in women.

Other important host factors include the normal flora of the periurethral area in women and prostate secretions in men.[37] In women, the normal flora of the periurethral area, which consists of organisms such as *Lactobacillus,* provides a defense against the colonization of uropathic bacteria. Alterations in the periurethral environment, such as occurs with a decrease in estrogen levels during menopause or the use of antibiotics, can alter the protective periurethral flora, allowing uropathogens to colonize and enter the urinary tract. In men, the prostatic fluid has antimicrobial properties that protect the urethra from colonization.

Pathogen Virulence. Not all bacteria are capable of adhering to and infecting the urinary tract. Of the many strains of *E. coli,* only those with increased ability to adhere to the epithelial cells of the urinary tract are able to produce UTIs. These bacteria have fine protein filaments, called *pili* or *fimbriae,* that help them adhere to receptors on the lining of urinary tract structures.[37] The two main types of pili (types 1 and P) found on the *E. coli* that cause UTIs are morphologically similar but differ in their ability to mediate hemagglutination in the presence of mannose. Type P pili are mannose resistant and were named because of their high incidence in *E. coli* that cause pyelonephritis and because of their association with the P blood group system. P pili have been observed in over 90% of *E. coli* strains causing pyelonephritis but less than 20% of strains causing lower UTIs.[37]

Obstruction and Reflux

Obstruction and reflux are other factors that increase the risk for UTIs. Any microorganisms that enter the bladder normally are washed out during voiding. When outflow is obstructed, urine remains in the bladder and acts as a medium for microbial growth; the microorganisms in the contaminated urine can then ascend along the ureters to infect the kidneys. The presence of residual urine correlates closely with bacteriuria and with its recurrence after treatment. Another aspect of bladder outflow obstruction and bladder distention is increased intravesical pressure, which compresses blood vessels in the bladder wall, leading to a decrease in the mucosal defenses of the bladder.

In UTIs associated with stasis of urine flow, the obstruction may be anatomic or functional. Anatomic obstructions include urinary tract stones, prostatic hyperplasia, pregnancy, and malformations of the ureterovesical junction. Functional obstructions include neurogenic bladder, infrequent voiding, detrusor (bladder) muscle instability, and constipation.

A phenomenon called *urethrovesical reflux* occurs when urine from the urethra moves into the bladder. In women, urethrovesical reflux can occur during activities such as coughing or squatting, in which an increase in intra-abdominal pressure causes the urine to be squeezed into the urethra and then to flow back into the bladder as the pressure decreases. This also can happen when voiding is abruptly interrupted. Because the urethral orifice frequently is contaminated with bacteria, the reflux mechanism may cause bacteria to be drawn back into the bladder. A second type of reflux mechanism, *vesicoureteral reflux,* occurs at the level of the bladder and ureter (see Chapter 25). It allows urine and bacteria to ascend from the bladder to the kidney and is associated with pyelonephritis and infections of the upper urinary tract.

Catheter-Induced Infection

Urinary catheters are a source of urethral irritation and provide a means for entry of microorganisms into the urinary tract. Catheter-associated bacteriuria remains the most frequent cause of gram-negative septicemia in hospitalized patients. Studies have shown that bacteria adhere to the surface of the catheter and initiate the growth of a biofilm that then covers the surface of the catheter (see Chapter 14, Fig. 14-6).[41] The biofilm tends to protect the bacteria from the action of antibiotics and makes treatment difficult. A closed drainage system (i.e., closed to air and other sources of contamination) and careful attention to perineal hygiene (i.e., cleaning the area around the urethral meatus) help to prevent infections in persons who require an indwelling catheter. Careful handwashing and early detection and treatment of UTIs also are essential.

Clinical Features

The manifestations of UTI depend on whether the infection involves the lower (bladder) or upper (kidney) urinary tract and whether the infection is acute or chronic.

The majority of UTIs are acute uncomplicated bladder infections that occur in women. Upper UTIs affect the parenchyma and pelvis of the kidney (pyelonephritis). They are less common and occur more frequently in children and adults with urinary tract obstructions or other predisposing conditions such as diabetes (see Chapter 25).

An acute episode of cystitis (bladder infection) is characterized by frequency of urination, lower abdominal or back discomfort, and burning and pain on urination (i.e., dysuria).[36–38] Occasionally, the urine is cloudy and foul smelling. In adults, fever and other signs of infection usually are absent. If there are no complications, the symptoms disappear within 48 hours of treatment. The symptoms of cystitis also may represent urethritis caused by *Chlamydia trachomatis, Neisseria gonorrhoeae,* or herpes simplex virus, or vaginitis attributable to *Trichomonas vaginalis* or *Candida* species (see Chapter 41).

Diagnosis and Treatment

The diagnosis of UTI usually is based on symptoms and on examination of the urine for the presence of microorganisms. When necessary, x-ray films, ultrasonography, and CT and renal scans are used to identify contributing factors, such as obstruction.

Urine tests are used to establish the presence of bacteria in the urine and a diagnosis of UTI. A commonly accepted criterion for diagnosis of a UTI is the presence of 100,000 colony-forming units (CFU) or more bacteria per milliliter (mL) of urine.[36,37] Colonization usually is defined as the multiplication of microorganisms in or on a host without apparent evidence of invasiveness or tissue injury. Pyuria (the presence of less than five to eight leukocytes per high-power field) indicates a host response to infection rather than asymptomatic bacterial colonization. A Gram stain may be done to determine the type (gram positive or gram negative) of organism that is present.

Chemical screening (urine dipstick) for markers of infection may provide useful information but is less sensitive than microscopic analysis.[36,37] These tests are relatively inexpensive, are easy to perform, and can be done in the clinic setting or even in the home. A urine culture may be done to confirm the presence of pathogenic bacteria in urine specimens, allow for their identification, and permit the determination of their sensitivity to specific antibiotics.

The treatment of UTI is based on the pathogen causing the infection and the presence of contributing host–agent factors. Other considerations include whether the infection is acute, recurrent, or chronic. Most acute lower UTIs, which occur mainly in women and are generally caused by *E. coli,* are treated successfully with a short course of antimicrobial therapy. Forcing fluids may relieve signs and symptoms, and this approach is used as an adjunct to antimicrobial treatment.

Recurrent lower UTIs are those that recur after treatment. They are due either to bacterial persistence or reinfection.[38] Bacterial persistence usually is curable by removal of the infectious source (e.g., urinary catheter or infected bladder stones). Reinfection is managed principally through education regarding pathogen transmission and prevention measures. Cranberry juice or blueberry juice has been suggested as a preventive measure for persons with frequent UTIs. Studies suggest that these juices reduce bacterial adherence to the epithelial lining of the urinary tract.[42,43] Because of their mechanism of action, these juices are used more appropriately in prevention rather than treatment of an established UTI.

Chronic UTIs are more difficult to treat. Because they often are associated with obstructive uropathy or reflux flow of urine, diagnostic tests usually are performed to detect such abnormalities. When possible, the condition causing the reflux flow or obstruction is corrected. Most persons with recurrent UTIs are treated with antimicrobial agents for 10 to 14 days in doses sufficient to maintain high urine levels of the drug, and they are examined for obstruction or other causes of infection. Men in particular should be investigated for obstructive disorders or a prostatic focus of infection.

Infections in Special Populations

Urinary tract infections affect persons of all ages. In infants, they occur more often in boys than in girls. After the first year of life UTIs occur more often in girls. UTIs are more common in women than men, specifically between 16 and 35 years of age, at which time women are 40 times more likely to develop a UTI than age-matched men.[44] This is because of the shorter length of the female urethra and because the vaginal vestibule can be easily contaminated with fecal flora. In men, the longer length of the urethra and the antibacterial properties of the prostatic fluid provide some protection from ascending UTIs until approximately 50 years of age.[39] After this age, prostatic hyperplasia becomes more common, and with it may come obstruction and increased risk for UTI (see Chapter 39).

Urinary Tract Infections in Women

Approximately half of all adult women have at least one UTI during their lifetime. The major risk factors for women 16 to 35 years of age are related to sexual intercourse and use of spermicidal agents.[37,45] The anterior urethra usually is colonized with bacteria; urethral massage or sexual intercourse can force these bacteria back into the bladder. Using a diaphragm and spermicide enhances the susceptibility to infection.[39,45,46] A nonpharmacologic approach to the treatment of frequent UTIs associated with sexual intercourse is to increase fluid intake before intercourse and to void soon after intercourse. This procedure uses the washout phenomenon to remove bacteria from the bladder.

Urinary Tract Infections in Pregnant Women. Pregnant women are at increased risk for UTIs. Normal changes in the functioning of the urinary tract that occur during pregnancy predispose to UTIs.[47,48] These changes involve the collecting system of the kidneys and include dilation of the renal calyces, pelves, and ureters that begins during the first trimester and becomes

most pronounced during the third trimester. This dilation of the upper urinary system is accompanied by a reduction in the peristaltic activity of the ureters that is thought to result from the muscle-relaxing effects of progesterone-like hormones and mechanical obstruction from the enlarging uterus. In addition to the changes in the kidneys and ureters, the bladder becomes displaced from its pelvic position to a more abdominal position, producing further changes in ureteral position.

The complications of asymptomatic UTIs during pregnancy include persistent bacteriuria, acute and chronic pyelonephritis, and preterm delivery of infants with low birth weight. Evidence suggests that few women become bacteriuric during pregnancy. Rather, it appears that symptomatic UTIs during pregnancy reflect preexisting asymptomatic bacteriuria and that changes occurring during pregnancy simply permit the prior urinary colonization to progress to symptomatic infection and invasion of the kidneys. Because bacteriuria may occur as an asymptomatic condition in pregnant women, it is recommended that a urine culture be obtained at their first prenatal visit.[49] A repeat culture should be obtained during the third trimester. Women with bacteriuria should be followed closely, and infections should be properly treated to prevent complications. The choice of antimicrobial agent should address the common infecting organisms and should be safe for the mother and fetus.

Urinary Tract Infections in Children

Urinary tract infections occur in as many as 3% to 5% of female and 1% of male children.[50,51] In girls, the average age at first diagnosis is 5 years or younger, with peaks during infancy and toilet training. In boys, most UTIs occur during the first year of life and are more common in uncircumcised than in circumcised boys.[52,53] Children who are at increased risk for bacteriuria or symptomatic UTIs are premature infants discharged from neonatal intensive care units, children with systemic or immunologic disease or urinary tract abnormalities such as neurogenic bladder or vesicoureteral reflux, those with a family history of UTI or urinary tract anomalies with reflux, and girls younger than 5 years of age with a history of UTI.[50]

UTIs in children frequently involve the upper urinary tract (pyelonephritis). In children in whom renal development is not complete, pyelonephritis can lead to renal scarring and permanent kidney damage. Most UTIs that lead to scarring and diminished kidney growth occur in children younger than 4 years, especially infants younger than 1 year of age. The incidence of scarring is greatest in children with gross vesicoureteral reflux or obstruction, in children with recurrent UTIs, and in those with a delay in treatment.

Unlike adults, children frequently do not present with the typical signs of a UTI.[50,52,53] Many neonates with UTIs have bacteremia and may show signs and symptoms of septicemia, including fever, hypothermia, apneic spells, poor skin perfusion, abdominal distention, diarrhea, vomiting, lethargy, and irritability. Older infants may present with feeding problems, failure to thrive, diarrhea, vomiting, fever, and foul-smelling urine. Toddlers often present with abdominal pain, vomiting, diarrhea, abnormal voiding patterns, foul-smelling urine, fever, and poor growth. In older children with lower UTIs, the classic features—enuresis, frequency, dysuria, and suprapubic discomfort—are more common. Fever is a common sign of UTI in children, and the possibility of UTI should be considered in any child with unexplained fever.

Diagnosis is based on a careful history of voiding patterns and symptomatology; physical examination to determine fever, hypertension, abdominal or suprapubic tenderness, and other manifestations of UTI; and urinalysis to determine bacteriuria, pyuria, proteinuria, and hematuria. A positive urine culture that is obtained correctly is essential for the diagnosis. Additional diagnostic methods may be needed to determine the cause of the disorder. Vesicoureteral reflux is the most commonly associated abnormality in UTIs (see Chapter 25), and reflux nephropathy is an important cause of end-stage renal disease in children and adolescents. Children with a relatively uncomplicated first UTI may turn out to have significant reflux. Therefore, even a single documented UTI in a child requires careful diagnosis. Urinary symptoms in the absence of bacteriuria suggest vaginitis, urethritis, sexual molestation, the use of irritating bubble baths, pinworms, or viral cystitis. In adolescent girls, a history of dysuria and vaginal discharge makes vaginitis or vulvitis a consideration.

The approach to treatment is based on the clinical severity of the infection, the site of infection (i.e., lower versus upper urinary tract), the risk for sepsis, and the presence of structural abnormalities.[50,52–54] The immediate treatment of infants and young children is essential. Most infants with symptomatic UTIs and many children with clinical evidence of acute upper UTIs often require hospitalization, rehydration, and intravenous antibiotic therapy. Follow-up is essential for children with febrile UTIs to ensure resolution of the infection. Follow-up urine cultures often are done at the end of treatment. Imaging studies often are recommended for all children after their first UTI to detect renal scarring, vesicoureteral reflux, or other abnormalities.

Urinary Tract Infections in the Elderly

Urinary tract infections are relatively common in elderly persons.[51] They are the second most common form of infection, after respiratory tract infections, among otherwise healthy community-dwelling elderly. They are particularly prevalent in elderly persons living in nursing homes or extended care facilities.

Most of these infections follow invasion of the urinary tract by the ascending route. Several factors predispose elderly persons to UTIs, including immobility resulting in poor bladder emptying; bladder outflow obstruction caused by prostatic hyperplasia or kidney stones; bladder ischemia caused by urine retention; constipation; senile vaginitis; and diminished bactericidal activity of urine and prostatic secretions. Added to these risks are other

health problems that necessitate instrumentation of the urinary tract. UTIs develop in 1% of ambulatory patients after a single catheterization and within 3 to 4 days in essentially all patients with indwelling catheters.[55]

Elderly persons with bacteriuria have varying symptoms, ranging from the absence of symptoms to the presence of typical UTI symptoms. Even when symptoms of lower UTIs are present, they may be difficult to interpret because elderly persons without UTIs commonly experience urgency, frequency, and incontinence. Alternatively, elderly persons may have vague symptoms such as anorexia, fatigue, weakness, or change in mental status. Even with more serious upper UTIs (e.g., pyelonephritis), the classic signs of infection such as fever, chills, flank pain, and tenderness may be altered or absent in elderly persons.[51] Sometimes, no symptoms occur until the infection is far advanced.

In summary, UTI is the second most common type of bacterial infection seen by health care professionals. Infections can range from asymptomatic bacteriuria to severe kidney infections that cause irreversible kidney damage. Predisposition to infection is determined by host defenses and pathogen virulence. Host defenses include the washout phenomenon associated with voiding, the protective mucin lining of the bladder, and the local immune defenses. Pathogen virulence is enhanced by the presence of pili that facilitate adherence to structures in the urinary tract, lipopolysaccharides that bind to host cells and elicit an inflammatory reaction, and enzymes that break down red blood cells and make iron available for bacterial metabolism and multiplication.

Most UTIs ascend from the urethra and bladder. A number of factors interact in determining the predisposition to development of UTIs, including urinary tract obstruction, urine stasis and reflux, pregnancy-induced changes in urinary tract function, age-related changes in the urinary tract, changes in the protective mechanisms of the bladder and ureters, impaired immune function, and virulence of the pathogen. Urinary tract catheters and urinary instrumentation contribute to the incidence of UTIs. Early diagnosis and treatment of UTI are essential to preventing permanent kidney damage.

Cancer of the Bladder

Cancer of the bladder is the fourth most common malignancy in men and the eighth most common malignancy in women in the Western world.[56] For some as-yet unexplained reason, African Americans have only half the risk of white European Americans, but the overall survival rate among African Americans appears to be worse.

Approximately 90% to 95% of bladder cancers are derived from the transitional (urothelium) cells that line the bladder.[57] These tumors can range from papillary to flat, noninvasive to invasive, and low grade to high grade.[56–59] Low-grade carcinomas are always papillary and are rarely invasive, but may recur after removal. High-grade carcinomas can be papillary or occasionally flat; they tend to cover larger areas of the mucosal surface and invade deeper than do low-grade tumors. Stage II and III carcinomas of the bladder infiltrate surrounding structures, spread to regional lymph nodes, and occasionally metastasize to distant sites.[59]

Etiology and Pathogenesis

Although the cause of bladder cancer is unknown, evidence suggests that its origin is related to local influences, such as carcinogens that are excreted in the urine and stored in the bladder. These include the breakdown products of aromatic amines used in the dye industry and products used in the manufacture of rubber, textiles, paint, chemicals, and petroleum.[56,59,60] Smoking also deserves attention. Thirty to 50% of all bladder cancers are associated with cigarette smoking.[56,58] Chronic bladder infections and bladder stones also increase the risk for bladder cancer. Bladder cancer is more frequent among persons harboring the parasite *Schistosoma haematobium* in their bladder.[57] The parasite is endemic in Egypt and Sudan. It is not known whether the parasite excretes a carcinogen or produces its effects through irritation of the bladder.

Manifestations

The most common sign of bladder cancer is painless hematuria.[58–60] Gross hematuria is a presenting sign in 75% of persons with the disease, and microscopic hematuria is present in most others. Frequency, urgency, and dysuria occasionally accompany the hematuria. Because hematuria often is intermittent, the diagnosis may be delayed. Periodic urine cytology is recommended for all persons who are at high risk for the development of bladder cancer because of exposure to urinary tract carcinogens. Ureteral invasion leading to bacterial and obstructive renal disease and dissemination of the cancer are potential complications and ultimate causes of death. The prognosis depends on the histologic grade of the cancer and the stage of the disease at the time of diagnosis.

Diagnosis and Treatment

Diagnostic methods include cytologic studies, excretory urography, cystoscopy, and biopsy. Ultrasonography, CT scans, and MRI are used as aids for staging the tumor. Cytologic studies performed on biopsy tissues or cells obtained from bladder washings may be used to detect the presence of malignant cells.[58]

The treatment of bladder cancer depends on the extent of the lesion and the health of the patient. Endoscopic resection usually is done for diagnostic purposes and may be used as a treatment for superficial lesions. Segmental surgical resection may be used for removing a large single lesion. When the tumor is invasive, cystectomy with resection of

the pelvic lymph nodes frequently is the treatment of choice. Cystectomy requires urinary diversion, an alternative reservoir, usually created from the ileum (e.g., an ileal loop), that is designed to collect the urine. External-beam radiation therapy is an alternative to radical cystectomy in some patients with deeply infiltrating bladder cancer.[58]

Although a number of chemotherapeutic drugs have been used in the treatment of bladder cancer, no chemotherapeutic regimens for the disease have been established. Perhaps of more importance is the increasing use of intravesical chemotherapy, in which the cytotoxic drug is instilled directly into the bladder, thereby avoiding the side effects of systemic therapy.

In summary, cancer of the bladder is the most common cause of urinary tract cancer in the United States. Bladder cancers fall into two major groups: low-grade noninvasive tumors and high-grade invasive tumors that are associated with metastasis and a worse prognosis. Although the cause of cancer of the bladder is unknown, evidence suggests that carcinogens excreted in the urine may play a role. Microscopic and gross, painless hematuria are the most frequent presenting signs of bladder cancer. The methods used in treatment of bladder cancer depend on the cytologic grade of the tumor and the lesion's degree of invasiveness. The methods include surgical removal of the tumor, radiation therapy, and chemotherapy. In many cases, chemotherapeutic or immunotherapeutic agents can be instilled directly into the bladder, thereby avoiding the side effects of systemic therapy.

REVIEW EXERCISES

1. A 23-year-old man is recovering after the acute phase of a cervical (C6) spinal cord injury with complete loss of motor and sensory function below the level of injury. He is now experiencing spastic bladder contractions with involuntary and incomplete urination. Urodynamic studies reveal spastic contraction of the external sphincter with urine retention and high bladder pressures.

A. Explain the reason for the involuntary urination and incomplete emptying of the bladder despite high bladder pressures.
B. What are possible complications associated with overdistention and high pressure within the bladder?

2. A 66-year-old woman complains of leakage of urine during coughing, sneezing, laughing, or squatting down.

A. Explain the source of this woman's problem.
B. One of the recommended treatments for stress incontinence is the use of Kegel exercises, which focus on strengthening the muscles of the pelvic floor. Explain how these exercises contribute to the control of urine leakage in women with stress incontinence.

3. A 26-year-old woman makes an appointment with her health care provider, complaining of urinary frequency, urgency, and burning. She reports that her urine is cloudy and smells abnormal. A urine dipstick indicates the presence of infection, a urine sample is obtained for culture, and she is given a prescription for antibiotics.

A. What microorganism is most likely responsible for the infection?
B. What factors may have predisposed her to this disorder?
C. What could this woman do to prevent future infection?

REFERENCES

1. Tanagho E.A. (2008). Anatomy of the genitourinary tract. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 1–16). New York: McGraw-Hill Medical.
2. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 311–314). Philadelphia: Elsevier Saunders.
3. Andersson K.-E., Arner A. (2004). Urinary bladder contraction and relaxation: Physiology and pathophysiology. *Physiology Review* 84, 935–986.
4. Sugaya K., Miyazato M., Ogawa Y. (2005). Central nervous control of micturition and urine storage. *Journal of Smooth Muscle Research* 41, 117–132.
5. Tanagho E.A., Bella A.J., Luce T.F. (2008). Neuropathic bladder disorders. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 438–454). New York: McGraw-Hill Medical.
6. Dmochowski R.R., Appell R.A. (2000). Advances in pharmacologic management of overactive bladder. *Urology* 56(Suppl 6A), 41–49.
7. Ouslander J.G. (2004). Management of overactive bladder. *New England Journal of Medicine* 350, 786–799.
8. Tanagho E.A., Deng D.Y. (2008). Urodynamic studies. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 455–472). New York: McGraw-Hill Medical.
9. Tanagho E.A. (2008). Urinary obstruction and stasis. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 166–178). New York: McGraw-Hill Medical.
10. Seliu B.A., Subedi R. (2008). Urinary retention in adults: Diagnosis and initial management. *American Family Physician* 77(5), 643–650.
11. Fowler C.J., O'Malley K.J. (2003). Investigation and management of neurogenic bladder dysfunction. *Journal of Neurology, Neurosurgery, and Psychiatry* 74(Suppl IV), iv27–iv31.
12. Elliott D.S., Boone T.B. (2000). Recent advances in management of neurogenic bladder. *Urology* 56(Suppl 6A), 76–81.
13. Sasaki K., Yoshimura N., Chancellor M.B. (2003). Implication of diabetes mellitus in urology. *Urologic Clinics of North America* 30, 1–12.
14. Vinik A.I., Maser R.E., Mitchell B.D., et al. (2003). Diabetic autonomic neuropathy. *Diabetes Care* 26, 1553–1579.
15. Addison R., Lopez J. (2001). Bladder retraining. *Nursing Times* 97(5), 45–46.

16. Fantl J.A., Newman D.K., Colling J., et al., for the Agency for Health Care Policy and Research, Public Health Service. (1996). *Urinary incontinence in adults: Acute and chronic management*. Clinical practice guideline no. 2, 1996 update. AHCPR publication no. 96-0682. Rockville, MD: U.S. Department of Health and Human Services.
17. Walters M.D. (2005). Urinary incontinence in women. ACOG practice bulletin no. 63. Clinical practice guidelines for obstetricians and gynecologists. *Obstetrics and Gynecology* 105, 1533–1545.
18. Smith P.P., McCrery R.J., Appell R.A. (2006). Current trends in the evaluation and management of female urinary incontinence. *Canadian Medical Association Journal* 175, 1233–1240.
19. Sampselle C.M., Palmer M.H., Boyington A.R., et al. (2004). Prevention of urinary incontinence in adults. *Nursing Research* 53(6 Suppl), S61–S67.
20. Tanagho E.A., Bella A.J., Lue T.F. (2008). Urinary incontinence. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 473–491). New York: McGraw-Hill Medical.
21. Wilson M.G. (2006). Urinary incontinence: Selected current concepts. *Medical Clinics of North America* 90, 825–836.
22. Tarnay C.M., Bhatia N. (2003). Urogynecology. In DeCherney A.H., Nathan L. (Eds.), *Current obstetric and gynecologic diagnosis and treatment* (9th ed., pp. 806–811). New York: McGraw-Hill.
23. Hampel C., Wienhold D., Benken N., et al. (1997). Definition of overactive bladder and epidemiology of urinary incontinence. *Urology* 50(Suppl 6A), 4–14.
24. Wein A.J. (2001). Putting overactive bladder into clinical perspective. *Patient Care for the Nurse Practitioner* (Spring Suppl), 1–5.
25. Chu F.M., Dmochowski R. (2006). Pathology of overactive bladder. *American Journal of Medicine* 119(Suppl 3A), 3S–8S.
26. Abrams P., Cardozo L., Fall M., et al. (2002). The standardization of terminology in lower urinary tract function: Report from the standardization sub-committee on the international continence society. *Urology* 61, 37–49.
27. Scientific Committee of the First International Consultation on Incontinence. (2000). Assessment and treatment of incontinence. *Lancet* 355, 2153–2158.
28. Lavell J.P., Karram M., Chu F.M. (2006). Management of incontinence for family practice physicians. *American Journal of Medicine* 119(Suppl 3A), 37S–40S.
29. Gibbs C.F., Johnson T.M., Ouslander J.G. (2007). Office management of geriatric urinary incontinence. *American Journal of Medicine* 120, 213–220.
30. Thomas D.R. (2004). Pharmacologic management of urinary incontinence. *Clinics in Geriatric Medicine* 20, 511–523.
31. Wein A.J., Rovner E.S. (2002). Pharmacologic management of urinary incontinence in women. *Urologic Clinics of North America* 29, 537–550.
32. Lee S.Y., Phanumus D., Fields S.D. (2000). Urinary incontinence: A primary guide to managing acute and chronic symptoms in older adults. *Geriatrics* 55(11), 65–71.
33. Madersbacher H., Madersbacher S. (2005). Men's bladder health: Urinary incontinence in the elderly (Part I). *Journal of Men's Health & Gender* 2(1), 31–37.
34. Dubeau C.E. (2002). The continuum of urinary incontinence in an aging population. *Geriatrics* 57(Suppl 1), 12–17.
35. Kalusner A.P., Vapnek J.M. (2004). Urinary incontinence in the geriatric population. *Mount Sinai Journal of Medicine* 70, 54–61.
36. Menhert-Kay S.A. (2005). Diagnosis and management of uncomplicated urinary tract infections. *American Family Physician* 72, 451–456, 458.
37. Nguyen H.T. (2008). Bacterial infections of the genitourinary tract. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 193–215). New York: McGraw-Hill Medical.
38. Drekonja D.M., Johnson J.R. (2008). Urinary tract infections. *Primary Care Clinics in Office Practice* 35, 345–367.
39. Stamm W.E. (2002). Scientific and clinical challenges in the management of urinary tract infections. *American Journal of Medicine* 113(Suppl 1A), 1S–4S.
40. Stapleton A. (2002). Urinary tract infections in patients with diabetes. *American Journal of Medicine* 113(Suppl 1A), 80S–84S.
41. Saint S., Chenoweth C.E. (2003). Biofilms and catheter-associated urinary tract infections. *Infectious Disease Clinics of North America* 17, 411–432.
42. Raz R., Chazan B., Dan M. (2004). Cranberry juice and urinary tract infection. *Clinical Infectious Diseases* 38, 1413–1419.
43. Lynch D.M. (2004). Cranberry for prevention of urinary tract infections. *American Family Physician* 20, 2175–2177.
44. McLaughlin S.P., Carson C.D. (2004). Urinary tract infections in women. *Medical Clinics of North America* 88, 417–429.
45. Fihn S.D. (2003). Acute uncomplicated urinary tract infections in women. *New England Journal of Medicine* 349, 259–266.
46. Foster R.T. (2008). Uncomplicated urinary tract infections in women. *Obstetrics and Gynecology Clinics of North America* 35, 235–248.
47. Mittal P., Wing D.A. (2005). Urinary tract infections in pregnancy. *Clinics in Perinatology* 32, 749–764.
48. Macejko A.M., Schaeffer A.J. (2007). Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urology Clinics of North America* 34, 35–42.
49. American College of Obstetricians and Gynecologists. (1998). *Antimicrobial therapy for obstetric patients* (pp. 8–10). ACOG Educational Bulletin no. 245. Washington, DC: American College of Obstetricians and Gynecologists.
50. Elder J.S. (2007). Urologic disorders in infants and children. In Berman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2223–2228). Philadelphia: Saunders.
51. Shortliffe L.M., McCue J.D. (2002). Urinary tract infections at the age extremes: Pediatrics and geriatrics. *American Journal of Medicine* 113(Suppl 1A), 55S–66S.
52. Zorc J.L., Kiddoo D.A., Shaw K.N. (2005). Diagnosis and management of pediatric urinary tract infections. *Clinical Microbiology Reviews* 18, 417–422.
53. Chang S.L., Shortliffe L.D. (2006). Pediatric urinary tract infections. *Pediatric Clinics of North America* 53, 379–400.
54. Alper B.S., Curry S.H. (2005). Urinary tract infections in children. *American Family Physician* 72, 2483–2488.
55. Mouton C.P., Pierce B., Espino D.V. (2001). Common infections in older adults. *American Family Physician* 63, 257–268.
56. Kirkall Z., Chan T., Manoharan M., et al. (2005). Bladder cancer: Epidemiology, staging and grading, and diagnosis. *Urology* 66(Suppl 6A), 4–34.
57. Reuter V.E. (2006). The pathology of bladder cancer. *Urology* 67(Suppl 3A), 11–17.
58. Konety B.R., Carroll P. (2008). Urothelial carcinoma: Cancers of the bladder, ureter, and renal pelvis. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 308–327). New York: McGraw-Hill Medical Books.
59. Alpers C.E., Fogo A.B. (2008). The kidney and collecting system. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins basic pathology* (8th ed., pp. 575–578). Philadelphia: Saunders Elsevier.
60. Damjanov I. (2008). The lower urinary tract and male reproductive system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 752–758). Philadelphia: Lippincott Williams & Wilkins.

UNIT 8

Gastrointestinal and Hepatobiliary Function

Structure and Organization of the Gastrointestinal Tract
- *Upper Gastrointestinal Tract*
  - Esophagus
  - Stomach
- *Middle Gastrointestinal Tract*
- *Lower Gastrointestinal Tract*
- *Gastrointestinal Wall Structure*

Motility
- *Control of Gastrointestinal Motility*
  - Pacemaker-Generated Slow-Wave Activity
  - Enteric Nervous System
- *Swallowing and Esophageal Motility*
- *Gastric Motility*
- *Small Intestinal Motility*
- *Colonic Motility and Defecation*

Hormonal, Secretory, and Microflora Functions
- *Gastrointestinal Hormones*
- *Gastrointestinal Secretions*
  - Salivary Secretions
  - Gastric Secretions
  - Intestinal Secretions
- *Intestinal Flora*

Digestion and Absorption
- *Carbohydrate Digestion and Absorption*
- *Fat Digestion and Absorption*
- *Protein Digestion and Absorption*

Anorexia, Nausea, and Vomiting
- *Anorexia*
- *Nausea*
- *Retching and Vomiting*

Chapter 28

Structure and Function of the Gastrointestinal System

The gastrointestinal (GI) tract is an amazing structure. In this system, food is dismantled and its nutrients absorbed, wastes are collected and eliminated, vitamins are synthesized, and enzymes are produced. The GI tract is also becoming increasingly recognized as an endocrine organ that produces and augments hormones that contribute to the regulation of appetite and nutrient intake and function in the use and storage of nutrients.

As a matter of semantics, the GI tract also is referred to as the *digestive tract*, the *alimentary canal*, and, at times, the *gut*. The intestinal portion also may be called the *bowel*. For the purposes of this text, the liver and pancreas (discussed in Chapter 30), which produce secretions that aid in digestion, are considered *accessory organs*.

Structure and Organization of the Gastrointestinal Tract

The major physiologic functions of the GI tract are to digest food and absorb nutrients into the bloodstream. It carries out these functions through motility, secretion, digestion, and absorption. In the digestive tract, food and other materials move slowly along its length as they are systematically

broken down into ions and molecules that can be absorbed into the blood. In the large intestine, unabsorbed nutrients and wastes are collected for later elimination.

Structurally, the GI tract is a long, hollow tube, the lumen of which is an extension of the external environment (Fig. 28-1). Nutrients do not become part of the internal environment until they have passed through the intestinal wall and have entered the blood or lymph channels. For simplicity and understanding, the GI tract can be divided into three parts. The upper part—the mouth, esophagus, and stomach—acts as an intake source and receptacle through which food passes and in which initial digestive processes take place. The middle portion—the duodenum, jejunum, and ileum—is where most digestive and absorptive processes occur. The lower segment—the cecum, colon, and rectum—serves as a storage channel for the efficient elimination of waste. The accessory organs, which include the salivary glands, liver, and pancreas, produce secretions that aid in digestion.

Upper Gastrointestinal Tract

The mouth forms the entryway into the GI tract for food; it contains the teeth, used in the mastication of food, and the tongue and other structures needed to direct food toward the pharyngeal structures and the esophagus. The mouth also serves as a receptacle for saliva produced by the salivary glands. Saliva moistens and lubricates food, so it is easier to swallow, and it contains enzymes involved in the initial digestion of lipids and starches.

Esophagus

The esophagus is a straight, collapsible tube, about 25 cm (10 in) in length, that lies behind the trachea and connects the oropharynx with the stomach. The esophagus functions primarily as a conduit for the passage of food from the pharynx to the stomach. Its structure is uniquely designed for this purpose: the smooth muscle layers provide the peristaltic movements needed to move

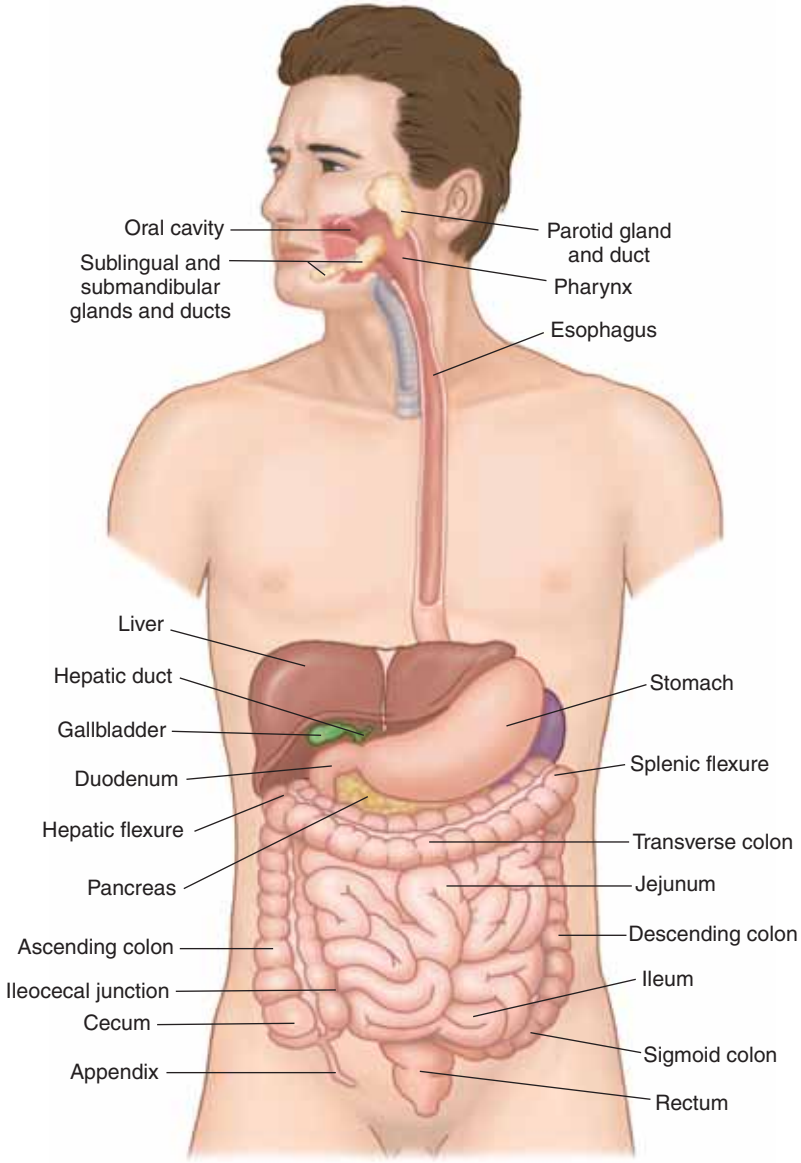


FIGURE 28-1. The gastrointestinal system.

food along its length, and the mucosal and submucosal glands secrete mucus, which protects its surface and aids in lubricating food.

There are sphincters at either end of the esophagus: an upper esophageal sphincter and a lower esophageal sphincter. The upper sphincter, the *pharyngoesophageal* sphincter, consists of a circular layer of striated muscle. It keeps air from entering the esophagus and stomach during breathing. The lower sphincter, the *gastroesophageal sphincter,* lies just above the area where the esophagus joins the stomach. The circular muscle in this area normally remains tonically contracted, creating a zone of high pressure that serves to prevent reflux of gastric contents into the esophagus. During swallowing, there is "receptive relaxation" of the lower esophageal sphincter, which allows easy propulsion of the esophageal contents into the stomach. The lower esophageal sphincter passes through an opening, or *hiatus,* in the diaphragm as it joins with the stomach, which is located in the abdomen. The portion of the diaphragm that surrounds the lower esophageal sphincter helps to maintain the zone of high pressure needed to prevent reflux of stomach contents into the esophagus.

Stomach

The stomach is a pouchlike structure that lies in the left side of the abdomen and serves as a food storage reservoir during the early stages of digestion. The esophagus opens into the stomach through an opening called the *cardiac orifice,* so named because of its proximity to the heart. The small part of the stomach that surrounds the cardiac orifice is called the *cardiac region,* the dome-shaped region that bulges above the cardiac region is called the *fundus,* the middle portion is called the *body,* and the funnel-shaped portion that connects with the small intestine is called the *pyloric region* (Fig. 28-2). The wider and more superior part of the pyloric region, the *antrum,* narrows to form the pyloric canal as it approaches the small intestine. At the end of the pyloric canal, the circular layer smooth muscle thickens to form the *pyloric sphincter.* This muscle serves as a valve that controls the rate of stomach emptying and prevents the regurgitation of intestinal contents back into the stomach.

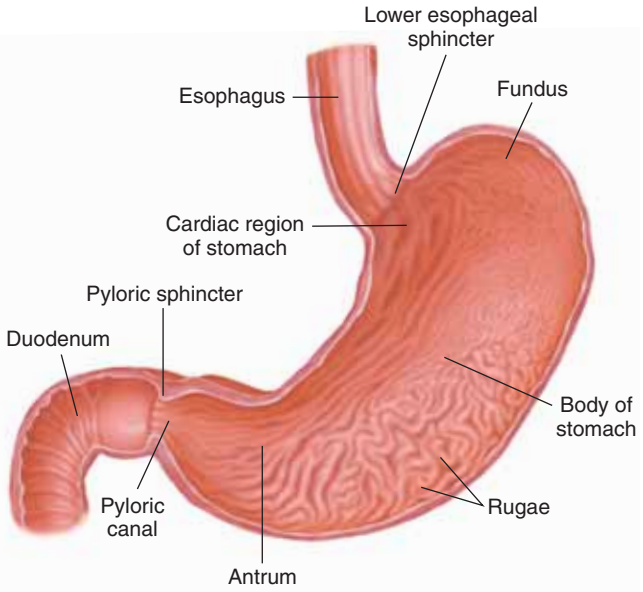


FIGURE 28-2. Structures of the stomach.

Structure and Function of the Gastrointestinal Tract

- The gastrointestinal tract is a long, hollow tube that extends from the mouth to the anus; food and fluids that enter the gastrointestinal tract do not become part of the internal environment until they have been broken down and absorbed into the blood or lymph channels.
- The wall of the GI tract is essentially a four-layered tube: an inner mucosal layer; a supporting submucosal layer; a muscularis layer consisting of an inner circular layer and outer longitudinal layer of smooth muscle that functions to propel its contents in a proximal-to-distal direction; and an outer serosa layer that covers those parts of the GI tract that are suspended in the abdominopelvic cavity.
- The nutrients contained in ingested foods and fluids must be broken down into molecules that can be absorbed across the wall of the intestine. Gastric acids and pepsin from the stomach begin the digestive process: bile from the liver, digestive enzymes from the pancreas, and brush border enzymes break carbohydrates, fats, and proteins into molecules that can be absorbed from the intestine.

Middle Gastrointestinal Tract

The small intestine, which forms the middle portion of the digestive tract, consists of three subdivisions: the duodenum, jejunum, and ileum (see Fig. 28-1). The duodenum, which is approximately 22 cm (10 in) long, connects the stomach to the jejunum and contains the opening for the common bile duct and the main pancreatic duct. Bile and pancreatic juices enter the intestine through these ducts. It is in the jejunum and ileum, which together are approximately 7 m (23 ft) long and must be folded onto themselves to fit into the abdominal cavity, that food is digested and absorbed.

Lower Gastrointestinal Tract

The large intestine, which forms the lower GI tract, is approximately 1.5 m (5 ft) long. It is divided into the cecum, colon, rectum, and anal canal (see Fig. 28-1). The cecum is a blind pouch that projects down at the junction

of the ileum and the colon. The ileocecal valve lies at the upper border of the cecum and prevents the return of feces from the cecum into the small intestine. The appendix arises from the cecum approximately 2.5 cm (1 in) from the ileocecal valve. The colon is further divided into ascending, transverse, descending, and sigmoid portions. The ascending colon extends from the cecum to the undersurface of the liver, where it turns abruptly to form the right colic (hepatic) flexure. The transverse colon crosses the upper half of the abdominal cavity from right to left and then curves sharply downward beneath the lower end of the spleen, forming the left colic (splenic) flexure. The descending colon extends from the colic flexure to the rectum. The rectum extends from the sigmoid colon to the anus. The anal canal passes between the two medial borders of the levator ani muscles. Powerful sphincter muscles guard against fecal incontinence.

Gastrointestinal Wall Structure

The digestive tract, below the upper third of the esophagus, is essentially a four-layered tube (Fig. 28-3). The inner *mucosal layer* is made up of a lining of epithelium, an underlying connective tissue called the *lamina propria,* and the muscularis mucosa, composed of smooth muscle cells that can contract and change the shape and surface area of the mucosal layer. This mucosal layer performs numerous functions in its role as an interface between the body and the external environment, including production of the mucus that lubricates and protects the inner surface of the alimentary canal, secretion of the digestive enzymes and substances that break down food, absorption of the breakdown products of digestion, and maintenance of a barrier to prevent the entry of noxious substances and pathogenic organisms; lymphatics within the mucosa serve as the body's first line of immune defense. The epithelial cells in the mucosal layer have a rapid turnover rate and are replaced every 4 to 5 days. Because of the regenerative capabilities of the mucosal layer, injury to this layer heals rapidly without leaving scar tissue. The *submucosal* or second layer consists of dense connective tissue and aggregates of adipose tissue. It contains the blood vessels, nerves, and structures responsible for secreting digestive enzymes. The submucosal glands either deliver their secretions directly to the lumen of the mucosal glands or via ducts that pass through the mucosa to the luminal surface. The third layer, the *muscularis externa,* consists of an inner layer of circularly arranged smooth muscle cells and an outer layer of longitudinally arranged smooth muscle layers, which facilitate movement of contents of the GI tract. The fourth or *serosal layer* is a serous membrane consisting of a layer of simple squamous epithelium, called the *mesothelium,* and a small amount of underlying connective tissue. It is equivalent to the visceral peritoneum and is the most superficial layer of those parts of the digestive tract that are suspended in the peritoneal cavity.

The peritoneum is the largest serous membrane in the body, having a surface area approximately equal to that of the skin. The peritoneum consists of two continuous layers: the *visceral peritoneum* and the *parietal peritoneum,* which lines the wall of the abdominopelvic cavity. Between the two layers is the *peritoneal cavity,* a potential space containing fluid secreted by the serous membranes. This serous fluid forms a moist and slippery surface that prevents friction between the continuously moving abdominal structures.

The *mesentery* is the double layer of peritoneum that encloses a portion or all of one of the abdominal viscera and attaches it to the abdominal wall (Fig. 28-4A). The mesentery contains the blood vessels, nerves, and lymphatic vessels that supply the intestinal wall

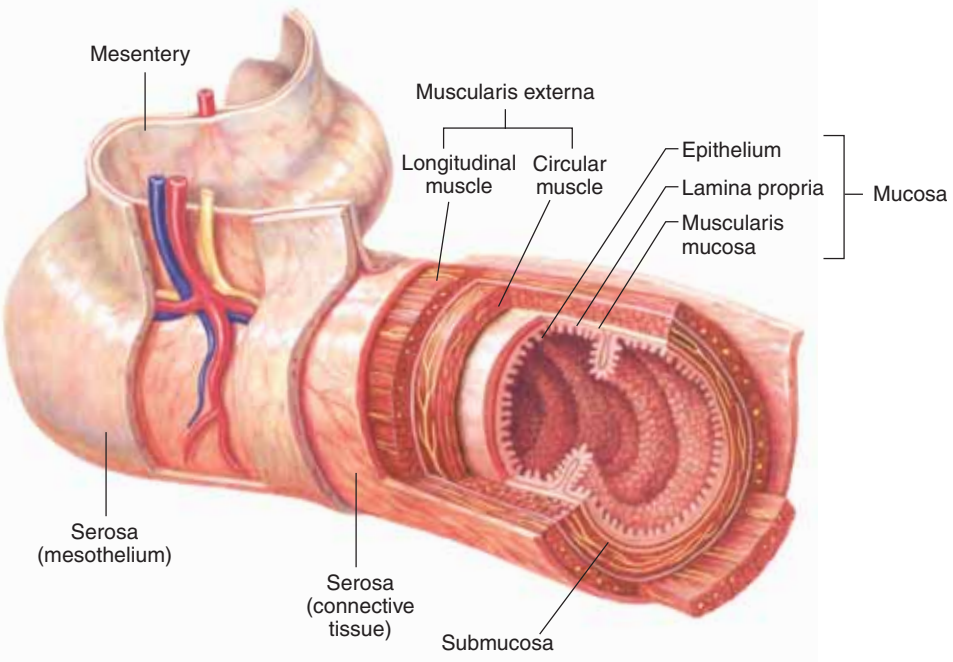


FIGURE 28-3. Transverse section of the gastrointestinal system.

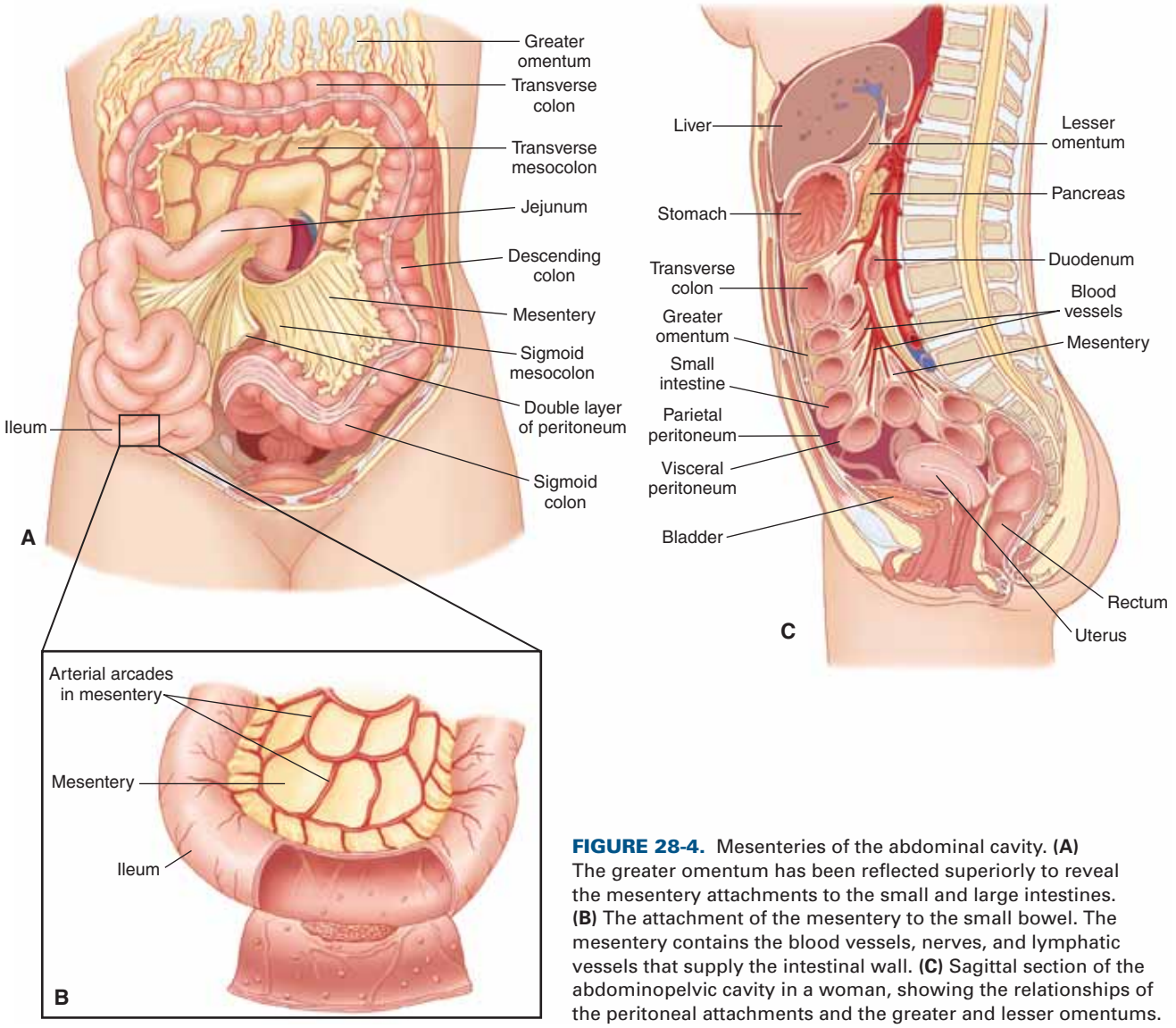


FIGURE 28-4. Mesenteries of the abdominal cavity. **(A)** The greater omentum has been reflected superiorly to reveal the mesentery attachments to the small and large intestines. **(B)** The attachment of the mesentery to the small bowel. The mesentery contains the blood vessels, nerves, and lymphatic vessels that supply the intestinal wall. **(C)** Sagittal section of the abdominopelvic cavity in a woman, showing the relationships of the peritoneal attachments and the greater and lesser omentums.

(see Fig. 28-4B). It also holds the organs in place and stores fat. There are dorsal as well as ventral mesenteries; however, in most places the mesentery is dorsal and attaches to the posterior abdominal wall. The mesentery that encloses the jejunum and ileum is gathered in folds that attach to the dorsal abdominal wall along a short line of insertion, giving a fan-shaped appearance, with the intestines at the edge.

An *omentum* is a double-layered extension or fold of peritoneum that passes from the stomach or proximal part of the duodenum to adjacent organs in the abdominal cavity or abdominal wall. The *greater omentum* extends from the stomach to cover the transverse colon and the folds of the intestine, whereas the *lesser omentum* extends between the transverse fissure of the liver and the lesser curvature of the stomach (see Fig. 28-4C). The greater omentum always contains some fat, which in obese persons can be a considerable amount. It has considerable mobility and moves around in the peritoneal cavity with the peristaltic movements of the intestines. It often forms adhesions (i.e., bands of fibrous scar tissue) adjacent to inflamed organs such as the appendix, walling off the infection and thereby preventing its spread. The greater omentum also cushions the abdominal organs against injury and provides insulation against the loss of body heat.

In summary, the GI tract is a long, hollow tube, the lumen of which is an extension of the external environment. The GI tract can be divided into three parts: an upper part, consisting of the mouth, esophagus, and stomach; a middle part, consisting of the duodenum, jejunum, and ileum; and a lower part, consisting of the cecum, colon, and rectum. The accessory organs consist of the salivary glands, the liver, and the pancreas.

Throughout its length, except for the mouth, throat, and upper esophagus, the GI tract is composed of four layers: an inner mucosal layer, a submucosal layer, a layer of circular and longitudinal smooth muscle fibers, and an outer serosal layer that forms the peritoneum and is continuous with the mesentery.

Motility

Control of Gastrointestinal Motility

The motility of the GI tract propels food and fluids along its length, from mouth to anus, in a manner that facilitates digestion and absorption. The movements of the GI tract can be either rhythmic or tonic. The *rhythmic movements* consist of intermittent contractions that are responsible for mixing and moving food along the digestive tract. Rhythmic movements are found in the esophagus, antrum of the stomach, and small intestine. The *tonic movements* consist of a constant level of contraction or tone without regular periods of relaxation. They are found in the lower esophagus, the upper region of the stomach, the ileocecal valve, and the internal anal sphincter.

Pacemaker-Generated Slow-Wave Activity

All of the contractile tissue in the GI tract is smooth muscle, except for that in the pharynx, the upper third of the esophagus, and the external anal sphincter. Although the smooth muscle found in each region of the GI tract exhibits structural and functional differences, certain basic properties are common to all of the muscle cells. All of the smooth muscle of the GI tract is unitary smooth muscle, in which the cells are electrically coupled by low-resistance pathways so that electrical signals initiating muscle contractions can move rapidly from one fiber to the next.

Like the self-excitable cardiac muscle cells in the heart, some smooth muscle cells of the GI tract function as pacemaker cells. These cells display rhythmic, spontaneous oscillations in membrane potentials, called *slow waves,* ranging in frequency from about three per minute in the stomach to 12 per minute in the duodenum. Slow waves are generated by a thin layer of interstitial cells (*interstitial cells of Cajal*) located between the longitudinal and circular muscle layers.

The amplitude and, to a lesser extent, the frequency of the slow waves can be modulated by the enteric nervous system, which lies entirely within the wall of the GI tract, and by the parasympathetic and sympathetic divisions of the autonomic nervous system (ANS). In addition, a number of peptides, including neurotransmitters and GI hormones (to be discussed), assist in regulating GI motility.

Enteric Nervous System

The enteric nervous system consists of the myenteric and submucosal plexuses in the wall of the GI tract. These two plexuses are networks of nerve fibers and ganglion cell bodies. Interneurons in the plexuses connect afferent sensory fibers, efferent motor neurons, and secretory cells to form reflex circuits that are located entirely within the GI tract wall.

The *myenteric* (Auerbach) *plexus* consists mainly of a linear chain of interconnecting neurons that is located between the circular and longitudinal muscle layers. Because it lies between the two muscle layers and extends all the way down the intestinal wall, it is concerned mainly with motility along the length of the gut. The *submucosal* (Meissner) *plexus,* which lies between the mucosal and muscle layers of the intestinal wall, is mainly concerned with controlling the function of each segment of the intestinal tract. It integrates signals received from the mucosal layer into local control of motility, intestinal secretions, and absorption of nutrients.

The activity of the neurons in the myenteric and submucosal plexuses is regulated by local influences, input from the ANS, and interconnecting fibers that transmit information between the two plexuses. Mechanoreceptors monitor the stretch and distention of the GI tract wall, and chemoreceptors monitor the chemical composition (i.e., osmolality, pH, and digestive products of protein and fat metabolism) of its contents. These receptors can communicate directly with ganglionic cells in the intramural plexuses or with visceral afferent fibers that influence ANS control of GI function.

Autonomic Nervous System Innervation. The autonomic innervation of the GI system is mediated by both the sympathetic and parasympathetic nervous systems (Fig. 28-5). In general, stimulation of the parasympathetic nervous system causes a general increase in activity of the entire enteric nervous system, whereas sympathetic stimulation inhibits activity causing many effects opposite to those of the parasympathetic system.

Parasympathetic innervation to the stomach, small intestine, cecum, ascending colon, and transverse colon occurs through the vagus nerve. The remainder of the colon is innervated by parasympathetic fibers that exit the sacral segments of the spinal cord, by way of the pelvic nerves. Preganglionic parasympathetic fibers can synapse with intramural plexus neurons, or they can act directly on intestinal smooth muscle. In addition, these same nerve bundles provide many afferent nerves whose receptors lie within the various tissues of the gut. Their nerves project to the spinal cord and brain to provide sensory input for integration. Most parasympathetic innervation is excitatory. Numerous vagovagal reflexes influence motility and secretions of the digestive tract.

Sympathetic innervation occurs through the thoracic chain of sympathetic ganglia and the celiac, superior mesenteric, and inferior mesenteric ganglia. The sympathetic nervous system exerts several effects on GI function. It controls the extent of mucus secretion by the mucosal glands, reduces motility by inhibiting the activity of intramural plexus neurons, enhances sphincter function, and increases the vascular smooth muscle tone of the blood vessels that supply the GI tract. The effect of sympathetic stimulation is to block the release of the

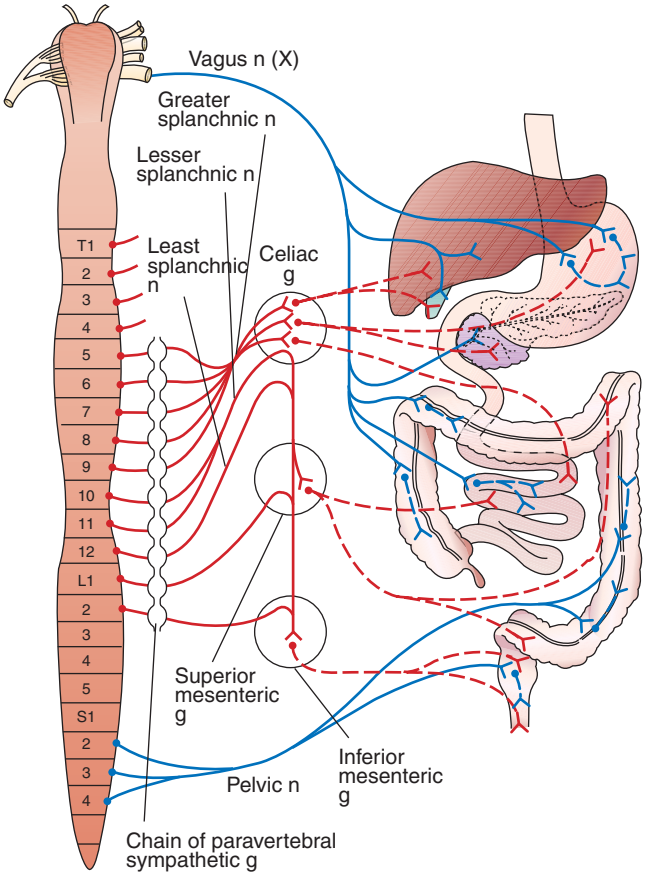


FIGURE 28-5. Autonomic innervation of the gastrointestinal tract (g, ganglion; n, nerve). Parasympathetic innervation is indicated in *blue* and sympathetic in *red.*

excitatory neuromediators in the intramural plexuses, inhibiting GI motility.

Swallowing and Esophageal Motility

Chewing begins the digestive process—it breaks the food into particles of a size that can be swallowed, lubricates it by mixing it with saliva, and mixes starch-containing food with salivary amylase. Although chewing usually is considered a voluntary act, it can be carried out involuntarily by a person who has lost the function of the cerebral cortex.

The swallowing reflex is a rigidly ordered sequence of events that results in the propulsion of food from the mouth to the stomach through the esophagus. Although swallowing is initiated as a voluntary activity, it becomes involuntary as food or fluid reaches the pharynx. Sensory impulses for the reflex begin at tactile receptors in the pharynx and esophagus and are integrated with the motor components of the response in an area of the reticular formation of the medulla and lower pons called the *swallowing center.* The motor impulses for the oral and pharyngeal phases of swallowing are carried in the trigeminal (V), glossopharyngeal (IX), vagus (X), and hypoglossal (XII) cranial nerves, and impulses for the esophageal phase are carried by the vagus nerve. Diseases that damage these brain centers or their cranial nerves disrupt the coordination of swallowing and predispose an individual to food and fluid lodging in the trachea and bronchi, leading to the risk of asphyxiation or aspiration pneumonia.

Swallowing consists of three phases: an oral, or voluntary, phase; a pharyngeal phase; and an esophageal phase (Fig. 28-6A). During the *oral phase,* the bolus is collected at the back of the mouth so the tongue can lift the food upward until it touches the posterior wall of the pharynx. At this point, the *pharyngeal phase* of swallowing is initiated (Fig. 28-6B). The soft palate is pulled upward, the palatopharyngeal folds are pulled together so that food does not enter the nasopharynx, the vocal cords are pulled together, and the epiglottis is moved so that it covers the larynx. Respiration is inhibited, and the bolus is moved backward into the esophagus by constrictive movements of the pharynx. Although the striated muscles of the pharynx are involved in the second stage of swallowing, it is an involuntary stage.

The third phase of swallowing is the *esophageal phase* (Fig. 28-6C). As food enters the esophagus and stretches its walls, local and central nervous system (CNS) reflexes that initiate peristalsis are triggered. There are two types of peristalsis—primary and secondary. Primary peristalsis is controlled by the swallowing center in the brain stem and begins when food enters the esophagus. Secondary peristalsis is partially mediated by smooth muscle fibers in the esophagus and occurs when primary peristalsis is inadequate to move food through the esophagus. Peristalsis begins at the site of distention and moves downward. Before the peristaltic wave reaches the stomach, the lower esophageal sphincter relaxes to allow the bolus of food to enter the stomach. The pressure in the lower esophageal sphincter normally is greater than that in the stomach, an important factor in preventing the reflux of gastric contents.

Gastric Motility

The stomach serves as a food storage reservoir where the chemical breakdown of proteins begins and food is converted to a creamy mixture called *chyme.* Although an empty stomach has a volume of about 50 mL, it can expand to as much as 1000 mL before the intraluminal pressure begins to rise.

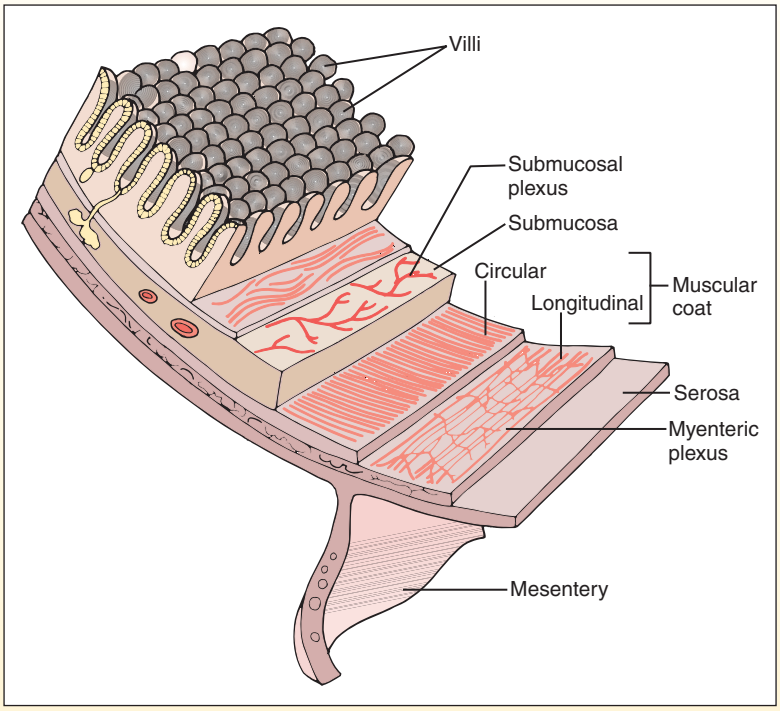
Motility of the stomach results in the churning and mixing of solid foods and regulates the emptying of the gastric contents, or chyme, into the duodenum. Peristaltic mixing and churning contractions begin in a pacemaker area in the middle of the stomach and move toward the antrum. They occur at a frequency of three to five contractions per minute, each lasting 2 to 20 seconds. As the peristaltic wave approaches the antrum, it speeds up, and the entire terminal 5 to 10 cm of the antrum contracts, occluding the pyloric opening. Contraction of the antrum reverses the movement of the chyme, returning the larger particles to the body of the stomach for further churning and kneading. Because the pyloric sphincter is contracted during antral contraction, the gastric contents are emptied into the duodenum between contractions. Constriction of the pyloric sphincter prevents the backflow of

UNDERSTANDING → Intestinal Motility

Motility of the small intestine is organized to optimize the digestion and absorption of nutrients and the propulsion of undigested material toward the colon. Peristaltic movements mix the ingested foodstuffs with digestive enzymes and secretions and circulate the intestinal contents to facilitate contact with the intestinal mucosa. The regulation of motility results from an interplay of input from the (1) enteric and (2) autonomic nervous (ANS) systems and the intrinsic pacemaker activity of the (3) intestinal smooth muscle cells.

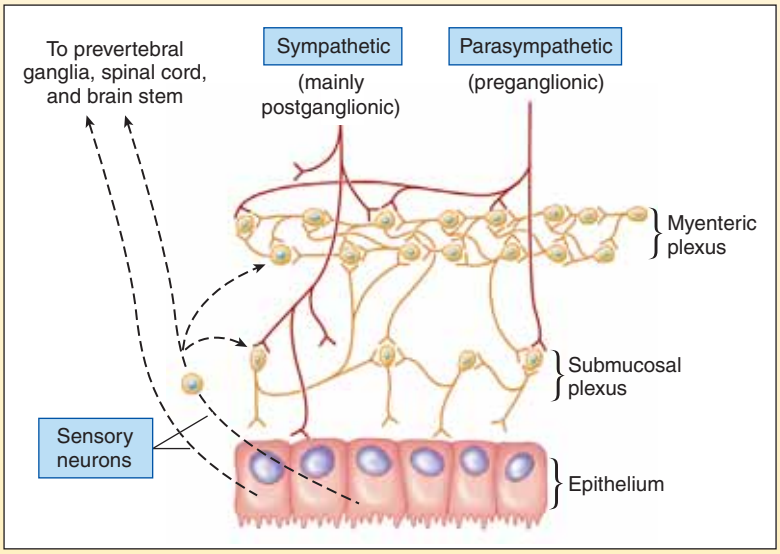
1

Enteric Nervous System Innervation. The gastrointestinal system has its own nervous system, called the *enteric nervous system*. The enteric nervous system is composed mainly of two plexuses: (1) the outer *myenteric (Auerbach) plexus* that is located between the longitudinal and circular layers of smooth muscle cells and (2) an inner *submucosal (Meissner) plexus* that lies between the mucosal and circular muscle layers. The myenteric plexus controls mainly intestinal movements along the length of the gut, whereas the submucosal plexus is concerned mainly with controlling the function within each segment of the intestine. Fibers in the submucosal plexus also use signals originating from the intestinal epithelium to control intestinal secretion and local blood flow.

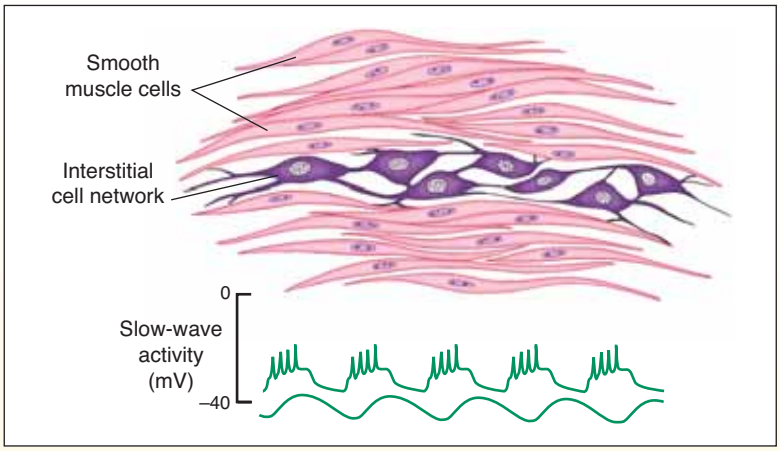


2

ANS Innervation. The intestine is also innervated by the parasympathetic and sympathetic branches of the ANS (see Fig. 28-5). *Parasympathetic innervation* is supplied mainly by the vagus nerve with postganglionic neurons located primarily in the myenteric and submucosal plexuses. Stimulation of these parasympathetic nerves causes a general increase in both intestinal motility and secretory activity. *Sympathetic innervation* is supplied by nerves that run between the spinal cord and the prevertebral ganglia and between these ganglia and the intestine. Stimulation of the sympathetic nervous system is largely inhibitory, producing a decrease in intestinal motility and secretory activity.



3 **Intestinal Smooth Muscle.** Intestinal smooth muscle has its own intrinsic slow-wave activity, which varies from about 12 per minute in the duodenum to 8 or 9 per minute in the ileum. This slow-wave activity is thought to reside in a network of specialized pacemaker cells that are interposed between the smooth muscle cells. Slow waves are not action potentials and they do not directly induce muscle contraction; instead, they are rhythmic, wavelike fluctuations in the membrane potential that cyclically bring the membrane closer to threshold. If the peak voltage of the slow wave exceeds the cell's threshold potential, one or more action potentials may be triggered. Because action potentials occur at the peak of a slow wave, slow-wave frequency determines the rate of smooth muscle contractions. Stretching the intestinal smooth muscle and parasympathetic nervous system stimulation increase excitability of the smooth muscle cells, whereas sympathetic stimulation decreases excitability.



gastric contents and allows them to flow into the duodenum at a rate commensurate with the ability of the duodenum to accept them. This is important because the regurgitation of bile salts and duodenal contents can damage the mucosal surface of the antrum and lead to gastric ulcers. Likewise, the duodenal mucosa can be damaged by the rapid influx of highly acid gastric contents.

The rate at which the stomach empties is regulated by neural and humoral signals from both the stomach and the duodenum. However, the duodenum provides by far the most potent of the signals, controlling the emptying of the chyme into the duodenum at a rate no greater than the rate at which the chyme can be digested and absorbed. Gastric emptying is slowed by hypertonic solutions in the duodenum, by duodenal pH below 3.5, and by the presence of amino acids and peptides in the duodenum. The presence of fatty acids in the duodenum also dramatically decreases the rate of gastric emptying. These reflexes are mediated directly from the duodenum to the stomach by the enteric nervous system and its connections with the sympathetic and parasympathetic nervous systems. Not only do nervous reflexes from the duodenum to the stomach inhibit gastric emptying, but hormones released from the upper intestine do so as well. Both cholecystokinin and glucose-dependent insulinotropic peptide (formerly known as *gastric inhibitory peptide*) are thought to slow gastric emptying. The stimulus for releasing these inhibitory hormones is mainly fats entering the duodenum; other foods may decrease gastric emptying, but to a lesser degree.

Disorders of gastric motility can occur when the rate is too slow or too fast (see Chapter 29). A rate that is too slow leads to gastric retention. It can be caused by obstruction or gastric atony. Obstruction can result from the formation of scar tissue in the pyloric area after a peptic ulcer. Another example of obstruction is *hypertrophic pyloric stenosis*, which can occur in infants with an abnormally thick muscularis layer in the terminal pylorus. Myotomy, or surgical incision of the muscular ring, may be done to relieve the obstruction. Gastric atony can occur as a complication of visceral neuropathies in diabetes mellitus. Surgical procedures that

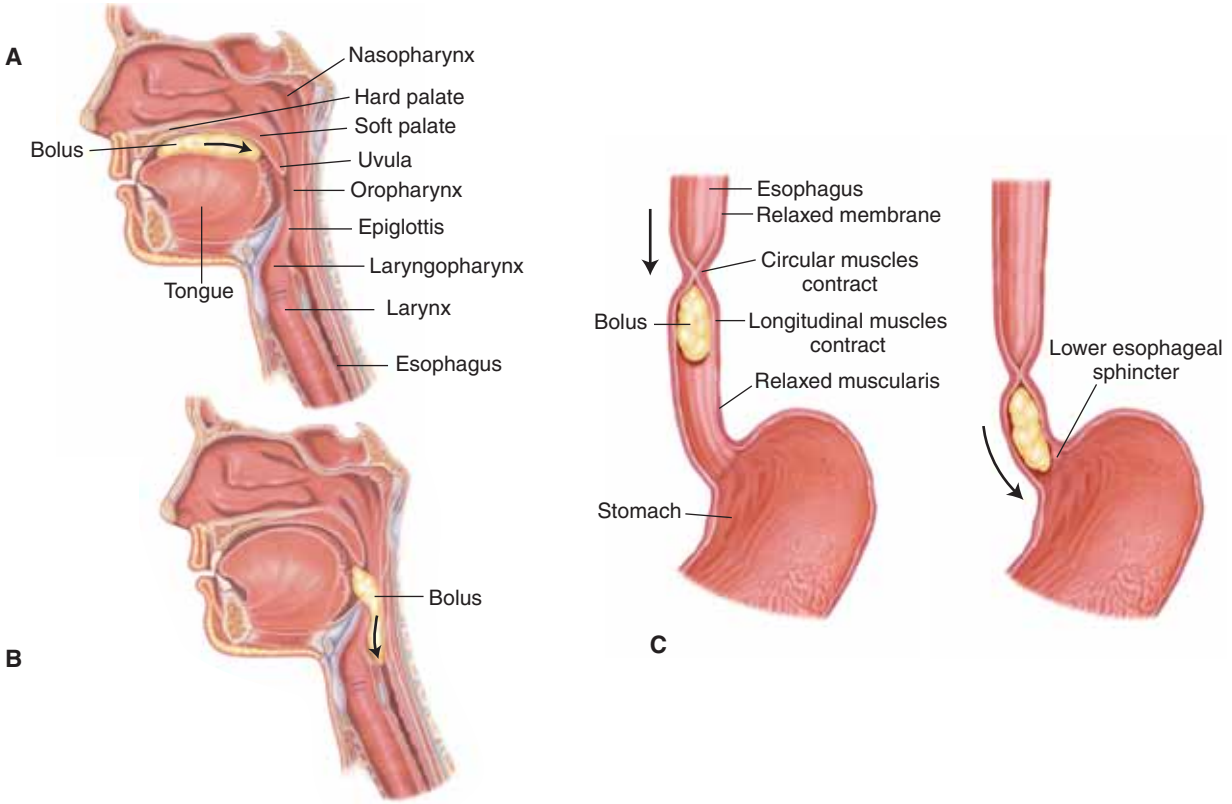


FIGURE 28-6. Steps in the swallowing reflex: **(A)** The *oral* or *voluntary phase* during which the bolus is collected at the back of the mouth so the tongue can lift the food upward and into the pharynx; **(B)** the *pharyngeal phase* during which food movement into the respiratory passages is prevented as the tongue is elevated and pressed against the soft palate closing the epiglottis, the upper esophageal sphincter relaxes, and the superior constrictor muscle contracts, forcing food into the esophagus; and **(C)** the *esophageal phase* during which peristalsis moves food through the esophagus and into the stomach.

disrupt vagal activity also can result in gastric atony. Abnormally fast emptying occurs in a condition called the *dumping syndrome*, which can occur as a complication of certain types of gastric surgeries. This condition is characterized by the rapid dumping of highly acidic and hyperosmotic gastric secretions into the duodenum and jejunum.

Small Intestinal Motility

The small intestine is the major site for the digestion and absorption of food; its movements are mixing and propulsive. There are two patterns of contractions in the small intestine: segmentation and peristaltic contractions. With *segmentation waves*, slow contractions of the circular muscle layer occlude the lumen and drive the contents forward and backward (Fig. 28-7A). Most of the contractions that produce segmentation waves are local events involving only 1 to 4 cm of intestine at a time. They function mainly to mix the chyme with the digestive enzymes from the pancreas and to ensure adequate exposure of all parts of the chyme to the mucosal surface of the intestine, where absorption takes place. The frequency of segmenting activity increases after a meal. Presumably, it is stimulated by receptors in the stomach and intestine.

In contrast to the segmentation contractions, *peristaltic movements* are rhythmic propulsive movements designed to propel the chyme along the small intestine toward the large intestine. They occur when the smooth muscle layer constricts, forming a contractile band that forces the intraluminal contents forward. Normal peristalsis always moves in the direction from the mouth toward the anus. Regular peristaltic movements begin in the duodenum near the entry sites of the common duct and the main hepatic duct. These propulsive movements occur with synchronized activity in a section 10 to 20 cm long. They are accomplished by contraction of the proximal portion of the intestine with the sequential relaxation of its distal, or caudal, portion (see Fig. 28-7B). After material has been propelled to the ileocecal junction by peristaltic movement, stretching of the distal ileum produces a local reflex that relaxes the sphincter and allows fluid to squirt into the cecum.

Motility disturbances of the small bowel are common, and auscultation of the abdomen can be used to assess bowel activity. Inflammatory changes often increase motility. In many instances, it is not certain whether

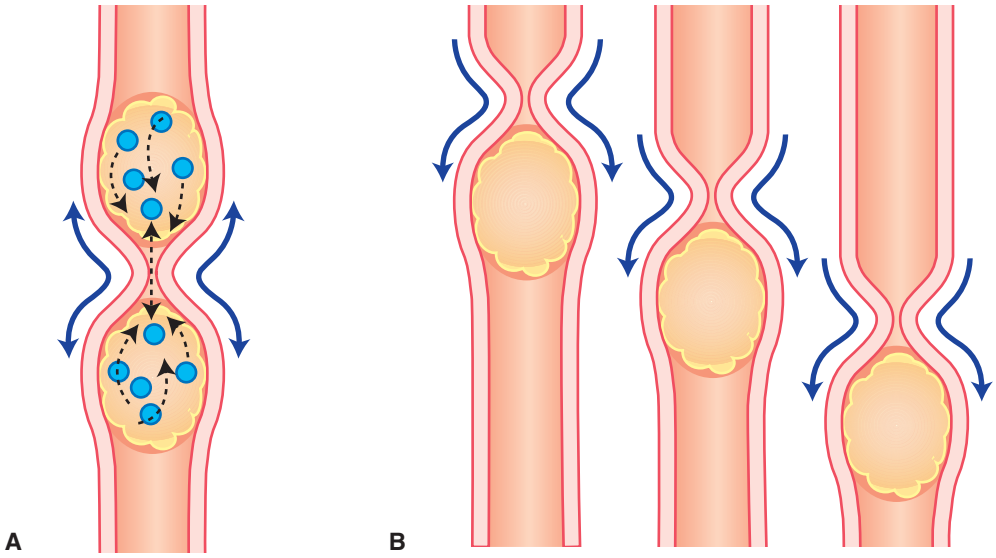


FIGURE 28-7. Two types of small intestine movements: **(A)** Mixing *segmentation waves* in which slow contractions of the circular muscle layer occlude the lumen and drive the contents forward and backward; and **(B)** propulsive *peristaltic movements* in which segmental contractions followed by sequential relaxation moves the contents forward.

changes in motility occur because of inflammation or are secondary to the effects of toxins or unabsorbed materials. Delayed passage of chyme in the small intestine also can be a problem. Transient interruption of intestinal motility often occurs after GI surgery. Intubation with suction often is required to remove the accumulating intestinal contents and gases until activity is resumed.

Colonic Motility and Defecation

The storage function of the colon dictates that movements in this section of the gut are different from those in the small intestine. Movements in the colon are of two types. First are the segmental mixing movements, called *haustrations*, so named because they occur within sacculations called *haustra*. These movements produce a local digging-type action, which ensures that all portions of the fecal mass are exposed to the intestinal surface. Second are the propulsive mass movements, in which a large segment of the colon (≥20 cm) contracts as a unit, moving the fecal contents forward as a unit. Mass movements last approximately 30 seconds, followed by a 2- to 3-minute period of relaxation, after which another contraction occurs. A series of mass movements lasts only for 10 to 30 minutes and may occur only several times a day. Defecation normally is initiated by the mass movements. The normal colonic transit time is 24 to 48 hours, with normal stool weights of up to 250 g/day.

Defecation is controlled by the action of two sphincters, the internal and external anal sphincters. The internal sphincter is a several-centimeters-long, circular thickening of smooth muscle that lies inside the anus. The external sphincter, which is composed of striated voluntary muscle, surrounds the internal sphincter. The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic nervous system and therefore under voluntary control. Defecation is controlled by defecation reflexes. One of these reflexes is the intrinsic myenteric reflex mediated by the local enteric nervous system. It is initiated by distention of the rectal wall, with initiation of reflex peristaltic waves that spread through the descending colon, sigmoid colon, and rectum. A second defecation reflex, the parasympathetic reflex, is integrated at the level of the sacral cord. When the nerve endings in the rectum are stimulated, signals are transmitted first to the sacral cord and then reflexively back to the descending colon, sigmoid colon, rectum, and anus by the pelvic nerves. These impulses greatly increase peristaltic movements as well as relax the internal sphincter.

To prevent involuntary defecation from occurring, the external anal sphincter is under the conscious control of the cortex. As afferent impulses arrive at the sacral cord, signaling the presence of a distended rectum, messages are transmitted to the cortex. If defecation is inappropriate, the cortex initiates impulses that constrict the external sphincter and inhibit efferent parasympathetic activity. Normally, the afferent impulses in this reflex loop fatigue easily, and the urge to defecate soon ceases. At a more convenient time, contraction of the abdominal muscles compresses the contents in the large bowel, reinitiating afferent impulses to the cord.

In summary, motility of the GI tract propels food products and fluids along its length from the mouth to the anus. Although the activity of GI smooth muscle is self-propagating and can continue without input from the nervous system, its rate and strength of contractions are regulated by a network of intramural neurons that receive input from the autonomic nervous system and local receptors that monitor wall stretch and the chemical composition of luminal contents. Parasympathetic innervation occurs through the vagus nerve and nerve fibers from sacral segments of the spinal cord; it increases GI motility. Sympathetic activity occurs

through thoracolumbar output from the spinal cord; its paravertebral ganglia; and celiac, superior mesenteric, and inferior mesenteric ganglia. Sympathetic stimulation enhances sphincter function and reduces motility by inhibiting the activity of intramural plexus neurons.

Hormonal, Secretory, and Microflora Functions

Gastrointestinal Hormones

The GI tract is the largest endocrine organ in the body. It produces hormones that act locally, pass into the general circulation for distribution to more distant sites, and interact with the CNS through the enteric and autonomic nervous systems. Among the hormones produced by the GI tract are gastrin, ghrelin, secretin, cholecystokinin, and incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]). These hormones influence appetite, GI motility, enzyme activity, electrolyte levels, and the secretion and actions of hormones such as growth hormone, insulin, and glucagon. The actions of many of these hormones overlap: two or more GI hormones may affect the same process in the same direction, or they may inhibit each other. The GI tract hormones and their functions are summarized in Table 28-1.

The stomach is the source of two important GI hormones: gastrin and ghrelin. Gastrin is produced by G cells, located predominantly in the antrum of the stomach. The primary function of *gastrin* is the stimulation of gastric acid secretion. Gastrin also has a trophic, or growth-producing, effect on the mucosa of the small intestine, colon, and acid-secreting area of the stomach. Removal of the tissue that produces gastrin results in atrophy of these structures. *Ghrelin* is a newly discovered peptide hormone produced by endocrine cells in the mucosal layer of the fundus of the stomach. It displays potent growth hormone–releasing activity and has a stimulatory effect on food intake and digestive function, while reducing energy expenditure. The isolation of this hormone has led to new insights into the gut–brain regulation of growth hormone secretion and energy balance.

The intestine is the source of secretin, cholecystokinin, and incretin hormones. *Secretin,* which is secreted by S cells in the mucosa of the duodenum and jejunum, inhibits gastric acid secretion. The entry of an acid chyme into the intestine stimulates the release of secretin, which inhibits the release of gastrin. Secretin also stimulates the pancreas to secrete large quantities of fluid with a high bicarbonate concentration and low chloride concentration. The primary function of *cholecystokinin* (CCK), secreted by I cells in the intestinal mucosa, is the stimulation of pancreatic enzyme secretion. It potentiates the action of secretin, increasing the pancreatic bicarbonate response to low circulating levels of secretin; stimulates biliary secretion of fluid and bicarbonate; and regulates gallbladder

TABLE 28-1 Selected Gastrointestinal Hormones and Their Actions

Hormone	Site of Secretion	Stimulus for Secretion	Action
Cholecystokinin	Duodenum, jejunum	Products of protein digestion and long-chain fatty acids	Stimulates contraction of gallbladder and secretion of pancreatic enzymes; slows gastric emptying; inhibits food intake
Gastrin	Antrum of stomach, duodenum	Vagal stimulation; epinephrine; neutral amino acids; calcium-containing foods such as milk; alcohol Secretion inhibited by acid content of stomach antrum (pH <2.5)	Stimulates secretion of gastric acid and pepsinogen; increases gastric blood flow; stimulates gastric smooth muscle contractions; stimulates growth of gastric and intestinal mucosal cells
Ghrelin	Fundus of stomach	Nutritional (fasting) and hormonal (decreased levels of growth hormone)	Stimulates secretion of growth hormone; acts as an appetite-stimulating signal from stomach when an increase in metabolic efficiency is necessary
Glucagon-like peptide-1 (GLP-1)	Distal small intestine	High-carbohydrate meal	Augments insulin release; suppresses glucagon release; slows gastric emptying; decreases appetite and body weight
Glucose-dependent insulinotropic polypeptide (GIP)	Small intestine, mainly jejunum	High-carbohydrate meal	Augments insulin release
Secretin	Duodenum	Acid pH or chyme entering duodenum (pH <3.0)	Stimulates secretion of bicarbonate-containing fluids by pancreas and liver

contraction and gastric emptying. CCK has also been shown to inhibit food intake and to be an important mediator for appetite and the control of meal size.

Several gut-derived hormones have been identified as having what is termed an *incretin* effect, meaning that they increase insulin release after an oral glucose load. This suggests that gut-derived factors can stimulate insulin secretion after a predominantly carbohydrate meal. The two hormones that account for about 90% of the incretin effect are GLP-1, which is released from L cells in the distal small bowel, and GIP, which is released by K cells in the upper gut (mainly the jejunum). Because increased levels of GLP-1 and GIP can lower blood glucose levels by augmenting insulin release in a glucose-dependent manner (i.e., at low blood glucose levels no further insulin is secreted, minimizing the risk of hypoglycemia), these hormones have been targeted as possible antidiabetic drugs. Moreover, GLP-1 can exert other metabolically beneficial effects, including suppression of glucagon release, slowing of gastric emptying, augmenting of net glucose clearance, and decreasing appetite and body weight.

Gastrointestinal Secretions

Throughout the GI tract, secretory glands serve two basic functions: (1) production of mucus to lubricate and protect the mucosal layer of the GI tract wall and (2) secretion of fluids and enzymes to aid in the digestion and absorption of nutrients. Each day, approximately 7000 mL of fluid is secreted into the GI tract (Table 28-2). Approximately 50 to 200 mL of this fluid leaves the body in the stool; the remainder is reabsorbed in the small and large intestines. These secretions are mainly water and have sodium and potassium concentrations similar to those of extracellular fluid. Because water and electrolytes for digestive tract secretions are derived from the extracellular fluid compartment, excessive secretion or impaired absorption can lead to extracellular fluid deficit.

The secretory and digestive functions of the gut are influenced by local, humoral, and neural influences. Neural control of GI secretory activity is mediated through the ANS. Secretory activity, like motility, is increased with parasympathetic stimulation and inhibited with sympathetic activity. Many of the local influences, including pH, osmolality, and chyme, consistently act as stimuli for neural and humoral mechanisms.

TABLE 28-2 Secretions of the Gastrointestinal Tract

Secretions	Amount Daily (mL)
Salivary	1200
Gastric	2000
Pancreatic	1200
Biliary	700
Intestinal	2000
Total	7100

Salivary Secretions

Saliva is secreted by the salivary glands. The salivary glands consist of the parotid, submaxillary, sublingual, and buccal glands. Saliva has three functions. The first is protection and lubrication. Saliva is rich in mucus, which protects the oral mucosa and coats the food as it passes through the mouth, pharynx, and esophagus. The sublingual and buccal glands produce only mucus-type secretions. The second function of saliva is its protective antimicrobial action. The saliva cleans the mouth and contains the enzyme lysozyme, which has an antibacterial action. Third, saliva contains ptyalin and amylase, which initiate the digestion of dietary starches. Secretions from the salivary glands are primarily regulated by the ANS. Parasympathetic stimulation increases flow and sympathetic stimulation decreases flow. The dry mouth that accompanies anxiety attests to the effects of sympathetic activity on salivary secretions.

Mumps, or parotitis, is an infection of the parotid glands. Although most of us associate mumps with the contagious viral form of the disease, inflammation of the parotid glands can occur in the seriously ill person who does not receive adequate oral hygiene and who is unable to take fluids orally.

Gastric Secretions

In addition to mucus-secreting cells that line the entire surface of the stomach, the stomach mucosa has several other types of cells, including the parietal (or oxyntic) cells, chief cells, and G cells. The parietal and chief cells are located in the proximal 80% (body and fundus) of the stomach. The parietal cells secrete hydrochloric acid (HCl) and intrinsic factor. The chief cells secrete pepsinogen, an enzyme that initiates proteolysis or breakdown of proteins. The antrum is located in the distal 20% of the stomach. This area contains the G cells, which secrete gastrin.

The luminal surface and gastric pits of the stomach are lined with mucus-producing epithelial cells, with the parietal and chief cells situated in the bases of the gastric pits (Fig. 28-8). There are approximately 1 billion parietal cells in the stomach; together they produce and secrete approximately 20 mEq of HCl in several hundred milliliters of gastric juice each hour. The pepsinogen that is secreted by the chief cells is rapidly converted to pepsin when exposed to the low pH of the gastric juices. Intrinsic factor, which is produced by the parietal cells, is necessary for the absorption of vitamin B_{12} (see Chapter 13).

One of the important characteristics of the gastric mucosa is resistance to the highly acid secretions that it produces. When the gastric mucosa is damaged by aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), ethyl alcohol, or bile salts, this barrier is disrupted, and hydrogen ions move into the tissue. As the hydrogen ions accumulate in the mucosal cells, intracellular pH decreases, enzymatic reactions become impaired, and cellular structures are disrupted. The result is local ischemia, vascular stasis, hypoxia, and tissue necrosis. The mucosal surface is further protected by prostaglandins. Aspirin and NSAIDs decrease prostaglandin synthesis by inhibition of cyclooxygenase (known as COX; hence, these agents are

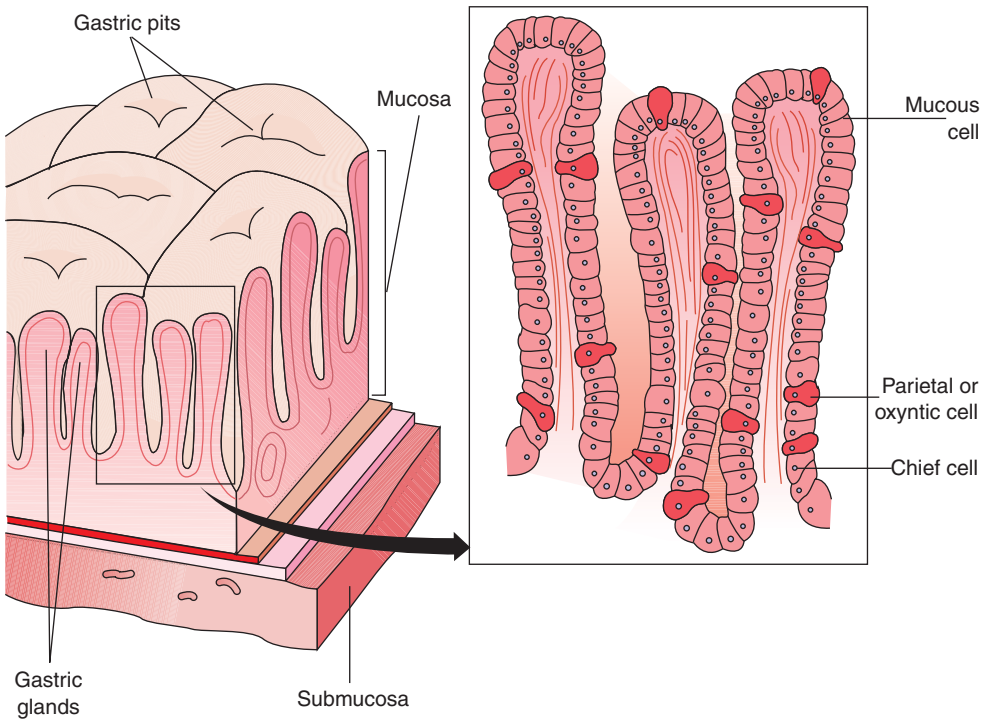


FIGURE 28-8. Gastric pit from body of the stomach.

also known as COX inhibitors), which also impairs the integrity of the mucosal surface.

Gastric Acid Secretion. The cellular mechanism for HCl secretion by the parietal cells in the stomach involves the hydrogen ion (H^+)/potassium ion (K^+)-adenosine triphosphatase (ATPase) transporter and chloride ion (Cl^-) channels located on their luminal membrane (Fig. 28-9). During the process of HCl secretion, carbon dioxide (CO_2) produced by aerobic metabolism combines with water (H_2O), catalyzed by carbonic anhydrase, to form carbonic acid (H_2CO_3), which readily dissociates into H^+ and bicarbonate (HCO_3^-). The H^+ is secreted with Cl^- into the stomach, and the HCO_3^- moves out of the cell and into blood from the basolateral membrane. The absorbed HCO_3^- is responsible for the alkaline tide (increased pH) that occurs after a meal. At the luminal side of the membrane, H^+ is secreted into the stomach by the H^+/K^+-ATPase transporter (also known as the *proton pump*). Chloride follows H^+ into the stomach by diffusing through Cl^- channels in the luminal membrane. The proton pump inhibitors (e.g., omeprazole), which are used in the treatment of acid reflux and peptic ulcer, inhibit gastric acid secretion by binding irreversibly to the sulfhydryl groups of the H^+/K^+-ATPase transporter.

Three substances stimulate HCl secretion by the parietal cells: acetylcholine, gastrin, and histamine. Although each substance binds to different receptors on the parietal cell and has a different mechanism of action, they all serve to stimulate an increase in H^+ secretion through the H^+/K^+-ATPase transporter. Acetylcholine is released from vagal nerves innervating the stomach and binds to acetylcholine receptors on the parietal cells. Gastrin is secreted by G cells in the antrum of the stomach and reaches the parietal cells through the circulation. It binds to as-yet uncharacterized receptors on the parietal cells. Histamine is released from special endocrine cells in the gastric mucosa and diffuses to nearby parietal cells, where it binds to histamine-2 (H_2) receptors. H_2 receptor blockers (e.g., cimetidine), used in the treatment of peptic ulcer and gastroesophageal reflux, bind to H_2 receptors and block

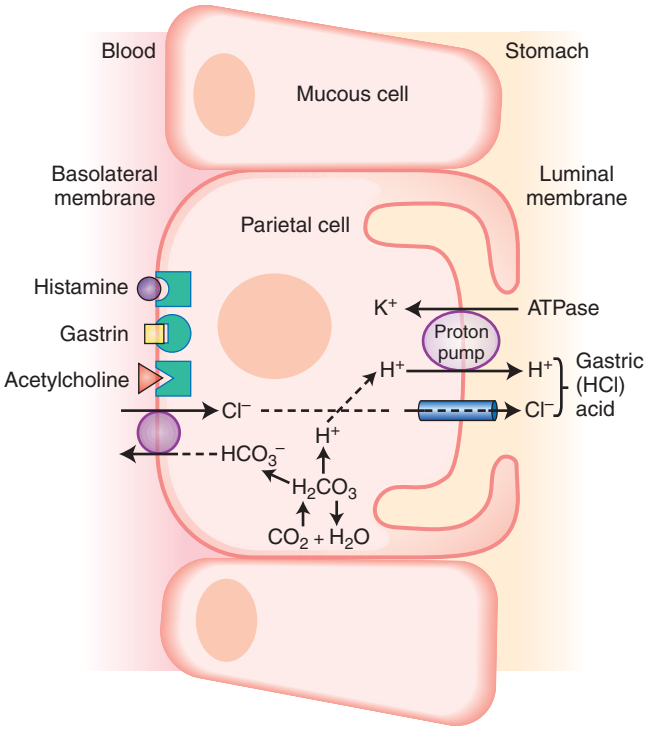


FIGURE 28-9. Mechanism of gastric acid secretion by the parietal cells in the stomach.

the action of histamine on parietal cells. In contrast to these acid-stimulatory factors, prostaglandin E_2 (after binding to its receptor) inhibits acid secretion and stimulates mucus production. Hence, it is an important factor in the maintenance of the gastric mucosal barrier. Gastric acid secretion and its relation to gastroesophageal reflux and peptic ulcer are discussed further in Chapter 29.

Intestinal Secretions

The small intestine secretes digestive juices and receives secretions from the liver and pancreas (see Chapter 30). An extensive array of mucus-producing glands, called *Brunner glands,* is concentrated at the site where the contents from the stomach and secretions from the liver and pancreas enter the duodenum. These glands secrete large amounts of alkaline mucus that protect the duodenum from the acid content in the gastric chyme and from the action of the digestive enzymes. The activity of Brunner glands is strongly influenced by ANS activity. For example, sympathetic stimulation causes a marked decrease in mucus production, leaving this area more susceptible to irritation. Between 75% and 80% of peptic ulcers occur at this site.

In addition to mucus, the intestinal mucosa produces two other types of secretions. The first is a serous fluid (pH 6.5 to 7.5) secreted by specialized cells (i.e., crypts of Lieberkühn) in the intestinal mucosal layer. This fluid, which is produced at the rate of 2000 mL/day, acts as a vehicle for absorption. The second type of secretion consists of surface enzymes that aid absorption. These enzymes are the peptidases, or enzymes that separate amino acids, and the disaccharidases, or enzymes that split sugars.

The large intestine usually secretes only mucus. ANS activity strongly influences mucus production in the bowel, as in other parts of the digestive tract. During intense parasympathetic stimulation, mucus secretion may increase to the point that the stool contains large amounts of obvious mucus. Although the bowel normally does not secrete water or electrolytes, these substances are lost in large quantities when the bowel becomes irritated or inflamed.

Intestinal Flora

The gut is the natural habitat of a large and diverse bacterial community. The major functions of the gut microflora include metabolic activities that salvage energy and absorbable nutrients, trophic effects on intestinal epithelial cells, and protection of the colonized host against invasion by pathogenic organisms.

The stomach and small intestine contain only a few species of bacteria, probably because of the composition of luminal contents (i.e., acids, bile, pancreatic secretions), which kills most ingested microorganisms, and the propulsive movements of this area, which impedes their colonization. The large intestine, on the other hand, contains a large and complex microbial ecosystem. It has been estimated that each individual has 300 to 500 different species of intestinal bacteria, with anaerobic bacteria outnumbering aerobic bacteria by a large percentage.

Colonization of the GI tract begins shortly after birth and is influenced by passage through the birth canal and the type of diet (breast milk versus formula) the infant receives. Other environmental factors also have a role because differences exist between the intestinal flora of infants born in industrialized countries and those born in developing countries.

The major metabolic function of colonic microflora is the fermentation of undigestible dietary residue and endogenous mucus produced by the epithelial cells. The genetic diversity of the microorganisms in the gut provides various enzymes and biochemical pathways that are distinct from those of the host. Fermentation of nondigestible carbohydrates, including resistant starches, cellulose, pectins, and unabsorbed sugars, is a major source of energy in the colon. The metabolic end point is the generation of short-chain fatty acids, which play a major role in epithelial cell growth and differentiation. Colonic microorganisms also play a role in vitamin synthesis and in absorption of calcium, magnesium, and iron. Vitamin K, for example, is synthesized by the colonic flora; the newborn infant does not synthesize an adequate amount of vitamin K for the first week or so of life until the normal colonic bacterial flora becomes established. Lastly, the resident gut flora provides a crucial line of resistance to colonization by exogenous microbes, and therefore is highly protective against invasion of tissues by pathogens. Colonization resistance also applies to opportunistic bacteria that are present in the gut but whose growth is restricted. The administration of broad-spectrum antibiotics can disrupt the microbial balance and allow overgrowth of species with potential pathogenicity, such as *Clostridium difficile* (see Chapter 29).

The role of probiotics as a supplement to the normal diet and as a treatment for several disease states has become increasingly recognized. Probiotics are live microorganisms that, when ingested, can modify the composition of enteric microflora. Commonly used probiotics are lactobacilli, bifidobacteria, and nonpathogenic *Escherichia coli.* Probiotics have shown value in several diseases, such as maintaining remission in ulcerative colitis.

In summary, the secretions of the GI tract include saliva, gastric juices, bile, and pancreatic and intestinal secretions. Each day, more than 7000 mL of fluid is secreted into the digestive tract; all but 50 to 200 mL of this fluid is reabsorbed. Water, derived from the extracellular fluid compartment, is the major component of GI tract secretions. Neural, humoral, and local mechanisms contribute to the control of these secretions. The parasympathetic nervous system increases secretion, and sympathetic activity exerts an inhibitory effect. In addition to secreting fluids containing digestive enzymes, the GI tract produces and secretes hormones, such as gastrin, ghrelin, secretin, CCK, and the incretin hormones (GLP-1 and GIP) that influence appetite, GI motility, enzyme activity, and the actions of hormones such as growth hormone, insulin, and glucagon.

The GI tract is also the natural habitat of a large and diverse bacterial community. The major functions of the gut microflora include metabolic activities that salvage energy and absorbable nutrients, impart trophic effects on intestinal epithelial cells, and protect the colonized host against invasion by pathogenic organisms.

Digestion and Absorption

Digestion is the process of dismantling foods into their constituent parts. Digestion requires hydrolysis, enzyme cleavage, and fat emulsification. Hydrolysis is the breakdown of a compound that involves a chemical reaction with water. The importance of hydrolysis to digestion is evidenced by the amount of water (7 to 8 L) that is secreted into the GI tract daily. The intestinal mucosa is impermeable to large molecules; therefore, proteins, fats, and carbohydrates must be broken down into smaller particles before they can be absorbed. Although some digestion of carbohydrates and proteins begins in the stomach, digestion takes place mainly in the small intestine. The breakdown of fats to free fatty acids and monoglycerides takes place entirely in the small intestine. The liver, with its production of bile, and the pancreas, which supplies a number of digestive enzymes, play important roles in digestion.

Absorption is the process of moving nutrients and other materials from the external environment in the lumen of the GI tract into the internal environment. Absorption is accomplished by active transport and diffusion. The absorptive function of the large intestine focuses mainly on water reabsorption. A number of substances require a specific carrier or transport system. For example, vitamin B_{12} is not absorbed in the absence of intrinsic factor, which is secreted by the parietal cells of the stomach. Transport of amino acids and glucose occurs mainly in the presence of sodium. Water is absorbed passively along an osmotic gradient.

The distinguishing characteristic of the small intestine is its large surface area, which in the adult is estimated to be approximately 250 m^2. Anatomic features that contribute to this enlarged surface area are the circular folds that extend into the lumen of the intestine and the villi, which are fingerlike projections of mucous membrane, numbering as many as 25,000, that line the entire small intestine (Fig. 28-10). Each villus is equipped with an artery, vein, and lymph vessel (i.e., lacteal), which bring blood to the surface of the intestine and transport the nutrients and other materials that have passed into the blood from the lumen of the intestine (Fig. 28-11). Fats rely largely on the lymphatics for absorption.

Each villus is covered with cells called *enterocytes* that contribute to the absorptive and digestive functions of the small bowel, and goblet cells that provide mucus. The crypts of Lieberkühn are glandular structures that open into the spaces between the villi. The enterocytes have a life span of approximately 4 to 5 days, and it is believed that replacement cells differentiate from progenitor cells

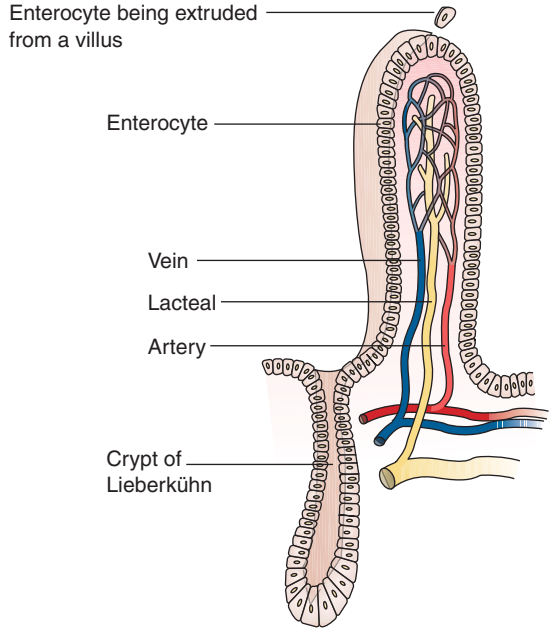


FIGURE 28-11. A single villus from the small intestine.

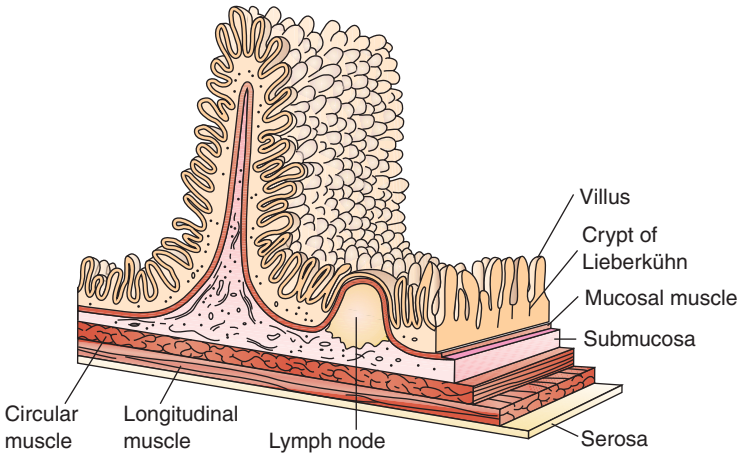


FIGURE 28-10. The mucous membrane of the small intestine. Note the numerous villi on a circular fold.

located in the area of the crypts. The maturing enterocytes migrate up the villus and eventually are extruded from the tip.

The enterocytes secrete enzymes that aid in the digestion of carbohydrates and proteins. These enzymes are called *brush border enzymes* because they adhere to the border of the villus structures. In this way they have access to the carbohydrate and protein molecules as they come in contact with the absorptive surface of the intestine. This mechanism of secretion places the enzymes where they are needed and eliminates the need to produce enough enzymes to mix with the entire contents filling the lumen of the small bowel. The digested molecules diffuse through the membrane or are actively transported across the mucosal surface to enter the blood or, in the case of fatty acids, the lacteal. These molecules are then transported through the portal vein or lymphatics into the systemic circulation.

Carbohydrate Digestion and Absorption

Carbohydrates must be broken down into monosaccharides, or single sugars, before they can be absorbed from the small intestine. The average daily intake of carbohydrate in the American diet is approximately 350 to 400 g. Starch makes up approximately 50% of this total, sucrose (i.e., table sugar) approximately 30%, lactose (i.e., milk sugar) approximately 6%, and maltose approximately 1.5%.

Digestion of starch begins in the mouth with the action of amylase. Pancreatic secretions also contain an amylase. Amylase breaks down starch into several disaccharides, including maltose, isomaltose, and α-dextrins. The brush border enzymes convert the disaccharides into monosaccharides that can be absorbed (Table 28-3). Sucrose yields glucose and fructose, lactose is converted to glucose and galactose, and maltose is converted to two glucose molecules. When the disaccharides are not broken down to monosaccharides, they cannot be absorbed but remain as osmotically active particles in the contents of the digestive system, causing diarrhea. Persons with a deficiency of lactase, the enzyme that breaks down lactose, experience diarrhea when they drink milk or eat dairy products.

Fructose is transported across the intestinal mucosa by facilitated diffusion, which does not require energy expenditure. Glucose and galactose move from the intestinal lumen into the intestinal cells by way of a sodium–glucose cotransporter (SGLT-1), against a chemical gradient. The energy for this step does not come directly from ATP, but from the sodium gradient created by the Na^+/K^+-ATPase pump located on the basolateral side of the membrane (Fig. 28-12). Glucose and galactose are transported from the cell into the blood across the basolateral membrane by facilitated diffusion using a glucose transporter-2 (GLUT-2) protein. Water absorption from the intestine is linked to absorption of osmotically active particles, such as glucose and sodium. It follows that an important consideration in facilitating the transport of water across the intestine (and decreasing diarrhea) after temporary

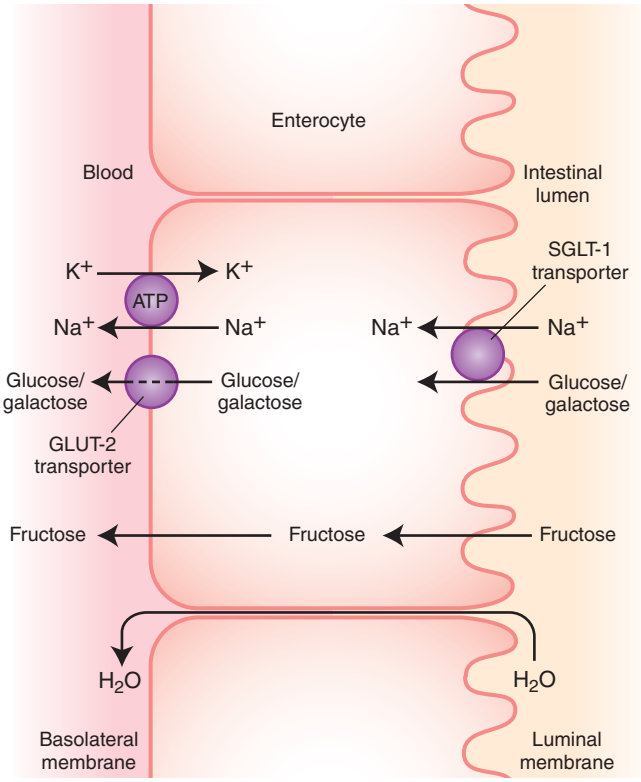


FIGURE 28-12. Intestinal transport of glucose, galactose, and fructose. Glucose and galactose are transported across the apical membrane by the sodium–glucose cotransporter (SGLT-1). Glucose moves out of the intestinal cell and into the blood using a glucose transporter-2 (GLUT-2) protein. Sodium is transported out of the cell by the Na^+/K^+-ATPase sodium pump. This creates the gradient needed to operate the transport system. Fructose is passively transported across the apical and basolateral membranes of the intestinal cell.

TABLE 28-3 Enzymes Used in Digestion of Carbohydrates

Dietary Carbohydrates	Enzyme	Monosaccharides Produced
Lactose	Lactase	Glucose and galactose
Sucrose	Lactase	Fructose and glucose
Starch	Amylase	Maltose, maltotriose, and α-dextrins
Maltose and maltotriose	Maltase	Glucose and glucose
α-Dextrins	α-Dextrinase	Glucose and glucose

disruption in bowel function is to include sodium and glucose in the fluids that are consumed.

Fat Digestion and Absorption

The average adult eats approximately 60 to 100 g of fat daily, principally as triglycerides. The first step in digestion of lipids is to break the large globules of dietary fat into smaller particles so that water-soluble digestive enzymes can act on the surface molecules. This process, which is called *emulsification*, begins in the stomach with agitation of the globules and continues in the duodenum under the influence of bile from the liver (Fig. 28-13). Emulsification greatly increases the number of triglyceride molecules exposed to pancreatic lipase, which splits triglycerides into free fatty acids and monoglycerides. Bile salts play an additional role by forming micelles that transport these substances to the surface of the intestinal villi, where they are taken into the epithelial cells and used to form new triglycerides. These new triglycerides are then released into the lymphatic system as chylomicrons. Small quantities of short- and medium-chain fatty acids are absorbed directly into the portal blood rather than being converted into triglycerides and absorbed by way of the lymphatics.

Fat that is not absorbed in the intestine is excreted in the stool. *Steatorrhea* is the term used to describe fatty stools. It usually indicates that there is 20 g or more of fat in a 24-hour stool sample.

Protein Digestion and Absorption

Protein digestion begins in the stomach with the action of pepsin. Pepsinogen, the enzyme precursor of pepsin, is

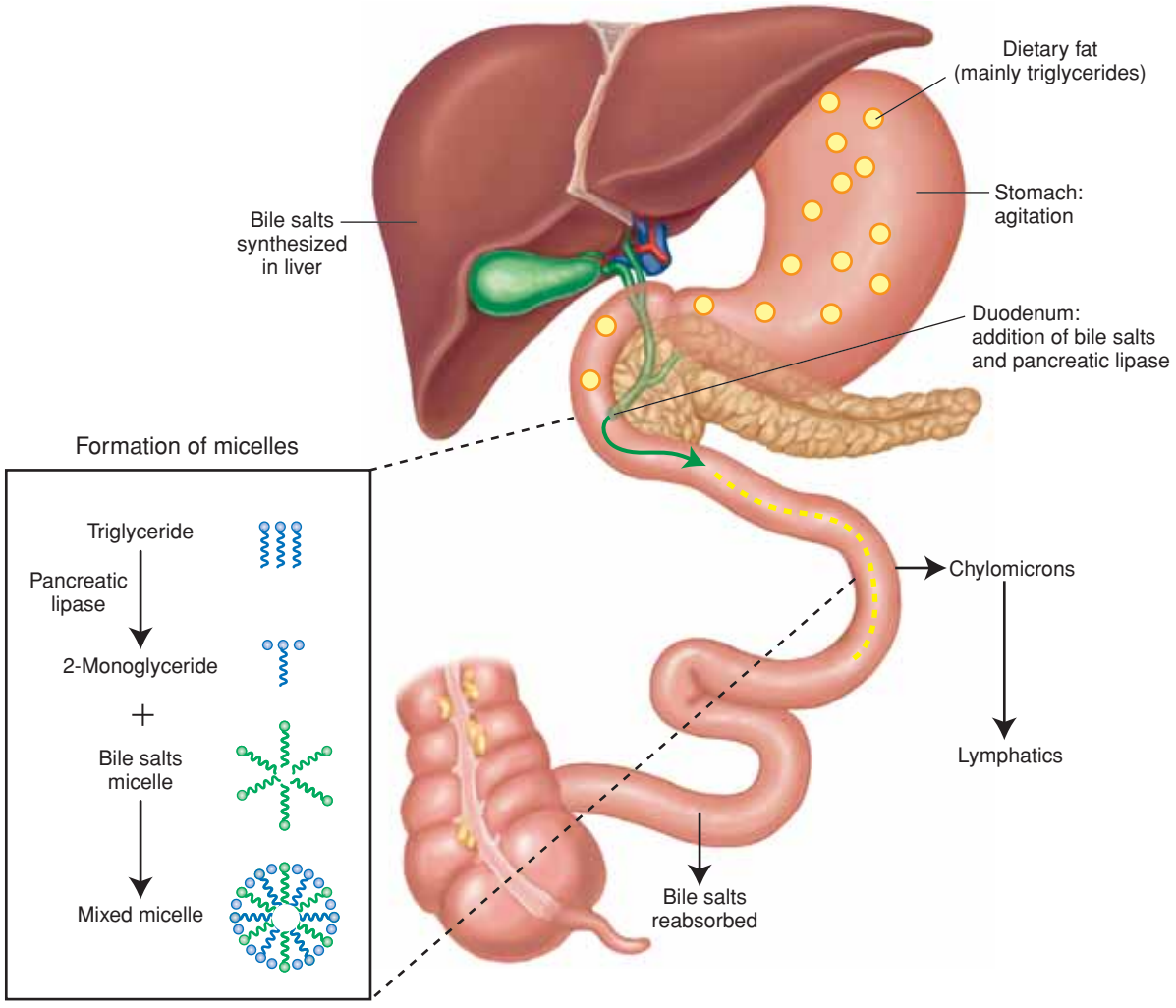


FIGURE 28-13. Mechanisms of dietary fat absorption. During digestion, agitation in the stomach and bile from the liver break large globules of dietary fat into small particles that facilitate the action of pancreatic lipase in splitting triglycerides into free fatty acids and monoglycerides (glycerol with one fatty acid chain attached). Bile salts also facilitate formation of micelles that transport the monoglycerides and free acids to the intestinal mucosa, where they are absorbed and converted to chylomicrons for transport in the lymphatic channels.

secreted by the chief cells in response to a meal and acid pH. Acid in the stomach is required for the conversion of pepsinogen to pepsin. Pepsin is inactivated when it enters the intestine by the alkaline pH.

Proteins are broken down further by pancreatic enzymes, such as trypsin, chymotrypsin, carboxypeptidase, and elastase. As with pepsin, the pancreatic enzymes are secreted as precursor molecules. Trypsinogen, which lacks enzymatic activity, is activated by an enzyme located on the brush border cells of the duodenal enterocytes. Activated trypsin activates additional trypsinogen molecules and other pancreatic precursor proteolytic enzymes. The amino acids are then liberated on the surface of the mucosal surface of the intestine by brush border enzymes that degrade proteins into peptides that are one, two, or three amino acids long. Similar to glucose, many amino acids are transported across the mucosal membrane in a sodium-linked process that uses ATP as an energy source. Some amino acids are absorbed by facilitated diffusion processes that do not require sodium.

In summary, the digestion and absorption of nutrients take place mainly in the small intestine. Digestion is the process of dismantling foods into their constituent parts. Digestion requires hydrolysis, enzyme cleavage, and fat emulsification. Proteins, fats, carbohydrates, and other components of the diet are broken down into molecules that can be transported from the intestinal lumen into the body fluids. Absorption is the process of moving nutrients and other materials from the external environment of the GI tract into the internal environment. Brush border enzymes break carbohydrates into monosaccharides that can be transported across the intestine into the bloodstream. The digestion of proteins begins in the stomach with the action of pepsin and is further facilitated in the intestine by the pancreatic enzymes, such as trypsin, chymotrypsin, carboxypeptidase, and elastase. Enzymes that break down proteins are released as proenzymes that are activated in the GI tract. The absorption of glucose and amino acids is facilitated by a sodium-dependent transport system. Fat in the diet is broken down by pancreatic lipase into triglycerides containing medium- and long-chain fatty acids. Bile salts form micelles that transport these substances to the surface of intestinal villi, where they are absorbed.

Anorexia, Nausea, and Vomiting

Anorexia, nausea, and vomiting are physiologic responses that are common to many GI disorders. These responses are protective to the extent that they signal the presence of disease and, in the case of vomiting, remove noxious agents from the GI tract. They also can contribute to impaired intake or loss of fluids and nutrients.

Anorexia

Anorexia represents a loss of appetite. Several factors influence appetite. One is hunger, which is stimulated by contractions of the empty stomach. Appetite or the desire for food intake is regulated by the hypothalamus and other associated centers in the brain. Smell plays an important role, as evidenced by the fact that appetite can be stimulated or suppressed by the smell of food. Loss of appetite is associated with emotional factors, such as fear, depression, frustration, and anxiety. Many drugs and disease states cause anorexia. For example, in uremia the accumulation of nitrogenous wastes in the blood contributes to the development of anorexia. Anorexia often is a forerunner of nausea, and most conditions that cause nausea and vomiting also produce anorexia.

Nausea

Nausea is an ill-defined and unpleasant subjective sensation. It is the conscious sensation resulting from stimulation of the medullary vomiting center that often precedes or accompanies vomiting. Nausea usually is preceded by anorexia, and stimuli such as foods and drugs that cause anorexia in small doses usually produce nausea when given in larger doses. A common cause of nausea is distention of the duodenum or upper small intestinal tract. Nausea frequently is accompanied by autonomic nervous system manifestations such as watery salivation and vasoconstriction with pallor, sweating, and tachycardia. Nausea may function as an early warning signal of a pathologic process.

Retching and Vomiting

Retching consists of the rhythmic spasmodic movements of the diaphragm, chest wall, and abdominal muscles. It usually precedes or alternates with periods of vomiting. Vomiting or emesis is the sudden and forceful oral expulsion of the contents of the stomach. It usually is preceded by nausea. The contents that are expelled are called *vomitus*. Vomiting, as a basic physiologic protective mechanism, limits the possibility of damage from ingested noxious agents by emptying the contents of the stomach and portions of the small intestine. Nausea and vomiting may also represent a total-body response to drug therapy, including overdose, cumulative effects, toxicity, and side effects.

Vomiting involves two functionally distinct medullary centers: the *vomiting center* and the *chemoreceptor trigger zone*. The act of vomiting is thought to be a reflex that is integrated in the vomiting center, which is located in the dorsal portion of the reticular formation of the medulla near the sensory nuclei of the vagus (Fig. 28-14). The chemoreceptor trigger zone is located in a small area on the floor of the fourth ventricle, where it is exposed to both blood and cerebrospinal fluid. It is thought to mediate the emetic effects of blood-borne drugs and toxins.

The act of vomiting consists of taking a deep breath, closing the airways, and producing a strong, forceful contraction of the diaphragm and abdominal muscles

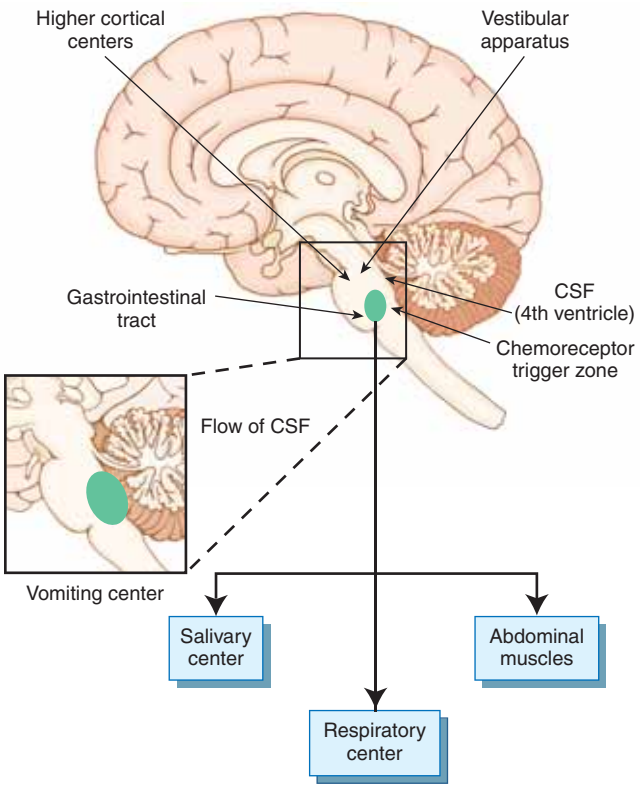


FIGURE 28-14. Physiologic events involved in vomiting. CSF, cerebrospinal fluid.

along with relaxation of the gastroesophageal sphincter. Respiration ceases during the act of vomiting. Vomiting may be accompanied by dizziness, lightheadedness, a decrease in blood pressure, and bradycardia.

The vomiting center receives input from the GI tract and other organs; from the cerebral cortex; from the vestibular apparatus, which is responsible for motion sickness; and from the chemoreceptor trigger zone, which is activated by many drugs and endogenous and exogenous toxins (see Fig. 28-14). Hypoxia exerts a direct effect on the vomiting center, producing nausea and vomiting. This direct effect probably accounts for the vomiting that occurs during periods of decreased cardiac output, shock, environmental hypoxia, and brain ischemia caused by increased intracranial pressure. Inflammation of any of the intra-abdominal organs, including the liver, gallbladder, or urinary tract, can cause vomiting because of the stimulation of the visceral afferent pathways that communicate with the vomiting center. Distention or irritation of the GI tract also causes vomiting through the stimulation of visceral afferent neurons.

Several neurotransmitters and receptor subtypes are implicated as neuromediators in nausea and vomiting. Dopamine, serotonin, and opioid receptors are found in the GI tract and in the vomiting center and chemoreceptor trigger zone. Dopamine antagonists, such as prochlorperazine, depress vomiting caused by stimulation of the chemoreceptor trigger zone. Serotonin is believed to be involved in the nausea and emesis associated with cancer chemotherapy and radiation therapy. Serotonin antagonists (e.g., granisetron, ondansetron) are effective in treating the nausea and vomiting associated with these stimuli. Motion sickness appears to be a CNS response to vestibular stimuli. Norepinephrine and acetylcholine receptors are located in the vestibular center. The acetylcholine receptors are thought to mediate the impulses responsible for exciting the vomiting center; norepinephrine receptors may have a stabilizing influence that resists motion sickness. Many of the motion sickness drugs (e.g., dimenhydrinate) have a strong CNS anticholinergic effect and act on the receptors in the vomiting center and areas related to the vestibular system.

In summary, the signs and symptoms of many GI tract disorders are manifested by anorexia, nausea, and vomiting. Anorexia, or loss of appetite, may occur alone or may accompany nausea and vomiting. Nausea, which is an ill-defined, unpleasant sensation, signals the stimulation of the medullary vomiting center. It often precedes vomiting and frequently is accompanied by autonomic responses, such as salivation and vasoconstriction with pallor, sweating, and tachycardia. The act of vomiting, which is integrated by the vomiting center, involves the forceful oral expulsion of the gastric contents. It is a basic physiologic mechanism that rids the GI tract of noxious agents.

REVIEW EXERCISES

1. Persons receiving chemotherapeutic agents, which interfere with mitosis of cancer cells as well as the cells of other rapidly proliferating tissues in the body, often experience disorders such as ulcerations in the mucosal tissues of the mouth and other parts of the GI tract. These disorders are resolved once the chemotherapy treatment has been completed.

A. Explain.

2. People with gastroesophageal reflux (movement of gastric contents into the esophagus) often complain of heartburn that becomes worse as the pressure in the stomach increases.

A. Use information on hormonal control of gastric emptying to explain why eating a meal that is high in fat content often exaggerates the problem.

3. Infections of the GI tract, such as the "GI flu," often cause profound diarrhea.

A. Describe the neural mechanisms involved in the increase in GI motility that produces the diarrhea.

B. Explain the rationale for using a "drink" that contains both glucose and sodium to treat the fluid deficit that often occurs with diarrhea.

4. Explain the physiologic mechanisms associated with the occurrence of diarrhea in persons with:

A. Lactase deficiency.
B. Obstruction of bile flow into the intestine.
C. Disruption of the normal intestinal flora due to antibiotic therapy.

5. Anticholinergic drugs are often effective in treating the nausea and vomiting that accompany motion sickness but are relatively ineffective in treating the nausea and vomiting associated with chemotherapy agents used in the treatment of cancer.

A. Explain.

BIBLIOGRAPHY

Berne R.M., Levy M.N., Koeppen B.M., et al. (Eds.). (2004). *Physiology* (5th ed., pp. 539–620). St. Louis: Mosby.

Brubaker P.L., Drucker D.J. (2004). Minireview: Glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. *Endocrinology* 145, 2653–2659.

Costanzo L.S. (2002). *Physiology* (2nd ed., pp. 300–346). Philadelphia: W.B. Saunders.

Gershon M.D. (1999). The enteric nervous system: A second brain. *Hospital Practice* 34(7), 31–52.

Grelot L., Miller A.D. (1994). Vomiting: Its ins and outs. *News in Physiological Sciences* 9, 142–147.

Guarner F., Malagelada J.-R. (2003). Gut flora in health and disease. *Lancet* 281, 512–519.

Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 771–824). Philadelphia: Elsevier Saunders.

Inul A., Asakawa A., Bowers C.Y., et al. (2004). Ghrelin, appetite, and gastric motility: The emerging role of the stomach as an endocrine organ. *FASEB Journal* 18, 439–456.

Johnson L.R. (2001). *Gastrointestinal physiology* (6th ed.). St. Louis: C.V. Mosby.

Kellert G.L., Brot-Larche E. (2005). A major pathway for intestinal sugar absorption. *Diabetes* 54, 3056–3062.

Lindley C. (2005). Nausea and vomiting. In Koda-Kimble M.A., Young L.Y., Kradian W.A., et al. (Eds.), *Applied therapeutics: The clinical use of drugs* (8th ed., pp. 8-1–8-18). Philadelphia: Lippincott Williams & Wilkins.

Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 231–305). Philadelphia: Lippincott Williams & Wilkins.

Moran T.H., Kinzig K.P. (2004). Gastrointestinal satiety signals: II. Cholecystokinin. *American Journal of Physiology: Gastrointestinal and Liver Physiology* 286, G183–G188.

Rhoades R.A., Tanner G.A. (2003). *Medical physiology* (2nd ed., pp. 449–511). Boston: Little, Brown.

Salehi M., D'Allessio D. (2006). New therapies for type 2 diabetes based on glucagon-like peptide 1. *Cleveland Clinic Journal of Medicine* 73, 382–389.

Sanders K.M., Koh S.D., Ward M. (2006). Interstitial cells of Cajal in the gastrointestinal tract. *Annual Review of Physiology* 68, 307–343.

Schiller L.R. (1994). Peristalsis. *Scientific American Science & Medicine* (November/December), 38–47.

Soybel D.I. (2005). Anatomy and physiology of the stomach. *Surgical Clinics of North America* 85, 875–894.

St.-Pierre D.H., Tache Y. (2003). Ghrelin: A novel player in the gut-brain regulation of growth hormone and energy balance. *News in Physiological Sciences* 18, 242–246.

Varga G., Ba'lint A., Burghardt B., et al. (2004). Involvement of endogenous CCK and CCK_1 receptors in colonic motor function. *British Journal of Pharmacology* 141, 1275–1284.

Ward S.M., Sanders K.M. (2001). Physiology and pathophysiology of the interstitial cells of Cajal: From bench to bedside. *American Journal of Physiology: Gastrointestinal and Liver Physiology* 281, G602–G611.

Disorders of the Esophagus
Disorders of Esophageal Structure and Function
Swallowing Disorders
Esophageal Diverticula
Esophageal Lacerations
Hiatal Hernia
Gastroesophageal Reflux
Gastroesophageal Reflux Disease
Gastroesophageal Reflux in Children
Cancer of the Esophagus
Disorders of the Stomach
Gastric Mucosal Barrier
Gastritis
Acute Gastritis
Chronic Gastritis
Peptic Ulcer Disease
Zollinger-Ellison Syndrome
Stress Ulcers
Cancer of the Stomach
Disorders of the Small and Large Intestines
Irritable Bowel Syndrome
Inflammatory Bowel Disease
Etiology and Pathogenesis
Crohn Disease
Ulcerative Colitis
Infectious Enterocolitis
Viral Infections
Bacterial Infections
Diverticular Disease
Appendicitis
Disorders of Intestinal Motility
Diarrhea
Diagnosis and Treatment
Constipation
Acute Intestinal Obstruction
Peritonitis
Disorders of Intestinal Absorption
Malabsorption Syndrome
Celiac Disease
Colorectal Neoplasms
Adenomatous Polyps
Colorectal Cancer

Chapter 29

Disorders of Gastrointestinal Function

Gastrointestinal disorders are not cited as the leading cause of death in developed countries of the world, nor do they receive the same publicity as heart disease and cancer. However, digestive diseases rank high in the total economic burden of illness, resulting in considerable human suffering, personal expenditures for treatment, and lost working hours, as well as a drain on the nation's economy. In 2004 alone, digestive disorders accounted for an estimated 72 million ambulatory visits in the United States.[1] Visits were common for all age groups, with the highest rate among persons 65 years and older. Even more important is the fact that proper nutrition or a change in health practices could prevent or minimize many of these disorders.

Disruption in structure and function can occur at any level of the gastrointestinal tract, from the esophagus to the colon and rectum. This chapter is divided into three sections: (1) disorders of the esophagus, (2) disorders of the stomach, and (3) disorders of the small and large intestines. Disorders of the hepatobiliary system and exocrine pancreas are presented in Chapter 30.

Disorders of the Esophagus

The esophagus is a tube that connects the oropharynx with the stomach. It lies posterior to the trachea and larynx and extends through the mediastinum, intersecting the diaphragm at the level of the T11 or T12 vertebra.[2] The esophagus functions primarily as a conduit for passage of food from the pharynx to the stomach, and the structures of its wall are designed for this purpose. It is lined with a mucosal layer of abrasion-resistant nonkeratinized stratified epithelium; its submucosal layer contains mucus-secreting glands that produce a lubricating fluid that protects its mucosal surface and aids in the passage of food; and its muscularis layer provides the peristaltic movements needed to move food along its length.

There are sphincters at either end of the esophagus: an upper esophageal, or pharyngoesophageal, sphincter that prevents reflux into the pharynx from the esophagus, and a lower esophageal, or gastroesophageal, sphincter that prevents reflux into the esophagus from the stomach.[3]

The gastroesophageal sphincter is a physiologic rather than a true anatomic sphincter. That is, it acts as a valve, but the only structural evidence of a sphincter is a slight thickening of the circular smooth muscle. The smooth muscle fibers in this portion of the esophagus normally remain tonically constricted except at times when a bolus of food is about to pass into the stomach or if a person is vomiting.[2] The lower esophageal sphincter passes through an opening, or *hiatus,* in the diaphragm as it joins with the stomach, which is located in the abdomen. The portion of the diaphragm that surrounds the lower esophageal sphincter helps to maintain the zone of high pressure needed to prevent reflux of stomach contents.

Disorders of Esophageal Structure and Function

Swallowing Disorders

Disorders of swallowing include dysphagia or difficulty in swallowing and achalasia or impaired relaxation of the lower esophageal sphincter. The act of swallowing depends on the coordinated action of the tongue, pharyngeal structures, and esophagus (see Chapter 28). These structures are innervated by the cranial nerve V (trigeminal), which innervates the muscles of mastication; IX (glossopharyngeal), which innervates the muscles of the pharynx; XII (hypoglossal), which innervates the tongue; and X (vagus), which innervates the muscles of the esophagus. The act of swallowing is complicated by the fact that the pharynx subserves respiration as well swallowing. Thus, it is important that breathing not be compromised because of swallowing.

In general, swallowing can be divided into three stages (see Chapter 28, Fig. 28-6). The first, or voluntary, stage occurs in the mouth. Once the food has been chewed and well mixed with saliva, the bolus (food mass) is forced into the pharynx by the tongue. The second stage, the involuntary pharyngeal–esophageal phase, transports food through the pharynx and into the esophagus. The parasympathetic nervous system (primarily the vagus) controls this part of swallowing and promotes motility of the gastrointestinal tract from this point on. Once food reaches the distal end of the esophagus, it passes through the lower esophageal sphincter into the stomach (stage 3).

Dysphagia can result from disorders that produce narrowing of the esophagus, lack of salivary secretion, weakness of the muscular structures that propel the food bolus, or disruption of the neural networks coordinating the swallowing mechanism. Lesions of the central nervous system (CNS), such as a stroke, often involve the cranial nerves that control swallowing. Cancer of the esophagus and strictures resulting from scarring can reduce the size of the esophageal lumen and make swallowing difficult. Scleroderma, an autoimmune disease that causes fibrous replacement of tissues in the muscularis layer of the gastrointestinal tract, is another important cause of dysphagia.[4,5] Persons with dysphagia usually complain of choking, coughing, or an abnormal sensation of food sticking in the back of the throat or upper chest when they swallow.

The term *achalasia* means "failure to relax" and in the context of esophageal function denotes an incomplete relaxation of the lower esophageal sphincter in relation to swallowing. In primary achalasia, the mesenteric ganglia that carry the vagal fibers for the lower esophagus are usually absent from the body of the esophagus. The condition usually becomes manifest in young adulthood, but may appear in infancy and childhood. Achalasia produces functional obstruction of the esophagus so that food has difficulty passing into the stomach and the esophagus above the lower esophageal sphincter becomes distended. Stasis of food may produce inflammation and ulceration proximal to the lower esophageal sphincter, and there is danger of aspiration of esophageal contents into the lungs when the person lies down. The most serious aspect of the condition is the potential for developing esophageal cancer.

Treatment of swallowing disorders depends on the cause and type of altered function that is present. Treatment often involves a multidisciplinary team of health professionals, including a speech therapist. Mechanical dilation or surgical procedures may be done to enlarge the lower esophageal sphincter in persons with esophageal strictures.

Esophageal Diverticula

A diverticulum of the esophagus is an outpouching of the esophageal wall caused by a weakness of the muscularis layer or motility problems (e.g., diffuse esophageal spasm, achalasia).[6,7] Esophageal diverticula tend to retain food. Complaints that the food stops before it reaches the stomach are common, as are reports of gurgling, belching, coughing, and foul-smelling breath. The trapped food may cause esophagitis and ulceration. Surgery is the optimal treatment for persons with severe symptoms or pulmonary complications.

Esophageal Lacerations

Longitudinal lacerations in the esophagus, also called the *Mallory-Weiss syndrome,* represent nonpenetrating mucosal tears at the gastroesophageal junction.[6–8] They are most often encountered in persons with chronic alcoholism after a bout of severe retching or vomiting, but may also occur during acute illness with severe vomiting. The presumed pathogenesis is inadequate relaxation of the esophageal sphincter during vomiting, with stretching and tearing of the esophageal junction during propulsive expulsion of gastric contents. The tears, which range in length from millimeters to a few centimeters, usually cross the gastroesophageal junction and also may be located in the proximal gastric mucosa. Esophageal lacerations account for about 10% of all upper gastrointestinal bleeding, which often presents as hematemesis.[6] Most often bleeding is not severe and does not require surgical intervention. Healing is usually prompt, with minimal or no residual effects.

Hiatal Hernia

Hiatal hernia is characterized by a protrusion or herniation of the stomach through the esophageal hiatus of the

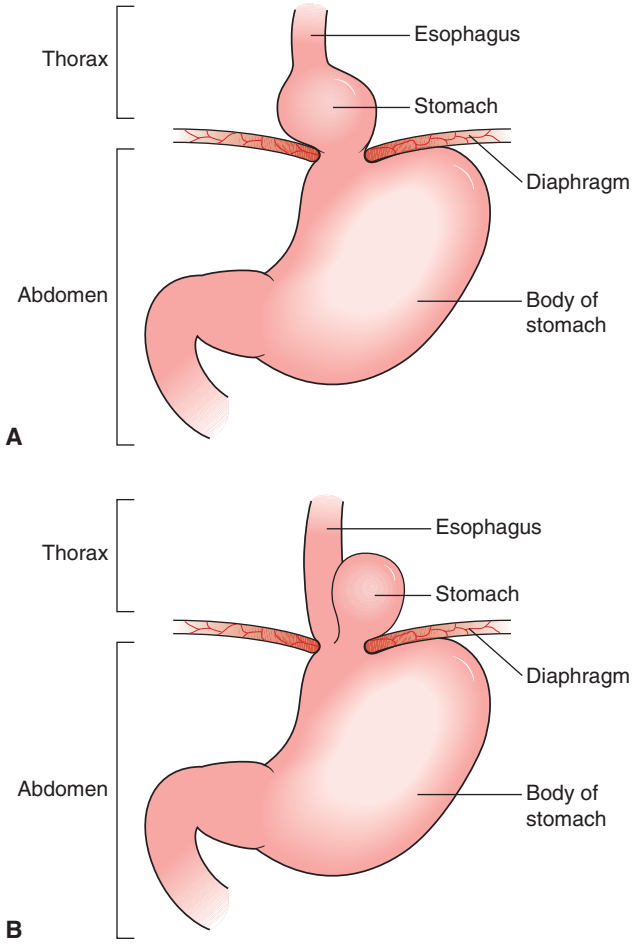


FIGURE 29-1. Hiatal hernia. **(A)** Sliding hiatal hernia. **(B)** Paraesophageal hiatal hernia.

diaphragm. There are two anatomic patterns of hiatal herniation: axial or sliding, and nonaxial or paraesophageal.[6] The sliding hiatal hernia is characterized by a bell-shaped protrusion of the stomach above the diaphragm (Fig. 29-1). Small sliding hiatal hernias are common and considered to be of no significance in asymptomatic people. In paraesophageal hiatal hernias, a separate portion of the stomach, usually along the fundus of the stomach, enters the thorax through a widened opening. The hernia progressively enlarges and increases in size. In extreme cases, most of the stomach herniates into the thorax. Large paraesophageal hernias may require surgical treatment.

Gastroesophageal Reflux

The term *reflux* refers to backward or return movement. In the context of gastroesophageal reflux, it refers to the backward movement of gastric contents into the esophagus, a condition that causes heartburn or pyrosis. Most people experience heartburn occasionally as a result of reflux. Such symptoms usually occur soon after eating, are short lived, and seldom cause more serious problems.

The gastroesophageal sphincter regulates the flow of food from the esophagus into the stomach. Both internal and external mechanisms function in maintaining the antireflux function of the lower esophageal sphincter. The circular muscles of the distal esophagus constitute the internal mechanisms, and the portion of the diaphragm that surrounds the esophagus constitutes the external mechanism (Fig. 29-2). The oblique muscles of the stomach, located below the lower esophageal sphincter, form a flap that contributes to the antireflux function of the internal sphincter. Relaxation of the lower esophageal sphincter is a brain stem reflex that is mediated by the vagus nerve in response to a number of afferent stimuli. Transient relaxation with reflux is common after meals. Gastric distention and meals high in fat increase the frequency of relaxation. Normally, refluxed material is returned to the stomach by secondary peristaltic waves in the esophagus and swallowed saliva neutralizes and washes away the refluxed acid.

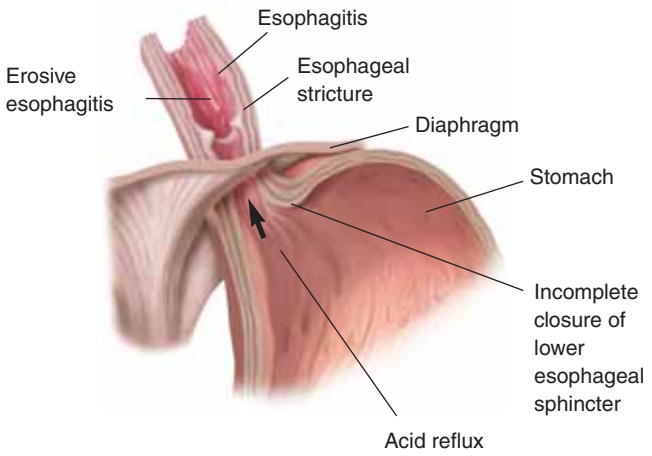


FIGURE 29-2. Gastroesophageal junction and site of gastroesophageal reflux. (From Anatomical Chart Company. [2004]. *Atlas of pathophysiology* [p. 171]. Springhouse, PA: Springhouse.)

Gastroesophageal Reflux Disease

The persistent reflux of gastric contents into the esophagus is referred to as *gastroesophageal reflux disease* (GERD).[8–10] It is thought to be associated with a weak or incompetent lower esophageal sphincter that allows reflux to occur, the irritant effects of the refluxate, and decreased clearance of the refluxed acid from the esophagus after it has occurred. In most cases, reflux occurs during transient relaxation of the esophagus. Delayed gastric emptying also may contribute to reflux by increasing gastric volume and pressure with greater chance for reflux. Esophageal mucosal injury may occur and is related to the destructive nature of the refluxate and the amount of time it is in contact with mucosa. The gastroesophageal reflux normally is cleared and neutralized by esophageal peristalsis and salivary bicarbonate. Decreased salivation and salivary buffering capacity may contribute to impaired clearing of acid reflux from the esophagus.

Clinical Features. The most frequent symptom of GERD is heartburn. It frequently is severe, occurring 30 to 60 minutes after eating. It often is made worse by

bending at the waist or assumption of the recumbent position and usually is relieved by sitting upright. The severity of heartburn is not indicative of the extent of mucosal injury; only a small percentage of people who complain of heartburn have mucosal injury. Often, the heartburn occurs during the night. Antacids give prompt, although transient, relief. Other symptoms include belching and chest pain. The pain usually is located in the epigastric or retrosternal area and often radiates to the throat, shoulder, or back. Because of its location, the pain may be confused with angina. The reflux of gastric contents also may produce respiratory symptoms such as wheezing, chronic cough, and hoarseness.[8]

Diagnosis of gastroesophageal reflux depends on a history of reflux symptomatology and selective use of diagnostic methods, including radiographic studies using a contrast medium such as barium, esophagoscopy, and ambulatory esophageal pH monitoring.[8–10]

The treatment of gastroesophageal reflux usually focuses on conservative measures. These measures include avoidance of positions and conditions that increase gastric reflux.[8–10] Avoidance of large meals and foods that reduce lower esophageal sphincter tone (e.g., caffeine, fats, chocolate), alcohol, and smoking is recommended. It is recommended that meals be eaten sitting up and that the recumbent position be avoided for several hours after a meal. Bending for long periods should be avoided because it tends to increase intra-abdominal pressure and cause gastric reflux. Sleeping with the head elevated helps to prevent reflux during the night. Weight loss usually is recommended in overweight people.

Pharmacologic treatment includes the use of antacids and inhibitors of gastric acid secretion. Antacids neutralize gastric acid and are used for rapid relief of occasional heartburn. Histamine-2 (H_2)–receptor antagonists inhibit gastric acid production. They are available as over-the-counter drugs and often are recommended when additional treatment is needed. The proton pump inhibitors act by inhibiting the gastric proton pump, which regulates the final pathway for acid secretion (see Chapter 28, Fig. 28-10). These agents may be used for persons who continue to have daytime symptoms, recurrent strictures, or large esophageal ulcerations. Surgical treatment may be indicated in some people.

Complications of GERD result from persistent reflux, which produces a cycle of hyperemia, edema, and erosion of the mucosal surface of the esophagus. Esophageal mucosal damage is related to the potency of refluxate. These complications include strictures of the esophagus and a condition called *Barrett esophagus*. Strictures are caused by a combination of scar tissue, spasm, and edema. They produce narrowing of the esophagus and cause dysphagia when the lumen becomes sufficiently constricted.

Barrett esophagus is characterized by a reparative process in which the squamous mucosa that normally lines the esophagus gradually is replaced by columnar epithelium resembling that in the intestines.[11] The diagnosis of Barrett esophagus is based on endoscopic evidence of abnormal mucosa above the level of the gastroesophageal junction (Fig. 29-3) and histologically documented intestinal metaplasia (called *specialized intestinal metaplasia*) that predisposes to the development of adenocarcinoma. Barrett esophagus can be subclassified as long segment, in which 3 cm or more of the esophagus is involved, or short segment, in which less than 3 cm is involved. It is not yet clear if the risk of adenocarcinoma in short-segment disease is less than in long-segment disease.[11]

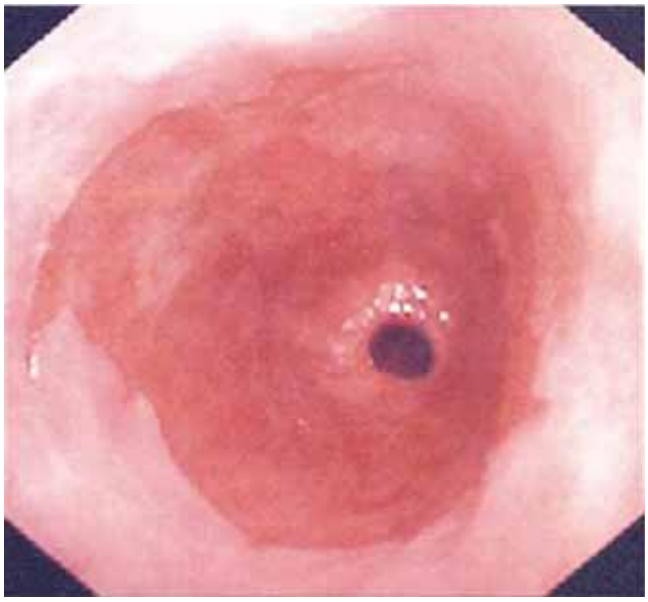


FIGURE 29-3. Endoscopic photograph showing long-segment Barrett esophagus in which the reddish columnar epithelium extends more than 3 inches above the gastroesophageal junction. (From Spechler S.J. [2002]. Barrett's esophagus. *New England Journal of Medicine* 346, 836.)

Gastroesophageal Reflux in Children

Gastroesophageal reflux is a common problem in infants and children. The small reservoir capacity of an infant's stomach coupled with frequent spontaneous reductions in sphincter pressure contributes to reflux. At least one episode of regurgitation a day occurs in as many as half of infants ages 0 to 3 months. By 6 months of age it becomes less frequent and usually abates as the child assumes a more upright posture and eats solid foods.[12,13] Although many infants have minor degrees of reflux, complications can occur in children with more frequent or persistent episodes. The condition occurs more frequently in children with cerebral palsy, Down syndrome, and other neurologic disorders.

In most cases, infants with simple reflux are thriving and healthy, and symptoms resolve between 9 and 24 months of age. The pathologic effects of esophageal reflux in infants and children can be classified into three categories: (1) esophagitis and pain, (2) regurgitation and malnutrition, and (3) respiratory problems.

Clinical Features. Symptoms of reflux esophagitis include evidence of pain when swallowing, hematemesis, anemia due to esophageal bleeding, heartburn, irritability, and sudden or inconsolable crying. Parents often report feeding problems in their infants.[12] These infants

often are irritable and demonstrate early satiety. Sometimes the problems progress to actual resistance to feeding. Tilting of the head to one side and arching of the back may be noted in children with severe reflux. The head positioning is thought to represent an attempt to protect the airway or reduce the pain-associated reflux. Sometimes regurgitation is associated with dental caries and recurrent otalgia. The ear pain is thought to occur through referral from the vagus nerve in the esophagus to the ear.

A variety of respiratory symptoms are caused by damage to the respiratory mucosa when gastric reflux enters the esophagus. Reflux may cause laryngospasm, apnea, and bradycardia. Asthma may co-occur with GERD in about 50% of asthmatic children. Asthmatic children who are particularly likely to have GERD as a provocative factor are those with symptoms of reflux, those with refractory or steroid-dependent asthma, and those with nocturnal worsening of symptoms.[14]

Diagnosis of gastroesophageal reflux in infants and children often is based on parental and clinical observations. The diagnosis may be confirmed by esophageal pH probe studies or barium fluoroscopic esophagography. In severe cases, esophagoscopy may be used to demonstrate reflux and obtain a biopsy.

Various treatment methods are available for infants and children with gastroesophageal reflux. Small, frequent feedings are recommended because of the association between gastric volume and transient relaxation of the esophagus. Thickening an infant's feedings with cereal tends to decrease the volume of reflux, decrease crying and energy expenditure, and increase the calorie density of the formula.[12] In infants, positioning on the left side seems to decrease reflux. In older infants and children, raising the head of the bed and keeping the child upright may help. Medications usually are not added to the treatment regimen until pathologic reflux has been documented by diagnostic testing. Antacids are the most commonly used antireflux therapy and are readily available over the counter. H_2-receptor antagonists and proton pump inhibitors may be used in children with persistent reflux. Prokinetic agents (e.g., metoclopramide, a dopamine-2 and 5-hydroxytryptamine [5-HT_3] receptor antagonist; bethanechol, a cholinergic agonist) may be used in selected cases.

Cancer of the Esophagus

Worldwide, the incidence of esophageal cancer varies widely, undoubtedly reflecting environmental and dietary influences. It is relatively uncommon in the United States, accounting for about 2% of cancer deaths.[7] There are two types of esophageal cancer: adenocarcinoma and squamous cell carcinoma.[6,7,15]

Adenocarcinomas typically arise in a background of Barrett esophagus and long-standing GERD. They usually occur in the distal third of the esophagus and may invade adjacent areas of the stomach. Risk of adenocarcinoma is greater in those with documented esophageal dysplasia and is further increased by tobacco use, obesity, and prior radiation therapy. Esophageal carcinomas occur more frequently in Caucasians and are seven times more common in men than women.[6] Molecular studies have suggested that the pathogenesis of adenocarcinoma from Barrett esophagus is a multistep process, with the development of dysplasia being a critical step in the process.[6] Thus, endoscopic surveillance of persons with Barrett esophagus provides the means for detecting adenocarcinoma at an earlier stage, when it is most amenable to curative surgical resection.[15]

In contrast to adenomas, squamous carcinomas tend to occur in the middle of the esophagus. Risk factors include alcohol and tobacco use, esophageal injury, achalasia, and frequent consumption of very hot beverages.[6] The regions with the highest incidences are Iran, central China, Hong Kong, Brazil, and South Africa.[6] The majority of esophageal squamous carcinomas in Europe and the United States are at least partially attributable to alcohol and tobacco use. However, this form of cancer is also common in areas where alcohol and tobacco use are uncommon. Thus, nutritional deficiencies, as well as polycyclic hydrocarbons, nitrosamines, and other mutagenic compounds such as those found in fungus-contaminated food, may be important.[6]

Dysphagia is by far the most frequent complaint of persons with esophageal cancer. It is apparent first with ingestion of bulky food, later with soft food, and finally with liquids. Unfortunately, it is a late manifestation of the disease. Unintentional weight loss, anorexia, fatigue, and pain on swallowing also may occur.

Treatment of esophageal cancer depends on tumor stage.[15] Surgical resection provides a means of cure when done in early disease and palliation when done in late disease. Radiation may be used as an alternative to surgery. Chemotherapy may be used before surgery to decrease the size of the tumor or it may be used along with irradiation and surgery in an effort to increase survival. The prognosis for persons with cancer of the esophagus, although poor, has improved. Even with modern forms of therapy, however, the long-term survival is limited because, in many cases, the disease has already metastasized by the time the diagnosis is made.

In summary, the esophagus is a tube that connects the oropharynx with the stomach; it functions primarily as a conduit for passage of food from the pharynx to the stomach. Dysphagia refers to difficulty in swallowing; it can result from altered neuromuscular function or from disorders that produce narrowing of the esophagus. A diverticulum of the esophagus is an outpouching of the esophageal wall caused by a weakness of the muscularis layer. Hiatal hernia is characterized by a protrusion or herniation of the stomach through the esophageal hiatus of the diaphragm. There are two anatomic patterns of herniation: the sliding hiatal hernia, which is the most common type and is characterized by bell-shaped

protrusion of the stomach above the diaphragm, and the paraesophageal hernia, in which a portion of the stomach enters the thorax through a widened opening.

Gastroesophageal reflux refers to the backward movement of gastric contents into the esophagus, a condition that causes heartburn. Although most persons experience occasional heartburn, the persistent reflux of gastric contents into the esophagus can result in a condition called *gastroesophageal reflux disease* (GERD), in which there is a frequent occurrence of heartburn, particularly after eating. Complications of GERD, which result from erosion of the mucosal surface of the esophagus, include strictures of the esophagus and Barrett esophagus. Gastroesophageal reflux is a common problem in infants and children. Reflux commonly corrects itself with age, and symptoms abate in most children by 2 years of age. Although many infants have minor degrees of reflux, some infants and small children have significant reflux that interferes with feeding, causes esophagitis, and results in respiratory symptoms and other complications.

Cancer of the esophagus is a relatively uncommon form of cancer, accounting for about 2% of cancer deaths in the United States. There are two types of esophageal cancer: squamous cell carcinoma and adenocarcinoma. Most adenocarcinomas are more closely linked to gastroesophageal reflux and Barrett esophagus, whereas squamous cell carcinomas are commonly attributed to alcohol and tobacco use.

Disruption of the Gastric Mucosa and Ulcer Development

- The stomach is protected by a mucosal barrier that prevents gastric secretions and other destructive agents from injuring the epithelial and deeper layers of the stomach wall.
- The integrity of the mucosal layer is maintained by tight cellular junctions and the presence of a protective mucous layer.
- Prostaglandins serve as chemical messengers that protect the stomach lining by improving blood flow, increasing bicarbonate secretion, and enhancing mucus production.
- Two of the major causes of gastric irritation and ulcer formation are aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) and infection with *Helicobacter pylori.*
- Aspirin and NSAIDs exert their destructive effects by irritating the stomach and inhibiting prostaglandin synthesis.
- *H. pylori* is an infectious agent that thrives in the acid environment of the stomach and disrupts the mucosal barrier that protects the stomach from the harmful effects of its digestive enzymes.

Disorders of the Stomach

The stomach is a reservoir for contents entering the digestive tract. It lies in the upper abdomen, anterior to the pancreas, splenic vessels, and left kidney. Anteriorly, the stomach is bounded by the anterior abdominal wall and the left inferior lobe of the liver. While in the stomach, food is churned and mixed with hydrochloric acid and pepsin before being released into the small intestine. Normally, the mucosal surface of the stomach provides a barrier that protects it from the hydrochloric acid and pepsin contained in gastric secretions. Disorders of the stomach include gastritis, peptic ulcer, and gastric carcinoma.

Gastric Mucosal Barrier

The stomach lining usually is impermeable to the acid it secretes, a property that allows the stomach to contain acid and pepsin without having its walls digested. Several factors contribute to the protection of the gastric mucosa, including an impermeable epithelial cell surface covering, coupled secretion of hydrogen (H^+) and bicarbonate (HCO_3^-) ions, and the characteristics of gastric mucus.[16] These mechanisms are collectively referred to as the *gastric mucosal barrier.*

The cells of the epithelial layer of the stomach are connected by tight junctions that prevent acid penetration, and they are covered with an impermeable hydrophobic lipid layer that prevents diffusion of ionized water-soluble molecules. Aspirin, which is nonionized and lipid soluble in acid solutions, rapidly diffuses across this lipid layer, increasing mucosal permeability and damaging epithelial cells.[16,17] Gastric irritation and occult bleeding occur in a significant number of persons who take aspirin on a regular basis. Alcohol, which is lipid soluble, can also disrupt the mucosal barrier. When aspirin and alcohol are taken in combination, as they often are, there is increased risk of gastric irritation. Bile acids also attack the lipid components of the mucosal barrier and afford the potential for gastric irritation when there is reflux of duodenal contents into the stomach.

Normally, the secretion of hydrochloric acid (HCl) by the parietal cells of the stomach is accompanied by secretion of HCO_3^- (see Chapter 28, Fig. 28-9). For every H^+ that is secreted, a HCO_3^- is produced, and as long as HCO_3^- production is equal to H^+ secretion, mucosal injury does not occur. Changes in gastric blood flow, as in shock, tend to decrease HCO_3^- production. This is particularly true in situations in which decreased blood flow is accompanied by acidosis.[16] Prostaglandins, chemical mediators derived from cell membrane lipids, play an important role in protecting the gastric mucosa from injury.[6] The prostaglandins exert their effects through several mechanisms, including improved mucosal blood flow, decreased acid secretion, increased bicarbonate secretion, and enhanced mucus production. The fact that drugs such

as aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis may contribute to their ability to produce gastric mucosal irritation and injury.

Gastritis

Gastritis refers to inflammation of the gastric mucosa. There are many causes of gastritis, most of which can be classified as either acute or chronic gastritis.

Acute Gastritis

Acute gastritis is characterized by an acute mucosal inflammatory process, usually transient in nature. The inflammation may be accompanied by hemorrhage into the mucosa and, in severe cases, by sloughing of the superficial mucosa and acute gastric bleeding. The condition is most commonly associated with local irritants such aspirin or other NSAIDs, alcohol, or bacterial toxins.[6] Oral administration of corticosteroid drugs, which inhibit prostaglandin synthesis, may also cause acute hemorrhagic gastritis. Any serious illness or trauma that is accompanied by profound physiologic stress renders the gastric mucosa more vulnerable to acute hemorrhagic gastritis (discussed under stress ulcers).[7] Uremia, treatment with cancer chemotherapy drugs, and gastric radiation are other causes of acute gastritis.

The complaints of persons with acute gastritis vary. Persons with aspirin-related gastritis can be totally unaware of the condition or may complain only of heartburn or sour stomach. Gastritis associated with excessive alcohol consumption is often a different situation; it often causes transient gastric distress, which may lead to vomiting and, in more severe situations, to bleeding and hematemesis. Gastritis caused by the toxins of infectious organisms, such as the staphylococcal enterotoxins, usually has an abrupt and violent onset, with gastric distress and vomiting ensuing approximately 5 hours after the ingestion of a contaminated food source. Acute gastritis usually is a self-limiting disorder, with complete regeneration and healing occurring within several days of removal of the inciting agent.

Chronic Gastritis

Chronic gastritis is a separate entity from acute gastritis. It is characterized by the absence of grossly visible erosions and the presence of chronic inflammatory changes, eventually leading to atrophy of the glandular epithelium of the stomach. There are three major types of chronic gastritis: *Helicobacter pylori* gastritis, autoimmune gastritis, and chemical gastropathy.[7]

***Helicobacter pylori* Gastritis.** *H. pylori* gastritis is a chronic inflammatory disease of the antrum and body of the stomach caused by the bacterium *H. pylori*.[6,7,18,19] It is the most common cause of chronic gastritis in the United States and is estimated to infect more than half of the world's population, particularly in developing countries.

H. pylori are small, S-shaped, gram-negative rods that can colonize the mucus-secreting epithelial cells of the stomach (Fig. 29-4). The mode of transmission is not well defined, although oral–oral, fecal–oral, and environmental spread are among the possible routes. *H. pylori* have multiple flagella, which allow them to move through the mucous layer of the stomach, and they secrete urease, which enables them to produce sufficient ammonia to buffer the acidity of their immediate environment. These properties help to explain why the organism is able to survive in the acidic environment of the stomach.

FIGURE 29-4. Infective gastritis. *Helicobacter pylori* appear on silver staining as small, curved rods on the surface of the gastric mucosa. (From Mitos F.A., Rubin E. [2008]. The gastrointestinal tract. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathophysiology: Clinicopathologic foundations of medicine* [5th ed., p. 563]. Philadelphia: Lippincott Williams & Wilkins.)

H. pylori produce enzymes and toxins that have the capacity to interfere with the local protection of the gastric mucosa against acid and produce a continuous inflammatory response. This inflammatory response initially consists of recruitment of neutrophils, followed by T and B lymphocytes. The inflammation may be confined to the superficial gastric epithelium or extend deeper into the gastric glands, resulting in varying degrees of atrophy (atrophic gastritis) and metaplasia that converts the gastric epithelium to intestinal-type epithelium. Several *H. pylori* proteins are immunogenic and may induce intense systemic and mucosal immune responses. This antibody production does not lead to eradication of infection but may contribute to tissue damage.

The clinical course of *H. pylori* infection is highly variable and is influenced by both microbial and host factors. Acute infection with *H. pylori* may cause a transient illness characterized by nausea and abdominal pain that may last several days. After these symptoms resolve, most individuals progress to an asymptomatic infection

with chronic mucosal inflammation. Chronic infection with *H. pylori* can lead to gastric atrophy and peptic ulcer, and is associated with increased risk of gastric adenocarcinoma and low-grade B-cell gastric lymphoma.

Methods for establishing the presence of *H. pylori* infection include the carbon (C) urea breath test using a radioactive carbon isotope (^{13}C or ^{14}C), the stool antigen test, and endoscopic biopsy for urease testing. Blood tests to obtain serologic titers of *H. pylori* antibodies also can be done. The serologic test can establish that a person has been infected with *H. pylori,* but it cannot distinguish how recently the infection occurred.

The goal for *H. pylori* gastritis treatment is complete elimination of the organism. Current treatment requires combination therapy that includes the use of two antibiotics with a proton pump inhibitor. Treatment is usually continued for 10 to 14 days. *H. pylori* mutate rapidly to develop antibiotic-resistant strains. The combination of two or more antimicrobial agents increases the rates of cure and reduces the risk of resistant strains developing. The antibiotics that have shown the greatest efficacy against *H. pylori* are clarithromycin, metronidazole, amoxicillin, and tetracycline. The proton pump inhibitors have direct antimicrobial properties against *H. pylori,* and by raising the intragastric pH they suppress bacterial growth and optimize antibiotic efficacy.

Chronic Autoimmune Gastritis. Autoimmune gastritis accounts for less than 10% of cases of chronic gastritis and is often associated with other autoimmune disorders such as type 1 diabetes mellitus, Hashimoto thyroiditis, and Addison disease.[6] The disorder is characterized by autoantibodies to the gastric parietal cells and the intrinsic factor, defective gastric acid secretion, and vitamin B_{12} deficiency.[6,7] In contrast to *H. pylori* gastritis, autoimmune gastritis typically affects the body and fundus of the stomach, sparing the antrum. Lack of intrinsic factor disables vitamin B_{12} absorption, leading to a B_{12} deficiency and slow-onset megaloblastic anemia (pernicious anemia, see Chapter 13). Atrophy of the fundic pyloric and chief cells can lead to development of metaplastic changes that predispose to the development of gastric adenocarcinoma. The absence of acid production (achlorhydria) stimulates gastrin release, resulting in hypergastrinemia and hyperplasia of antral gastrin-producing cells. Rarely, this may progress to form low-grade neuroendocrine or carcinoid tumors.

Chronic autoimmune gastritis is noted for its slow onset and progression. Antibodies to parietal cells and intrinsic factor are present early in disease; progression to gastric atrophy probably occurs over several decades. Because of the slow onset and variable progression, persons with the disorder are diagnosed only after being affected for a number of years. Clinical presentation may be related to anemia. In addition, vitamin B_{12} deficiency may cause atrophic glossitis, in which the tongue becomes smooth and beefy red; malabsorptive diarrhea; and neuropathies. The most frequent manifestations of peripheral neuropathy are paresthesias and numbness. Cerebral manifestations range from mild personality changes and memory loss to psychosis. In contrast to anemia, neurologic changes are not reversed by vitamin B_{12} replacement therapy.[6]

Chemical Gastropathy. Chemical gastropathy represents the effects of chronic gastric injury resulting from reflux of alkaline duodenal contents, pancreatic secretions, and bile into the stomach. It is most commonly seen in persons who have had gastroduodenostomy or gastrojejunostomy surgery. A milder form may occur in persons with gastric ulcer, gallbladder disease, or various motility disorders of the distal stomach.

Peptic Ulcer Disease

Peptic ulcer disease is a term used to describe a group of ulcerative disorders that occur in areas of the upper gastrointestinal tract that are exposed to acid–pepsin secretions.[6,7,20,21] The most common forms of peptic ulcer are duodenal and gastric ulcers. Peptic ulcer disease, with its remissions and exacerbations, is a chronic health problem. Approximately 10% of the population have or will develop peptic ulcer.[7]

A peptic ulcer can affect one or all layers of the stomach or duodenum (Fig. 29-5). The ulcer may penetrate only the mucosal surface, or it may extend into the smooth muscle layers. Occasionally, an ulcer penetrates the outer wall of the stomach or duodenum. Spontaneous remissions and exacerbations are common. Healing of the muscularis layer involves replacement with

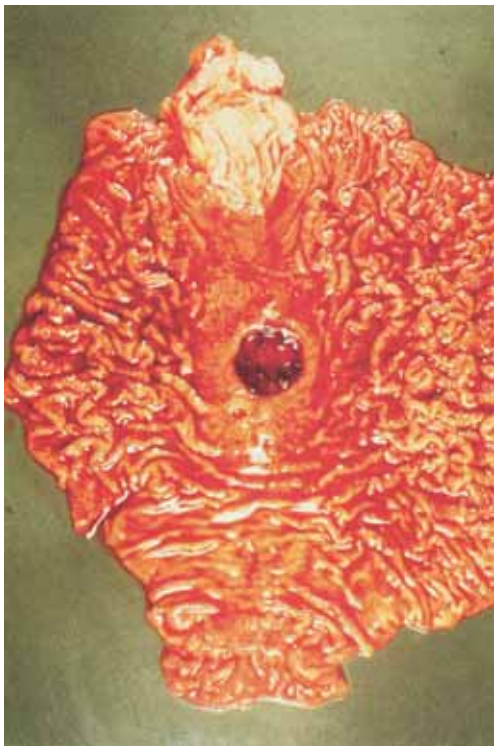


FIGURE 29-5. Gastric ulcer. The stomach has been opened to reveal a sharply demarcated, deep peptic ulcer on the lesser curvature. (From Rubin E., Farber J.L. [Eds.]. [1999]. *Pathology* [3rd ed., p. 693]. Philadelphia: Lippincott Williams & Wilkins.)

scar tissue; although the mucosal layers that cover the scarred muscle layer regenerate, the regeneration often is less than perfect, which contributes to repeated episodes of ulceration.

Since the early 1980s, there has been a radical shift in thinking regarding the cause of peptic ulcer. No longer is peptic ulcer thought to result from a genetic predisposition, stress, or dietary indiscretions. A variety of risk factors have been shown to have an association with peptic ulcer disease. The two most important are infection with the bacteria *H. pylori* and use of aspirin and other NSAIDs.[20,21] Aspirin appears to be the most ulcerogenic of the NSAIDs. In contrast to peptic ulcer from other causes, NSAID-induced gastric injury often is without symptoms, and life-threatening complications can occur without warning. There is reportedly less gastric irritation with the newer class of NSAIDs that selectively inhibit cylcooxygenase-2 (COX-2–selective NSAIDs), the principal enzyme involved in prostaglandin synthesis at the site of inflammation, than with the nonselective NSAIDs that also inhibit COX-1, the enzyme involved in prostaglandin production in the gastric mucosa.

Epidemiologic studies have identified independent factors that augment the effect of *H. pylori* infection and NSAID-produced peptic ulcer disease. These factors include advancing age, a prior history of peptic ulcer, multiple NSAID use, and concurrent use of warfarin (an anticoagulant) and corticosteroid drugs. Smoking may augment the risk of peptic ulcer by impairing healing.

The clinical manifestations of uncomplicated peptic ulcer focus on discomfort and pain. The pain, which is described as burning, gnawing, or cramplike, usually is rhythmic and frequently occurs when the stomach is empty—between meals and at 1 or 2 o'clock in the morning. The pain usually is located over a small area near the midline in the epigastrium near the xiphoid, and may radiate below the costal margins, into the back, or, rarely, to the right shoulder. Superficial and deep epigastric tenderness and voluntary muscle guarding may occur with more extensive lesions. An additional characteristic of ulcer pain is periodicity. The pain tends to recur at intervals of weeks or months. During an exacerbation, it occurs daily for a period of several weeks and then remits until the next recurrence. Characteristically, the pain is relieved by food or antacids.

The most common complications of peptic ulcer are hemorrhage, perforation and penetration, and gastric outlet obstruction. Hemorrhage is caused by bleeding from granulation tissue or from erosion of an ulcer into an artery or vein. It occurs in up to 20% of persons with peptic ulcer.[7] Evidence of bleeding may consist of hematemesis or melena. Bleeding may be sudden, severe, and without warning, or it may be insidious, producing only occult blood in the stool. Up to 20% of persons with bleeding ulcers have no antecedent symptoms of pain; this is particularly true in persons using NSAIDs. Acute hemorrhage is evidenced by the sudden onset of weakness; dizziness; thirst; cold, moist skin; the desire to defecate; and the passage of loose, tarry, or even red stools and coffee-ground emesis. Signs of circulatory shock develop depending on the amount of blood lost.

Perforation occurs when an ulcer erodes through all the layers of the stomach or duodenum wall. Perforation develops in approximately 5% of persons with peptic ulcers, usually from ulcers on the anterior wall of the stomach or duodenum.[7] With perforation, gastrointestinal contents enter the peritoneum and cause peritonitis. Radiation of the pain into the back, severe night distress, and inadequate pain relief from eating foods or taking antacids in persons with a long history of peptic ulcer may signify perforation. Penetration is a process similar to perforation, but with penetration the ulcer crater erodes into adjacent organs, including the small bowel, pancreas, liver, or biliary tree.[20] Typically, it has a subtle presentation marked by a gradual increase in severity and frequency of pain.

Outlet obstruction is caused by edema, spasm, or contraction of scar tissue and interference with the free passage of gastric contents through the pylorus or adjacent areas. The presentation of an obstruction is typically insidious, with symptoms of early satiety, feeling of epigastric fullness and heaviness after meals, gastroesophageal reflux, weight loss, and abdominal pain. With severe obstruction, there is vomiting of undigested food.

Diagnosis and Treatment. Diagnostic procedures for peptic ulcer include history taking, laboratory tests, radiologic imaging, and endoscopic examination. The history should include careful attention to aspirin and NSAID use. Peptic ulcer should be differentiated from other causes of epigastric pain. Laboratory findings of hypochromic anemia and occult blood in the stools indicate bleeding. Endoscopy (i.e., gastroscopy and duodenoscopy) can be used to visualize the ulcer area and obtain biopsy specimens to test for *H. pylori* and exclude malignant disease. X-ray studies with a contrast medium such as barium are used to detect the presence of an ulcer crater and to exclude gastric carcinoma.

The treatment of peptic ulcer has changed dramatically over the past several decades and now aims to eradicate the cause and promote a permanent cure for the disease. Pharmacologic treatment focuses on eradicating *H. pylori,* relieving ulcer symptoms, and healing the ulcer crater. Aspirin and NSAID use should be avoided when possible. With current therapies aimed at neutralization of gastric acid, inhibition of gastric acid (H_2 antagonists and proton pump inhibitors), and promotion of mucosal protection, most ulcers heal within a matter of weeks. When surgery is needed, it usually is performed using minimally invasive methods.

Zollinger-Ellison Syndrome

The Zollinger-Ellison syndrome is a rare condition caused by gastrin-secreting tumors (gastrinomas) that are most commonly found in the small intestine or pancreas.[7,22] In persons with this disorder, gastric acid secretion reaches such levels that ulceration becomes inevitable. The increased gastric secretions cause symptoms related to peptic ulcer. Diarrhea may result from hypersecretion of acid or from the activation of intestinal lipase and impaired fat digestion that occurs with a

decrease in intestinal pH. Most gastrinomas are solitary or multifocal nodules that are potentially respectable. Over two thirds of gastrinomas are malignant and one third have metastasized at the time of diagnosis.[8]

The diagnosis of Zollinger-Ellison syndrome is based on elevated serum gastrin and basal gastric acid levels. Computed tomography (CT), abdominal ultrasonography, and selective angiography are used to localize the tumor and determine if metastatic disease is present. Treatment of Zollinger-Ellison syndrome involves control of gastric acid secretion by proton pump inhibitors. Surgical removal is indicated when the tumor is malignant and has not metastasized.

Hypergastrinemia may also occur in an autosomal dominant disorder called *multiple endocrine neoplasia type 1* (MEN 1). The syndrome is characterized by hyperparathyroidism and multiple endocrine tumors. These individuals tend to have multiple or metastatic gastrinomas that are difficult to resect. Approximately 25% of gastrinomas are due to MEN 1.[6]

Stress Ulcers

A stress ulcer, sometimes called a *Curling ulcer,* refers to gastrointestinal ulcerations that develop in relation to major physiologic stress.[7,23,24] Persons at high risk for development of stress ulcers include those with large–surface-area burns, trauma, sepsis, acute respiratory distress syndrome, severe liver failure, and major surgical procedures. These lesions occur most often in the fundus of the stomach and proximal duodenum and are thought to result from ischemia, tissue acidosis, and bile salts entering the stomach in critically ill persons with decreased gastrointestinal tract motility. Another form of stress ulcer, called *Cushing ulcer,* consists of gastric, duodenal, and esophageal ulcers arising in persons with intracranial injury, operations, or tumors. They are thought to be caused by hypersecretion of gastric acid resulting from stimulation of vagal nuclei by increased intracranial pressure.

Persons admitted to hospital intensive care units are at particular risk for development of stress ulcers. They usually manifest with painless upper gastrointestinal tract bleeding. H_2-receptor antagonists and proton pump inhibitors are used in the prevention and treatment of stress ulcers.

Cancer of the Stomach

Although the incidence of cancer of the stomach has declined over the past 50 years in the United States, it continues to remain a leading cause of cancer deaths worldwide.[6] However, its incidence varies widely, being particularly high in countries such as Japan, Chile, Costa Rica, and Eastern Europe.[6] It is more common in lower socioeconomic groups and exhibits a male-to-female ratio of about 2:1.

Among the factors that increase the risk of gastric cancer are genetic predisposition, carcinogenic factors in the diet (e.g., *N*-nitroso compounds and benzo[α]pyrene found in smoked and preserved foods), autoimmune gastritis, and gastric adenomas or polyps. The incidence of stomach cancer in the United States has decreased fourfold since 1930, presumably because of improved storage of food with decreased consumption of smoked and preserved foods.[6,7] Chronic infection with *H. pylori* appears to serve as a cofactor in some types of gastric carcinomas. However, the vast majority of people with *H. pylori* infection do not develop gastric cancer, and not all *H. pylori* infections increase the risk of gastric cancer, suggesting that other factors may be involved.[7] Autoimmune gastritis, like *H. pylori* infection, increases the risk of gastric cancer, presumably due to chronic inflammation and intestinal metaplasia.

Most gastric cancers involve the antrum of the stomach, with the lesser curvature being involved more often than the greater curvature. Compared with benign ulcers, which have smooth margins and are concentrically shaped, gastric cancers tend to be bulky and irregularly shaped and have firm and jagged edges. Unfortunately, stomach cancers often are asymptomatic until late in their course. Symptoms, when they do occur, usually are vague and include indigestion, anorexia, weight loss, vague epigastric pain, vomiting, and an abdominal mass. Because these symptoms are essentially nonspecific, early detection is often difficult.

Diagnosis of gastric cancer is accomplished by a variety of techniques, including barium x-ray studies, endoscopic studies with biopsy, and cytologic studies (e.g., Papanicolaou smear) of gastric secretions.[25] Cytologic studies can prove particularly useful as routine screening tests for persons with atrophic gastritis or gastric polyps. CT and endoscopic ultrasonography often are used to delineate the spread of a diagnosed stomach cancer.

Depending on the location and extent of the lesion, surgery in the form of radical subtotal gastrectomy usually is the treatment of choice. Irradiation and chemotherapy have not proved particularly useful as primary treatment modalities in stomach cancer. These methods usually are used for palliative purposes or to control metastatic spread of the disease.

In summary, disorders of the stomach include gastritis, peptic ulcer, and cancer of the stomach. Gastritis refers to inflammation of the gastric mucosa. Acute gastritis is a transient inflammation of the gastric mucosa, most commonly caused by local irritants such as bacterial endotoxins, caffeine, alcohol, and aspirin. Chronic gastritis is characterized by the presence of chronic inflammatory changes leading eventually to atrophy of the glandular epithelium of the stomach. There are three main types of chronic gastritis: *H. pylori* gastritis, autoimmune gastritis, and chemical gastropathy. *H. pylori* are small "S"-shaped bacteria that colonize the mucus-secreting epithelial cells of the stomach. Infection increases the risk of chronic gastritis, peptic ulcer, gastric carcinoma, and low-grade B-cell lymphoma. Autoimmune gastritis is characterized by the presence of autoantibodies to parietal cells and intrinsic factor,

defective gastric acid production (achlorhydria), and vitamin B_{12} deficiency. Chemical gastropathy represents the result of chronic injury resulting from reflux of alkaline duodenal contents, pancreatic secretions, and bile into the stomach.

Peptic ulcer is a term used to describe a group of ulcerative disorders that occur in areas of the upper gastrointestinal tract that are exposed to acid–pepsin secretions, most commonly the duodenum and stomach. There are two main causes of peptic ulcer: *H. pylori* infection and aspirin or NSAID use. The most common complications of peptic ulcer are hemorrhage, perforation, and gastric outlet obstruction. The treatment of peptic ulcer focuses on eradication of *H. pylori,* avoidance of gastric irritation from NSAIDs, and conventional pharmacologic treatment directed at symptom relief and ulcer healing.

The Zollinger-Ellison syndrome is a rare condition caused by a gastrin-secreting tumor in which gastric acid secretion reaches such levels that ulceration becomes inevitable. Stress ulcers, also called *Curling ulcers,* occur in relation to major physiologic stresses such as burns and trauma and are thought to result from ischemia, tissue acidosis, and bile salts entering the stomach in critically ill persons with decreased gastrointestinal tract motility. Another form of stress ulcer, *Cushing ulcer*, occurs in persons with intracranial trauma or surgery and is thought to be caused by hypersecretion of gastric acid resulting from stimulation of vagal centers by increased intracranial pressure.

Although the incidence of cancer of the stomach has declined over the past 50 years in the United States, it remains a leading cause of cancer deaths worldwide. Among the factors thought to predispose to gastric cancer are carcinogenic factors in the diet (e.g., *N*-nitroso compounds and benzo[α]pyrene found in smoked and preserved food) and chronic gastritis. Because there are few early symptoms with this form of cancer, the disease often is far advanced at the time of diagnosis.

Disorders of the Small and Large Intestines

There are many similarities in conditions that disrupt the integrity and function of the small and large intestines. The walls of the small and large intestines consist of four layers (see Chapter 28, Fig. 28-3): the inner mucosal layer, which lines the lumen of the intestine; the submucosal layer, which lies beneath the mucosa; the muscularis externa, which is made up of an inner circular layer and an outer longitudinal layer of smooth muscle; and the outer serosal layer, which consists of a single layer of flat, serous fluid–producing cells, the visceral peritoneum. The visceral peritoneum is continuous with the parietal peritoneum, which lines the abdominopelvic cavity. Among the conditions that cause altered intestinal function are irritable bowel syndrome, inflammatory bowel disease, infectious enterocolitis, diverticulosis, appendicitis, disorders of bowel motility (i.e., diarrhea, constipation, and bowel obstruction), peritonitis, malabsorption syndrome, and cancer of the colon and rectum.

Irritable Bowel Syndrome

The term *irritable bowel syndrome* is used to describe a functional gastrointestinal disorder characterized by a variable combination of chronic and recurrent intestinal symptoms not explained by structural or biochemical abnormalities.[26–28] There is evidence to suggest that 10% to 20% of people in Western countries have the disorder, although most do not seek medical attention.

Irritable bowel disease is characterized by persistent or recurrent symptoms of abdominal pain, altered bowel function, and varying complaints of flatulence, bloating, nausea and anorexia, constipation or diarrhea, and anxiety or depression. A hallmark of irritable bowel syndrome is abdominal pain that is relieved by defecation and associated with a change in consistency or frequency of stools. Abdominal pain usually is intermittent, cramping, and in the lower abdomen. It does not usually occur at night or interfere with sleep. The condition is believed to result from dysregulation of intestinal motor and sensory functions modulated by the CNS. Persons with irritable bowel syndrome tend to experience increased motility and abnormal intestinal contractions in response to psychological and physiologic stresses. The role that psychological factors play in the disease is uncertain. Although changes in intestinal activity are normal responses to stress, these responses appear to be exaggerated in persons with irritable bowel syndrome. Women tend to be affected more often than men. Menarche often is associated with onset of the disorder. Women frequently notice an exacerbation of symptoms during the premenstrual period, suggesting a hormonal component.

The diagnosis of irritable bowel syndrome is usually based on signs and symptoms of abdominal pain or discomfort, bloating, and constipation or diarrhea, or alternating bouts of constipation and diarrhea. A commonly used set of diagnostic criteria require continuous or recurrent symptoms of at least 12 weeks' duration (which may be nonconsecutive) of abdominal discomfort or pain in the preceding 12 months, with two of three accompanying features: relief with defecation, onset associated with a change in bowel frequency, and associated with a change in form (appearance) of stool. Other symptoms that support the diagnosis of irritable bowel syndrome include abnormal stool frequency (more than three times per day or less than three times per week), abnormal stool form (lumpy/hard or loose/watery), abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, and bloating or feeling of abdominal distention. A history of lactose intolerance should be considered because intolerance to lactose and other sugars may be a precipitating factor in some persons. The acute onset of symptoms raises the likelihood of organic disease, as do weight loss, anemia, fever, occult blood in the stool, nighttime symptoms, or signs and symptoms of malabsorption. These signs and symptoms require additional investigation.

The treatment of irritable bowel syndrome focuses on methods of stress management, particularly those related to symptom production. Reassurance is important. Usually, no special diet is indicated, although adequate fiber intake usually is recommended. Avoidance of offending dietary substances such as fatty and gas-producing foods, alcohol, and caffeine-containing beverages may be beneficial. Various pharmacologic agents, including antispasmodic and anticholinergic drugs, have been used with varying success in treatment of the disorder. The 5-HT_3 antagonist alosetron was the first specific drug to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of irritable bowel disease. It acts by reducing intestinal secretion, decreasing visceral afferent nerve activity (thereby reducing abdominal pain), and reducing intestinal motility. The drug, which was indicated for treatment of women with the severe diarrheal form of the disease, was removed from the market in late 2000 because of serious side effects and then reintroduced in 2002 under a restricted prescribing program.

Inflammatory Bowel Disease

The term *inflammatory bowel disease* (IBD) is used to designate two related inflammatory intestinal disorders: Crohn disease and ulcerative colitis.[6,7,29–31] Although the two diseases differ sufficiently to be distinguishable, they have many features in common. Both diseases produce inflammation of the bowel, both conditions lack confirming evidence of a proven causative agent, both have a pattern of familial occurrence, and both can be accompanied by systemic manifestations. Crohn disease most commonly affects the distal small intestine and proximal colon but can affect any area of the gastrointestinal tract from the esophagus to the anus, whereas ulcerative colitis is confined to the colon and rectum (Fig. 29-6).

The clinical manifestations of both Crohn disease and ulcerative colitis are ultimately the result of activation of inflammatory cells with elaboration of inflammatory mediators that cause nonspecific tissue damage. Both diseases are characterized by remissions and exacerbations of diarrhea, fecal urgency, and weight loss. Acute complications, such as intestinal obstruction, may develop during periods of fulminant disease. The distinguishing characteristics of Crohn disease and ulcerative colitis are summarized in Table 29-1.

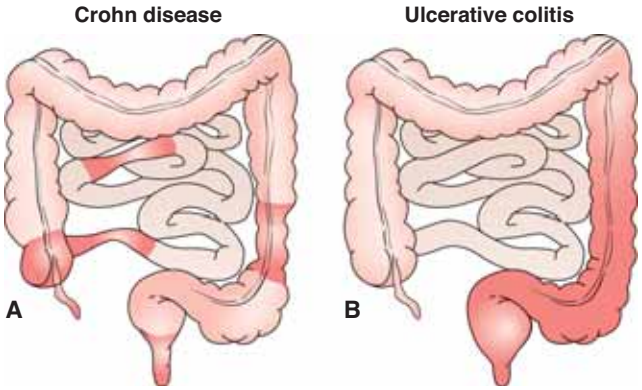


FIGURE 29-6. Distribution patterns of disease with **(A)** skip lesions in Crohn disease and **(B)** continuous involvement of the colon, beginning with the rectum, in ulcerative colitis.

A number of systemic manifestations have been identified in persons with Crohn disease and ulcerative colitis. These include axial arthritis affecting the spine and sacroiliac joints and oligoarticular arthritis affecting the large joints of the arms and legs; inflammatory conditions of the eye, usually uveitis; skin lesions, especially erythema nodosum; inflammation of the mucous membrane of the mouth (stomatitis); blood disorders (anemia, hypercoagulability); and inflammation of the bile duct (i.e., sclerosing cholangitis). Occasionally, these systemic manifestations may herald the recurrence of intestinal disease. In children, growth retardation may occur, particularly if the symptoms are prolonged and nutrient intake has been poor.

Etiology and Pathogenesis

The causes of Crohn disease and ulcerative colitis are largely uncertain. There is growing evidence that genetic factors predispose to an immune response, possibly triggered by a relatively innocuous environmental agent such as a dietary antigen or microbial agent.[6,7] The sites affected by inflammatory bowel disease, the distal ileum and the colon, are awash with bacteria. Despite the growing evidence that intestinal microorganisms contribute to

TABLE 29-1 Differentiating Characteristics of Crohn Disease and Ulcerative Colitis

Characteristic	Crohn Disease	Ulcerative Colitis
Types of inflammation	Granulomatous	Ulcerative and exudative
Level of involvement	Primarily submucosal	Primarily mucosal
Extent of involvement	Skip lesions	Continuous
Areas of involvement	Primarily ileum, secondarily colon	Primarily rectum and left colon
Diarrhea	Common	Common
Rectal bleeding	Rare	Common
Fistulas	Common	Rare
Strictures	Common	Rare
Perianal abscesses	Common	Rare
Development of cancer	Uncommon	Relatively common

IBD pathogenesis, their precise role remains to be described and is probably different in Crohn disease and ulcerative colitis. A variety of other factors are associated with IBD for unknown reasons. For example, an episode of appendicitis is associated with a decreased risk of developing ulcerative colitis. Also, smoking tobacco has the opposite effect on the two forms of inflammatory bowel disease. It predisposes to development of Crohn disease, yet is associated with a reduced incidence of ulcerative colitis.[22]

The genetic basis for IBD has long been suspected. The risk of disease is greater when there is an affected family member, with a family history of IBD being more common in Crohn disease than ulcerative colitis.[6,7] Both Crohn disease and ulcerative colitis have been linked to specific major histocompatibility class II (human leukocyte antigen [HLA]) alleles. Recent research has focused on association of the disease with non-HLA genes. One susceptibility locus for Crohn disease is located on chromosome 16. The product of the implicated gene is an intracellular receptor for a component of the cell walls of many bacteria and is thought to play a role in host responses to these bacteria.[29,30] Another area linked specifically to Crohn disease is located on chromosome 5. This area is rich in genes encoding several cytokines (e.g., interleukin [IL]-3, IL-4, IL-5, and IL-13) that may contribute to the disease. Studies suggest that individuals with this susceptibility locus may have a more severe disease requiring surgery. However, the exact cytokine genes or mutations remain to be established.

Crohn Disease

Crohn disease is a recurrent, granulomatous type of inflammatory response that can affect any area of the gastrointestinal tract. In nearly 40% of persons with the disease, the lesions are restricted to the small intestine; in 30%, only the large bowel is affected; and in the remaining 30%, the large bowel and small bowel are affected.[6] It is a slowly progressive, relentless, and often disabling disease. The disease usually strikes people in their twenties or thirties, with women being affected slightly more often than men.

A characteristic feature of Crohn disease is the sharply demarcated, granulomatous lesions that are surrounded by normal-appearing mucosal tissue. When the lesions are multiple, they often are referred to as *skip lesions* because they are interspersed between what appear to be normal segments of the bowel. All the layers of the bowel are involved, with the submucosal layer affected to the greatest extent. The surface of the inflamed bowel usually has a characteristic "cobblestone" appearance resulting from the fissures and crevices that develop, surrounded by areas of submucosal edema[6,7] (Fig. 29-7). There usually is a relative sparing of the smooth muscle layers of the bowel, with marked inflammatory and fibrotic changes of the submucosal layer. The bowel wall, after a time, often becomes thickened and inflexible; its appearance has been likened to a lead pipe or rubber hose. The adjacent mesentery may become inflamed, and the regional lymph nodes and channels may become enlarged.

FIGURE 29-7. Crohn disease. The mucosal surface of the colon displays a "cobblestone" appearance owing to the presence of linear ulcerations and edema and inflammation of the intervening tissue. (From Rubin E., Farber J.L. [Eds.]. [1999]. *Pathology* [3rd ed., p. 728]. Philadelphia: Lippincott Williams & Wilkins.)

The clinical course of Crohn disease is variable; often, there are periods of exacerbations and remissions, with symptoms being related to the location of the lesions. The principal symptoms include intermittent diarrhea, colicky pain (usually in the lower right quadrant), weight loss, fluid and electrolyte disorders, malaise, and low-grade fever.[32] Because Crohn disease affects the submucosal layer to a greater extent than the mucosal layer, there is less bloody diarrhea than with ulcerative colitis. Ulceration of the perianal skin is common, largely because of the severity of the diarrhea. The absorptive surface of the intestine may be disrupted; nutritional deficiencies may occur, related to the specific segment of the intestine involved. When Crohn disease occurs in childhood, one of its major manifestations may be retardation of growth and physical development.

Complications of Crohn disease include fistula formation, abdominal abscess formation, and intestinal obstruction. Fistulas are tubelike passages that form connections between different sites in the gastrointestinal tract. They also may develop between other sites, including the bladder, vagina, urethra, and skin. Perineal fistulas that originate in the ileum are relatively common. Fistulas between segments of the gastrointestinal tract may lead to malabsorption, syndromes of bacterial overgrowth, and diarrhea. They also can become infected and cause abscess formation.

Diagnosis and Treatment. The diagnosis of Crohn disease requires a thorough history and physical examination. Sigmoidoscopy is used for direct visualization of the affected areas and to obtain biopsies. Measures are taken to exclude infectious agents as the cause of the disorder. This usually is accomplished by the use of stool cultures and examination of fresh stool specimens for ova and parasites. In persons suspected of having Crohn disease, radiographic contrast studies provide a means for determining the extent of involvement of the small bowel and establishing the presence and nature

of fistulas. CT scans may be used to detect an inflammatory mass or abscess.

Treatment methods focus on terminating the inflammatory response and promoting healing, maintaining adequate nutrition, and preventing and treating complications. Nutritional deficiencies are common in Crohn disease because of diarrhea, steatorrhea, and other malabsorption problems. A nutritious diet that is high in calories, vitamins, and proteins is recommended. Because fats often aggravate the diarrhea, it is recommended that they be avoided. Elemental diets, which are nutritionally balanced but residue free and bulk free, may be given during the acute phase of the illness. These diets are largely absorbed in the jejunum and allow the inflamed bowel to rest. Total parenteral nutrition (i.e., parenteral hyperalimentation), which is administered intravenously, may be needed when food cannot be absorbed from the intestine.

Several medications have been successful in suppressing the inflammatory reaction, including 5-aminosalicylic acid (5-ASA) agents, corticosteroids, antibiotics, immunosuppressant drugs (azathioprine, 6-mercaptopurine, methotrexate), and anti–tumor necrosis factor (TNF) therapies (infliximab and adalimumab).[8,32] The 5-ASA agents act locally to affect multiple sites in the arachidonic acid pathway critical to the pathogenesis of inflammation. Much of the unformulated 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon in appreciable amounts. To overcome the rapid absorption of 5-ASA, a number of formulations (e.g., sulfasalazine, mesalamine) have been designed to deliver the drug to the distal small bowel and colon. Corticosteroids are used to suppress the acute clinical symptoms in persons with small and large bowel disease. Metronidazole is an antibiotic used to treat bacterial overgrowth in the small intestine. Azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine are immunomodulating drugs that are used in persons who do not respond to other forms of therapy.[8] The anti-TNF agents are monoclonal antibodies that target the destruction of TNF-α, a mediator of the inflammatory response that is known to be important in granulomatous inflammatory processes such as Crohn disease.[8] These agents are used to treat severe disease. Surgical resection of damaged bowel, drainage of abscesses, or repair of fistula tracts may be necessary.

Ulcerative Colitis

Ulcerative colitis is a nonspecific inflammatory condition of the colon. The disease is more common in the United States and Western countries. The disease may arise at any age, with a peak incidence in the third decade.[7] Unlike Crohn disease, which can affect various sites in the gastrointestinal tract, ulcerative colitis is confined to the rectum and colon.[6,7] The disease usually begins in the rectum and spreads proximally, affecting primarily the mucosal layer, although it can extend into the submucosal layer. The length of proximal extension varies. It may involve the rectum alone (ulcerative proctitis), the rectum and sigmoid colon (proctosigmoiditis), or the entire colon (pancolitis). The inflammatory process tends to be confluent and continuous instead of skipping areas, as it does in Crohn disease.

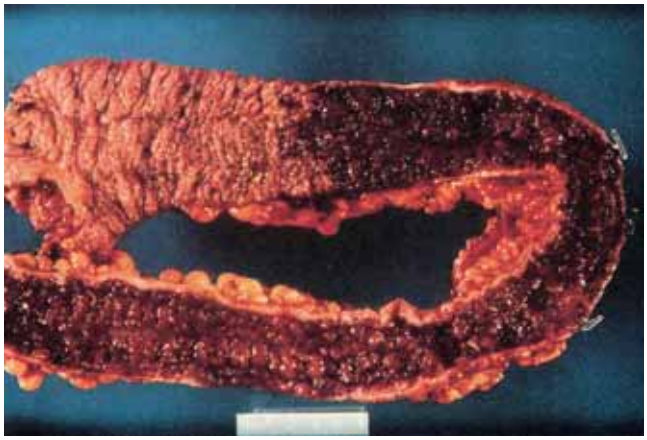


FIGURE 29-8. Ulcerative colitis. Prominent erythema and ulceration of the colon begin in the ascending colon and are most severe in the rectosigmoid area. (From Mitos F.A., Rubin E. [2008]. The gastrointestinal tract. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathophysiology: Clinicopathologic foundations of medicine* [5th ed., p. 597]. Philadelphia: Lippincott Williams & Wilkins.)

Characteristic of the disease are lesions that form in the crypts of Lieberkühn in the base of the mucosal layer (see Chapter 28, Fig. 28-11). The inflammatory process leads to the formation of pinpoint mucosal hemorrhages, which in time suppurate and develop into *crypt abscesses*. These inflammatory lesions may become necrotic and ulcerate. Although the ulcerations usually are superficial, they often extend, causing large denuded areas (Fig. 29-8). As a result of the inflammatory process, the mucosal layer often develops tonguelike projections that resemble polyps and therefore are called *pseudopolyps*. The bowel wall thickens in response to repeated episodes of colitis.

Ulcerative colitis typically presents as a relapsing disorder marked by attacks of diarrhea. The diarrhea may persist for days, weeks, or months and then subside, only to recur after an asymptomatic interval of several months to years or even decades. Because ulcerative colitis affects the mucosal layer of the bowel, the stools typically contain blood and mucus. Nocturnal diarrhea usually occurs when daytime symptoms are severe. There may be mild abdominal cramping and fecal incontinence. Anorexia, weakness, and fatigability are common.

Based on clinical and endoscopic findings, the disease is characterized by its severity and extent. Severity is defined as mild, moderate, severe, or fulminant.[33] The most common form of the disease is the mild form, in which the person has less than four stools daily, with or without blood; no systemic signs of toxicity; and a normal erythrocyte sedimentation rate (ESR). Persons with moderate disease have more than four stools daily but have minimal signs of toxicity. Severe disease is manifested by more than six bloody stools daily and evidence of toxicity as demonstrated by fever, tachycardia, anemia, and elevated ESR. Persons with fulminant disease have

features that include more than 10 bowel movements a day, continuous bleeding, fever and other signs of toxicity, abdominal tenderness and distention, need for blood transfusions, and colonic dilation on abdominal radiographs. These persons are at risk for development of toxic megacolon, which is characterized by dilation of the colon and signs of systemic toxicity. It results from extension of the inflammatory response, with involvement of neural and vascular components of the bowel.

Cancer of the colon is one of the feared complications of ulcerative colitis.[8] Because of the relatively high risk for development of cancer, regular annual or biannual surveillance colonoscopies with multiple biopsies are recommended for persons with extensive colitis, beginning 8 to 10 years after diagnosis.[33]

Diagnosis and Treatment. Diagnosis of ulcerative colitis is based on history and physical examination. The diagnosis usually is confirmed by sigmoidoscopy, colonoscopy, biopsy, and negative stool examinations for infectious or other causes. Colonoscopy should not be performed on persons with severe disease because of the danger of perforation, but may be performed after demonstrated improvement to determine the extent of disease and need for subsequent cancer surveillance.[8]

Treatment depends on the extent of the disease and severity of symptoms. It includes measures to control the acute manifestations of the disease and prevent recurrence. Some people with mild to moderate symptoms are able to control their symptoms simply by avoiding caffeine, lactose (milk), highly spiced foods, and gas-forming foods. Fiber supplements may be used to decrease diarrhea and rectal symptoms. Surgical treatment (i.e., removal of the rectum and entire colon) with the creation of an ileostomy or ileoanal anastomosis may be required for persons who do not respond to medications and conservative methods of treatment.

The medications used in treatment of ulcerative colitis are similar to those used in the treatment of Crohn disease. They include the nonabsorbable 5-ASA compounds (e.g., sulfasalazine, mesalamine).[8,33] The corticosteroids are used selectively to lessen the acute inflammatory response. Many of these medications can be administered rectally by suppository or enema. Immunomodulating drugs and anti-TNF therapies may be used to treat persons with severe colitis.

Infectious Enterocolitis

A number of microbial agents, including viruses, bacteria, and protozoa, can infect the gastrointestinal tract, causing a broad range of symptoms including diarrhea, abdominal pain, perianal discomfort, ulceration, and hemorrhage. Infectious enterocolitis is a global problem, causing more than 3 million deaths annually and accounting for up to one half of deaths in children younger than 5 years in some countries.[6] Although far less common in industrialized countries, these disorders still have infection rates second only to the common cold. Most infections are spread by the oral–fecal route, often through contaminated water or food.

Viral Infections

Most viral infections affect the superficial epithelium of the small intestine, destroying these cells and disrupting their absorptive function. Repopulation of the small intestinal villi with immature enterocytes and preservation of crypt secretory cells leads to net secretion of water and electrolytes compounded by incomplete absorption of nutrients and osmotic diarrhea. Symptomatic disease is caused by several distinct viruses, including the rotavirus, which most commonly affects children 6 to 24 months of age; the norovirus (previously known as the Norwalk virus), which is responsible for the majority of cases of nonbacterial food-borne epidemic gastroenteritis in all age groups: and enteric adenoviruses, which primarily affect children.[6]

Rotavirus. Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea in children younger than 5 years of age. In the United States, the disease causes 3 million cases of diarrhea, 80,000 hospitalizations, and 20 to 40 deaths per year.[34] The disease tends to be most severe in children 3 to 24 months of age. Infants younger than 3 months of age are relatively protected by transplacental antibodies and possibly by breast-feeding. The virus is spread by a fecal–oral route and outbreaks are common in children in day care centers. The virus is shed before and for days after clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

Rotavirus infection typically begins after an incubation period of less than 24 hours, with mild to moderate fever and vomiting, followed by onset of frequent watery stools. The fever and vomiting usually disappear on about the second day, but the diarrhea continues for 5 to 7 days. Dehydration may develop rapidly, particularly in infants. Treatment is largely supportive. Avoiding and treating dehydration are the main goals.

A live, oral, pentavalent vaccine for rotavirus (RotaTeq) was approved by the FDA in 2006.[34,35] The vaccine contains five reassortment rotaviruses isolated from human and bovine hosts.

Bacterial Infections

Infectious enterocolitis can be caused by a number of bacteria. There are several pathogenic mechanisms for bacterial enterocolitis: ingestion of preformed toxins that are present in contaminated food; infection by toxigenic organisms that proliferate in the gut lumen and produce an enterotoxin; and infection by enteroinvasive organisms, which proliferate in the lumen and invade and destroy mucosal epithelial cells. The pathogenic effects of bacterial infections depend on the ability of the organism to adhere to the mucosal epithelial cells, elaborate enterotoxins, and then invade the mucosal epithelial cells.

In general, bacterial infections produce more severe effects than viral infections. The complications of bacterial enterocolitis result from massive fluid loss or destruction of intestinal mucosa and include dehydration, sepsis, and perforation. Among the organisms

that cause bacterial enterocolitis are *Staphylococcus aureus* (toxins associated with "food poisoning"), *Escherichia coli, Shigella* species, *Salmonella,* and *Campylobacter.* Two particularly serious forms of bacterial enterocolitis are caused by *Clostridium difficile* and *E. coli* O157:H7.

***Clostridium difficile* Colitis.** *C. difficile* colitis is associated with antibiotic therapy.[36,37] *C. difficile* is a gram-positive, spore-forming bacillus that is part of the normal flora in 1% to 3% of humans.[36] The spores are resistant to the acid environment of the stomach and convert to vegetative forms in the colon. The species was named "*difficile*" because it was difficult to culture.[37] In general, *C. difficile* is noninvasive and development of *C. difficile* colitis requires disruption of normal intestinal flora, acquisition and germination of the spores, overgrowth of the bacillus, and toxin production. The toxins bind to and damage the intestinal mucosa, causing hemorrhage, inflammation, and necrosis. The toxins also interfere with protein synthesis, attract inflammatory cells, increase capillary permeability, and stimulate intestinal peristalsis. Treatment with broad-spectrum antibiotics predisposes to disruption of the normal protective bacterial flora of the colon. Almost any antibiotic may cause *C. difficile* colitis, but broad-spectrum antibiotics with activity against gram-negative enteric bacteria are the most frequent agents. After antibiotic therapy has made the bowel susceptible to infection, colonization by *C. difficile* occurs by the oral–fecal route. *C. difficile* infection usually is acquired in the hospital, where the organism is commonly encountered.

C. difficile colitis commonly manifests with diarrhea that is mild to moderate and sometimes is accompanied by lower abdominal cramping. Typically, symptoms begin within 1 to 2 weeks after antibiotic treatment has been initiated, although it can vary from 1 day to 6 weeks.[36] In most cases, systemic manifestations are absent, and the symptoms subside after the antibiotic has been discontinued. A more severe form of colitis, *pseudomembranous colitis,* is characterized by an adherent inflammatory membrane overlying the areas of mucosal injury. It is a life-threatening form of the disease. Persons with the disease are acutely ill, with lethargy, fever, tachycardia, abdominal pain and distention, and dehydration. The smooth muscle tone of the colon may be lost, resulting in toxic dilation of the colon. Prompt therapy is needed to prevent perforation of the bowel.

The diagnosis of *C. difficile* colitis requires a careful history, with particular emphasis on antibiotic use. Diagnostic findings include a history of antibiotic use and laboratory tests that confirm the presence of *C. difficile* toxins in the stool.[37] Treatment includes the immediate discontinuation of antibiotic therapy. Specific treatment aimed at eradicating *C. difficile* is used when symptoms are severe or persistent. Metronidazole is the drug of first choice, with vancomycin being reserved for persons who cannot tolerate metronidazole or do not respond to the drug. Both drugs are given orally.[37] Metronidazole is absorbed from the upper gastrointestinal tract and may cause side effects. Vancomycin is poorly absorbed, and its actions are limited to the gastrointestinal tract.

***Escherichia coli* O157:H7 Infection.** Enterohemorrhagic *E. coli* O157:H7 has become recognized as an important cause of epidemic and sporadic colitis.[38–40] *E. coli* O157:H7 is a strain of *E. coli* found in the feces and contaminated milk of healthy dairy and beef cattle, but it also has been found in contaminated pork, poultry, and lamb. Infection usually is by food-borne transmission, often by ingesting undercooked hamburger. The organism also can be transferred to nonmeat products such as fruits and vegetables. Transmission has also been reported in persons swimming in a fecally contaminated lake as well as among visitors to farms and petting zoos, where children are in direct contact with animals. Person-to-person transmission may occur, particularly in nursing homes, day care settings, and hospitals. The very young and the very old are particularly at risk for the infection and its complications.

Although most strains of *E. coli* are harmless, *E. coli* 0157:H7 produce *Shigella*-like toxins that attach to and damage the mucosal lining of the intestine, causing bloody diarrhea.[39,40] Subsequently, the *Shigella*-like toxins gain access to the circulatory system and travel in the plasma and on the surface of platelets and monocytes. The *Shigella*-like toxins bind to high-affinity galactose-containing receptors in the membranes of glomerular, cerebral, or microvascular endothelial cells; renal mesangial and tubular cells; and monocytes and platelets.[40] Two complications of the infection, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, reflect the effects of the *Shigella*-like toxins. The hemolytic uremic syndrome is characterized by hemolytic anemia, thrombocytopenia, and renal failure. It occurs predominantly in infants and young children and is the most common cause of acute renal failure in children. It has a mortality rate of 3% to 5%, and one third of the survivors are left with permanent disability.[40] Thrombotic thrombocytopenic purpura is manifested by thrombocytopenia, renal failure, fever, and neurologic manifestations. It often is regarded as the severe end of the disease that leads to hemolytic uremic syndrome plus neurologic problems.

No specific therapy is available for *E. coli* O157:H7 infection. Treatment is largely symptomatic and directed toward treating the effects of complications. The use of antibiotics or antidiarrheal agents in the early stages of diarrhea has been shown to increase the risk of hemolytic uremic syndrome because the gut is exposed to a greater amount of toxins for a longer time. Because of the seriousness of the infection and its complications, education of the public about techniques for decreasing primary transmission of the infection from animal sources is important. Undercooked meats and unpasteurized milk are sources of transmission. Food handlers and consumers should be aware of the proper methods for handling uncooked meat to prevent cross-contamination of other foods. Particular attention should be paid to hygiene in day care centers and nursing homes, where the spread of infection to the very young and very old may result in severe complications.

Diverticular Disease

Diverticulosis is a disorder characterized by pseudodiverticula of the colonic mucosa and submucosa.[6,7] The disorder is more common in Western society, affecting approximately 10% of the adults younger than 40 years and 50% to 70% of those 80 years of age or older.[41] Although the disorder is prevalent in the developed countries of the world, it is almost nonexistent in many African nations and underdeveloped countries. This suggests that factors such as lack of fiber in the diet, a decrease in physical activity, and poor bowel habits (e.g., neglecting the urge to defecate), along with the effects of aging, contribute to the development of the disease.

True diverticula involve all layers of the intestinal wall. The abnormal structures in diverticulosis are instead pseudodiverticula, in which only the mucosa and submucosa are herniated through the muscle layers.[6,7] The diverticula are often multiple, ranging from a solitary herniation to several hundred (Fig. 29-9). They are most often located in the sigmoid colon, but more extensive areas may be involved in severe cases. Microscopically, colonic diverticula are small, flasklike outpouchings, usually 0.5 to 1.0 cm in diameter, that occur in a regular distribution alongside the teniae coli (Fig. 28.10).

Colonic diverticula result from the unique structure and elevated luminal pressures in the sigmoid colon.[6] In the colon, the longitudinal muscle does not form a continuous layer, as it does in the small bowel. Instead, there are three separate longitudinal bands of muscle called the *teniae coli*. In a manner similar to the small intestine, bands of circular muscle constrict the large intestine. As the circular muscle contracts at each of these points (approximately every 2.5 cm), the lumen of the bowel becomes constricted, so that it is almost occluded. The combined contraction of the circular muscle and the lack of a continuous longitudinal muscle layer cause the intestine to bulge outward into pouches called *haustra*. Diverticula develop between the longitudinal muscle bands of the haustra, in the areas where blood vessels pierce the circular muscle layer to bring blood to the mucosal layer. An increase in intraluminal pressure in the haustra provides the force for creating these herniations.

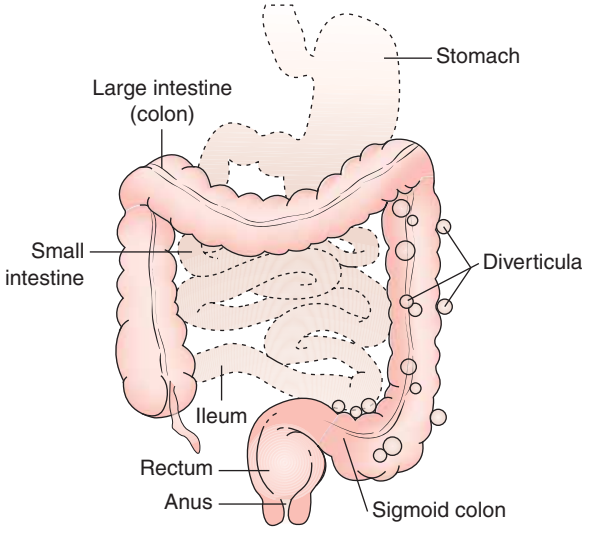


FIGURE 29-9. Location of diverticula in the sigmoid colon.

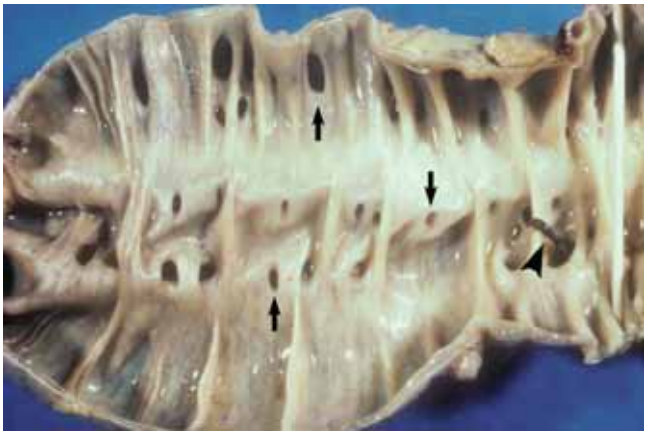


FIGURE 29-10. Diverticulosis of the colon. The colon was inflated with formalin. The mouths of numerous diverticula are seen between the taenia (*arrows*). There is a blood clot protruding from the mouth of one of the diverticula (*arrow*). (From Mitros F.A., Emanuel E. [2008]. The gastrointestinal tract. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 593]. Philadelphia: Lippincott Williams & Wilkins.)

Most people with diverticular disease remain asymptomatic.[41,42] The disease often is found when x-ray studies are done for other purposes. Ill-defined lower abdominal discomfort, a change in bowel habits (e.g., diarrhea, constipation), bloating, and flatulence are common. Diverticulitis is a complication of diverticulosis in which there is inflammation and gross or microscopic perforation of the diverticula.[43] One of the most common complaints of diverticulitis is pain in the lower left quadrant, accompanied by nausea and vomiting, tenderness in the lower left quadrant, a slight fever, and an elevated white blood cell count. These symptoms usually last for several days, unless complications occur, and usually are caused by localized inflammation of the diverticula with perforation and development of a small, localized abscess. Complications include perforation with peritonitis, hemorrhage, and bowel obstruction. Fistulas can form, usually involving the bladder (i.e., vesicosigmoid fistula) but sometimes involving the skin, perianal area, or small bowel. Pneumaturia (i.e., air in the urine) is a sign of vesicosigmoid fistula.

The diagnosis of diverticular disease is based on history and presenting clinical manifestations.[42] The disease may be confirmed by CT scans or ultrasonographic studies. CT scans are the safest and most cost-effective method. Because of the risk of peritonitis, barium enema studies should be avoided in persons who are suspected of having acute diverticulitis. Flat abdominal radiographs may be used to detect complications associated with acute diverticulitis.

The usual treatment for diverticular disease is to prevent symptoms and complications. This includes increasing the bulk in the diet and bowel retraining so that the person

has at least one bowel movement each day. The increased bulk promotes regular defecation and increases colonic contents and colon diameter, thereby decreasing intraluminal pressure. Acute diverticulitis is treated by withholding solid food and administering a broad-spectrum antibiotic. Hospitalization may be required for persons who show significant inflammation, are unable to tolerate oral fluids, or have significant comorbid conditions. Surgical treatment is reserved for complications.

Appendicitis

Acute appendicitis is extremely common. It is seen most frequently in the 20- to 30-year-old age group, but it can occur at any age.[6] The appendix becomes inflamed, swollen, and gangrenous, and it eventually perforates if not treated.[44] Although the cause of appendicitis is unknown, it is thought to be related to intraluminal obstruction with a fecalith (i.e., hard piece of stool) or to twisting.

Appendicitis usually has an abrupt onset, with pain referred to the epigastric or periumbilical area. This pain is caused by stretching of the appendix during the early inflammatory process. At approximately the same time that the pain appears, there are one or two episodes of nausea. Initially, the pain is vague, but over a period of 2 to 12 hours, it gradually increases and may become colicky. When the inflammatory process has extended to involve the serosal layer of the appendix and the peritoneum, the pain becomes localized to the lower right quadrant. There usually is an elevation in temperature and a white blood cell count greater than 10,000/mm^3, with 75% or more polymorphonuclear cells. Palpation of the abdomen usually reveals a deep tenderness in the lower right quadrant, which is confined to a small area approximately the size of the fingertip. It usually is located at approximately the site of the inflamed appendix. The person with appendicitis often is able to place his or her finger directly over the tender area. Rebound tenderness, which is pain that occurs when pressure is applied to the area and then released, and spasm of the overlying abdominal muscles are common.

Diagnosis is usually based on history and findings on physical examination. Ultrasonography or CT may be used to confirm the diagnosis.[44] Treatment consists of surgical removal of the appendix. Complications include peritonitis, localized periappendiceal abscess formation, and septicemia.

Disorders of Intestinal Motility

The movement of contents through the gastrointestinal tract is controlled by neurons located in the submucosal and myenteric plexuses of the gut (see Chapter 28). The axons from the cell bodies in the myenteric plexus innervate the circular and longitudinal smooth muscle layers of the gut. These neurons receive impulses from local receptors located in the mucosal and muscle layers of the gut and extrinsic input from the parasympathetic and sympathetic nervous systems. As a general rule, the parasympathetic nervous system tends to increase the motility of the bowel, whereas sympathetic stimulation tends to slow its activity.

Disorders of Gastrointestinal Motility

- The luminal contents move down the gastrointestinal tract as a result of peristaltic movements regulated by a complex interaction of electrical, neural, and hormonal control mechanisms.
- The enteric nervous system that is incorporated into the wall of the gut controls the basic movement of the gastrointestinal tract, with input from the autonomic nervous system.
- Local irritation and the composition and constituents of gastrointestinal contents influence motility through the submucosal afferent neurons of the enteric nervous system. Gastrointestinal wall distention, chemical irritants, osmotic gradients, and bacterial toxins exert many of their effects on gastrointestinal motility through these afferent pathways.
- Autonomic influences generated by factors such as medications, trauma, and emotional experiences interact with the enteric nervous system to alter gastrointestinal motility.

The large intestine has sphincters at both ends: the ileocecal sphincter, which separates it from the small intestine, and the anal sphincter, which prevents the movement of feces to the outside of the body. About 1500 mL of fluid and undigested food normally pass through the ileocecal valve into the large intestine each day. Most of the water and electrolytes in the fluid are absorbed in the colon, usually leaving less than 100 mL to be excreted in the feces.[2] The large intestine can absorb a maximum of 5 to 8 liters of fluid and electrolytes each day. When the total amount entering the large intestine through the ileocecal valve or by way of intestinal secretion exceeds this amount, the excess appears in the feces as diarrhea.

Diarrhea

The usual definition of *diarrhea* is excessively frequent passage of stools. Diarrhea can be acute or chronic and can be caused by infectious organisms, food intolerance, drugs, or intestinal disease. In developing countries, diarrhea is a common cause of mortality among children younger than 5 years of age, with an estimated 2 million deaths annually.[45] Even though diarrheal diseases are less prevalent in the United States than in other countries, they place a burden on the health care system.

Acute Diarrhea. Acute diarrheas are predominantly caused by infectious agents and follow a self-limited course of less than 2 weeks.[46] Acute diarrhea is commonly divided into noninflammatory (large-volume) and inflammatory

(small-volume) diarrhea, based on the characteristics of the diarrheal stool. Enteric organisms cause diarrhea in several ways. Some are noninvasive and do not cause inflammation, but secrete toxins that stimulate fluid secretion.[47,48] Others invade and destroy intestinal epithelial cells, thereby altering fluid transport so that secretory activity continues while absorption activity is halted.

Noninflammatory diarrhea is associated with large-volume watery and nonbloody stools, periumbilical cramps, bloating, and nausea or vomiting. It is commonly caused by toxin-producing bacteria (e.g., enterotoxigenic *E. coli, S. aureus, Vibrio cholerae*) or other agents (e.g., viruses, *Giardia*) that disrupt the normal absorption or secretory process in the small bowel. Prominent vomiting suggests viral enteritis or *S. aureus* food poisoning. Although typically mild, diarrhea that originates in the small intestine can be voluminous and result in dehydration with hypokalemia and metabolic acidosis. Because tissue invasion and inflammation do not occur, leukocytes are not present in the feces.

Inflammatory diarrhea is usually characterized by the presence of fever and bloody diarrhea (dysentery). It is caused by invasion of intestinal cells (e.g., *Shigella, Salmonella*, *Yersinia*, and *Campylobacter*) or the toxins associated with the previously described *C. difficile* or *E. coli* O157:H7 infection. Because infections associated with these organisms predominantly affect the colon, the diarrhea is small in volume (<1 L/day) and is associated with lower abdominal pain and the urgent desire to defecate. Infectious dysentery must be distinguished from acute ulcerative colitis, which may present with bloody diarrhea, fever, and abdominal pain. Diarrhea that persists for 14 days is usually not caused by bacterial pathogens (except for *C. difficile*), and the person should be evaluated for chronic diarrhea.

Chronic Diarrhea. Diarrhea is considered to be chronic when the symptoms persist for 3 to 4 weeks in children or adults and 4 weeks in infants. Chronic diarrhea is often associated with conditions such as irritable bowel and inflammatory bowel syndromes, malabsorption disorders, endocrine disorders (hyperthyroidism, diabetic autonomic neuropathy), or radiation colitis. There are four major causes of chronic diarrhea: presence of hyperosmotic luminal contents, increased intestinal secretory processes, inflammatory conditions, and infectious processes[8] (Chart 29-1). A condition called *factitious diarrhea* is caused by indiscriminate use of laxatives or excessive intake of laxative-type foods.

In *osmotic diarrhea*, water is pulled into the bowel by the hyperosmotic nature of its luminal contents. It occurs when osmotically active particles are not absorbed. In persons with lactase deficiency, the lactose in milk cannot be broken down and absorbed. Magnesium salts, which are contained in milk of magnesia and many antacids, are poorly absorbed and cause diarrhea when taken in sufficient quantities. Another cause of osmotic diarrhea is decreased transit time, which interferes with absorption. Osmotic diarrhea usually disappears with fasting.

Secretory diarrhea occurs when the secretory processes of the bowel are increased. Secretory diarrhea also occurs when excess bile acids remain in the intestinal contents as they enter the colon. This often happens with disease processes of the ileum because bile salts are absorbed there. It also may occur with bacterial overgrowth in the small bowel, which interferes with bile absorption. Some tumors, such as those of the Zollinger-Ellison syndrome and carcinoid syndrome, produce hormones that cause increased secretory activity of the bowel.

CHART 29-1 Chronic Diarrhea

- Hyperosmotic diarrhea
  - Saline cathartics
  - Lactase deficiency
- Secretory diarrhea
  - Acute infectious diarrhea
  - Failure to absorb bile salts
  - Fat malabsorption
  - Chronic laxative abuse
  - Carcinoid syndrome
  - Zollinger-Ellison syndrome
  - Fecal impaction
- Inflammatory bowel disease
  - Crohn disease
  - Ulcerative colitis
- Infectious disease
  - Shigellosis
  - Salmonellosis
- Irritable bowel syndrome

Inflammatory diarrhea commonly is associated with acute or chronic inflammation or intrinsic disease of the colon, such as ulcerative colitis or Crohn disease. Inflammatory diarrhea usually is evidenced by frequency and urgency and colicky abdominal pain. It commonly is accompanied by tenesmus (i.e., painful straining at stool), fecal soiling of clothing, and awakening during the night with the urge to defecate.

Chronic parasitic infections may cause chronic diarrhea through a number of mechanisms. Pathogens most commonly associated with chronic diarrhea include the protozoans *Entamoeba histolytica, Giardia,* and *Cyclospora.* Immunocompromised individuals are particularly susceptible to infectious organisms such as *Cryptosporidia,* cytomegalovirus (CMV), and *Mycobacterium avium-intracellulare* complex that can cause both acute and chronic diarrhea (see Chapter 16).

Diagnosis and Treatment

The diagnosis of diarrhea is based on complaints of frequent stools and a history of accompanying factors such as concurrent illnesses, medication use, and exposure to potential intestinal pathogens. Disorders such as Crohn disease and ulcerative colitis should be considered. If the onset of diarrhea is related to travel outside the United States, the possibility of traveler's diarrhea must be considered.

Although most acute forms of diarrhea are self-limited and require no treatment, diarrhea can be particularly

serious in infants and small children, persons with other illnesses, and the elderly. Thus, the replacement of fluids and electrolytes is considered to be a primary therapeutic goal in the treatment of diarrhea. Oral replacement therapy (ORT) can be used in situations of uncomplicated diarrhea that can be treated at home. First applied to the treatment of diarrhea in developing countries, ORT can be regarded as a case of reverse technology, in which the protocols originally implemented in these countries have changed health care practices in industrialized countries as well.[45] Complete ORT solutions contain carbohydrate, sodium, potassium, chloride, and base to replace that lost in the diarrheal stool.[45,49] Commonly used beverages such as apple juice and cola drinks, which have increased osmolarity because of their high carbohydrate and low electrolyte content, are not recommended. The effectiveness of ORT is based on the coupled transport of sodium and glucose or other actively transported small organic molecules. ORT can be particularly effective in treating dehydration associated with diarrheal diseases in infants and small children. Children who are severely dehydrated with changes in vital signs or mental status require emergency intravenous fluid resuscitation. After initial treatment with intravenous fluids, these children can be given ORT.

Evidence suggests that feeding should be continued during diarrheal illness, particularly in children.[49] Starch and simple proteins are thought to provide cotransport molecules with little osmotic activity, increasing fluid and electrolyte uptake by intestinal cells. The luminal contents associated with early refeeding are also known to contain growth factor for enterocytes and help facilitate repair after injury. It is recommended that children who require rehydration therapy because of diarrhea be fed an age-appropriate diet. Although there is little agreement on which foods are best, fatty foods and foods high in simple sugars are best avoided. Almost all infants with acute gastroenteritis can tolerate breast-feeding. For formula-fed infants, diluted formula does not provide an advantage over full-strength formula.

Drugs used in the treatment of diarrhea include diphenoxylate (Lomotil) and loperamide (Imodium), which are opium-like drugs. These drugs decrease gastrointestinal motility and stimulate water and electrolyte absorption. Adsorbents, such as kaolin and pectin, adsorb irritants and toxins in the bowel. These ingredients are included in many over-the-counter antidiarrheal preparations because they adsorb toxins responsible for certain types of diarrhea. Antidiarrheal medications should not be used in persons with bloody diarrhea, high fever, or signs of toxicity because of the risk of worsening the disease. Antibiotics should be reserved for use in persons with identified enteric pathogens.

Constipation

Constipation can be defined as the infrequent or difficult passage of stools.[50–52] The difficulty with this definition arises from the many individual variations of function that are normal. What is considered normal for one person (e.g., two or three bowel movements per week) may be considered evidence of constipation by another. Constipation can occur as a primary disorder of intestinal motility, as a side effect of drugs, as a problem associated with another disease condition, or as a symptom of obstructing lesions of the gastrointestinal tract. Some common causes of constipation are failure to respond to the urge to defecate, inadequate fiber in the diet, inadequate fluid intake, weakness of the abdominal muscles, inactivity and bed rest, pregnancy, and hemorrhoids.

The pathophysiology of constipation can be classified into three broad categories: normal-transit constipation, slow-transit constipation, and disorders of defecation. Normal-transit constipation (or functional constipation) is characterized by perceived difficulty in defecation and usually responds to increased fluid and fiber intake. Slow-transit constipation, which is characterized by infrequent bowel movements, is often caused by alterations in intestinal innervation. *Hirschsprung* disease is an extreme form of slow-transit constipation in which the ganglion cells in the distal bowel are absent because of a defect that occurred during embryonic development; the bowel narrows at the area that lacks ganglionic cells. Although most persons with this disorder present in infancy or early childhood, some with a relatively short segment of involved colon do not have symptoms until later in life. Defecatory disorders are most commonly due to dysfunction of the pelvic floor or anal sphincter.

Diseases associated with chronic constipation include neurologic diseases such as spinal cord injury, Parkinson disease, and multiple sclerosis; endocrine disorders such as hypothyroidism; and obstructive lesions in the gastrointestinal tract. Drugs such as narcotics, anticholinergic agents, calcium channel blockers, diuretics, calcium (antacids and supplements), iron supplements, and aluminum antacids tend to cause constipation. Elderly people with long-standing constipation may develop dilation of the rectum, colon, or both. This condition allows large amounts of stool to accumulate with little or no sensation. Constipation, in the context of a change in bowel habits, may be a sign of colorectal cancer.

Diagnosis of constipation usually is based on a history of infrequent stools, straining with defecation, the passing of hard and lumpy stools, or the sense of incomplete evacuation with defecation. Rectal examination is used to determine whether fecal impaction, anal stricture, or rectal masses are present. Constipation as a sign of another disease condition should be ruled out. Tests that measure colon transit time and defecatory function are reserved for refractory cases.

The treatment of constipation usually is directed toward relieving the cause. A conscious effort should be made to respond to the defecation urge. A time should be set aside after a meal, when mass movements in the colon are most likely to occur, for a bowel movement. Adequate fluid intake and bulk in the diet should be encouraged. Moderate exercise is essential, and persons on bed rest benefit from passive and active exercises. Laxatives and enemas should be used judiciously. They should not be used on a regular basis to treat simple constipation because they interfere with the defecation reflex and actually may damage the rectal mucosa.

Acute Intestinal Obstruction

Intestinal obstruction designates impaired movement of intestinal contents in a cephalocaudad direction. The condition can be acute or chronic and may affect the small intestine or colon. In contrast to chronic obstructions, which often involve the colon and may last for weeks or months, acute obstructions usually present as severe disorders of the small intestine that are potentially lethal if not recognized early.[53] Acute intestinal obstruction can be mechanical or nonmechanical, resulting from paralytic obstruction of the ileus.

Mechanical obstruction can result from a number of conditions, intrinsic or extrinsic, that encroach on the patency of the bowel lumen (Fig. 29-11). Major inciting causes include an external hernia (i.e., inguinal, femoral, or umbilical) and postoperative adhesions.[54,55] Less common causes are strictures, tumors, foreign bodies, intussusception, and volvulus. *Intussusception* involves the telescoping of bowel into the adjacent segment (Figs. 29-11A and 29-12). It is the most common cause of intestinal obstruction in children younger than 2 years of age.[55] The most common form is intussusception of the terminal ileum into the right colon, but other areas of the bowel may be involved. In most cases, the cause of the disorder is unknown. The condition can also occur in adults when an intraluminal mass or tumor acts as a traction force and pulls the segment along as it telescopes into the distal segment. *Volvulus* refers to a complete twisting of the bowel on an axis formed by its mesentery (see Fig. 29-11B). It can occur in any portion of the gastrointestinal tract, but most commonly involves the cecum, followed by the sigmoid colon. Mechanical bowel obstruction may be a simple obstruction, in which there is no alteration in blood flow, or a strangulated obstruction, in which there is impairment of blood flow and necrosis of bowel tissue.

FIGURE 29-12. Intussusception. A cross-section through the area of the obstruction shows "telescoped" small intestine surround by dilated small intestine. (From Mitos F.A., Rubin E. [2008]. The gastrointestinal tract. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathophysiology: Clinicopathologic foundations of medicine* [5th ed., p. 586]. Philadelphia: Lippincott Williams & Wilkins.)

Paralytic, or adynamic, obstruction of the ileus results from neurogenic or muscular impairment of peristalsis. Paralytic ileus is seen most commonly after abdominal surgery. It also accompanies inflammatory conditions of the abdomen, intestinal ischemia, pelvic fractures, and back

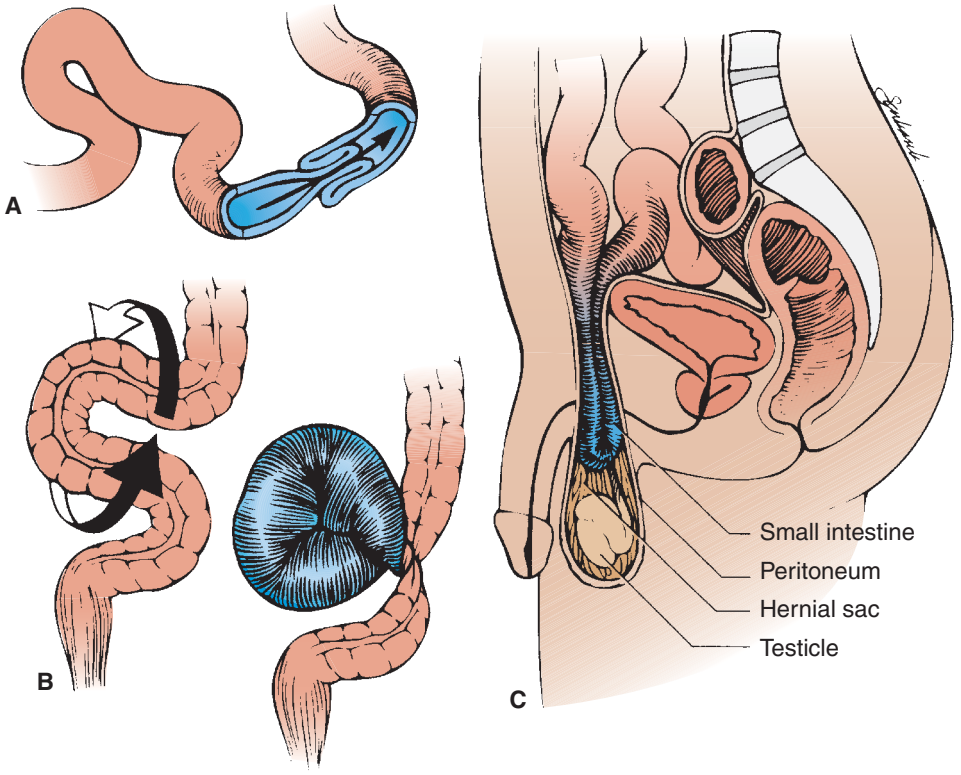


FIGURE 29-11. Three causes of intestinal obstruction. **(A)** Intussusception with invagination or shortening of the bowel caused by movement of one segment of the bowel into another. **(B)** Volvulus of the sigmoid colon; the twist is counterclockwise in most cases. Note the edematous section of bowel. **(C)** Hernia (inguinal). The sac of the hernia is a continuation of the peritoneum of the abdomen. The hernial contents are intestine, omentum, or other abdominal contents that pass through the hernial opening into the hernial sac. (From Smeltzer S.C., Bare B.G. [2004] *Brunner and Suddarth's textbook of medical-surgical nursing* [10th ed., p. 1055]. Philadelphia: Lippincott Williams & Wilkins.)

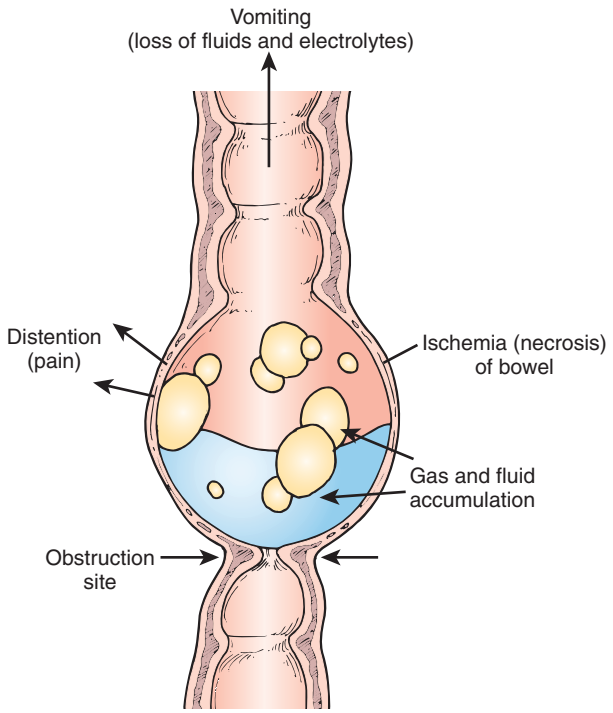


FIGURE 29-13. Pathophysiology of intestinal obstruction.

injuries. It occurs early in the course of peritonitis and can result from chemical irritation caused by bile, bacterial toxins, electrolyte imbalances as in hypokalemia, and vascular insufficiency.

The major effects of intestinal obstruction are abdominal distention and loss of fluids and electrolytes (Fig. 29-13). Distention is further aggravated by the accumulation of gases and fluid proximal to the site of obstruction. Approximately 70% to 80% of these gases are derived from swallowed air, and because this air is composed mainly of nitrogen, it is poorly absorbed from the intestinal lumen. As the process continues, the distention moves proximally (i.e., toward the mouth), involving additional segments of bowel. Either form of obstruction eventually may lead to strangulation (i.e., interruption of blood flow), gangrenous changes in the bowel wall, and, ultimately, perforation of the bowel. The increased pressure in the intestine tends to compromise mucosal blood flow, leading to necrosis and movement of blood into the luminal fluids. This promotes rapid growth of bacteria, especially anaerobes that grow rapidly in this favorable environment and produce a lethal endotoxin.[54]

The manifestations of intestinal obstruction depend on the degree of obstruction and its duration. The cardinal symptoms of acute intestinal obstruction are pain, absolute constipation, abdominal distention, and vomiting. With mechanical obstruction, the pain is severe and colicky, in contrast with the continuous pain and silent abdomen of paralytic ileus. There also is borborygmus (i.e., rumbling sounds made by propulsion of gas in the intestine); audible, high-pitched peristalsis; and peristaltic rushes. Visible peristalsis may appear along the course of the distended intestine. Extreme restlessness and conscious awareness of intestinal movements are experienced along with weakness, perspiration, and anxiety. Should strangulation of the bowel occur, there is a change in symptoms. The character of the pain shifts from the intermittent colicky pain caused by the hyperperistaltic movements of the intestine to a severe and steady type of pain. Vomiting and fluid and electrolyte disorders occur with both types of obstruction.

Diagnosis of intestinal obstruction usually is based on history and physical findings. Plain film radiography of the abdomen may be used to detect the presence of a gas-filled bowel. CT scans and ultrasonography may also be used to detect the presence of mechanical obstruction. Treatment depends on the cause and type of obstruction. Most cases of adynamic obstruction respond to decompression of the bowel through nasogastric suction and correction of fluid and electrolyte imbalances. Strangulation and complete bowel obstruction require surgical intervention.

Peritonitis

Peritonitis is an inflammatory response of the serous membrane that lines the abdominal cavity and covers the visceral organs.[6,54] It can be caused by bacterial invasion or chemical irritation. Most commonly, enteric bacteria enter the peritoneum because of a break in the wall of one of the abdominal organs. The most common causes of peritonitis are perforated peptic ulcer, ruptured appendix, perforated diverticulum, gangrenous bowel, pelvic inflammatory disease, and gangrenous gallbladder. Other causes are abdominal trauma and wounds.

The peritoneum has several characteristics that increase its vulnerability to or protect it from the effects of peritonitis. One weakness of the peritoneal cavity is that it is a large, unbroken space that favors the dissemination of contaminants. For the same reason, it has a large surface that permits rapid absorption of bacterial toxins into the blood. The peritoneum is particularly well adapted for producing an inflammatory response as a means of controlling infection. It tends, for example, to exude a thick, sticky, and fibrinous substance that adheres to other structures, such as the mesentery and omentum, as a means of sealing off the perforation and localizing the process. Localization is enhanced by sympathetic stimulation that limits intestinal motility. Although the diminished or absent peristalsis that occurs tends to give rise to associated problems, it does inhibit the movement of contaminants throughout the peritoneal cavity.

The onset of peritonitis may be acute, as with a ruptured appendix, or it may have a more gradual onset, as occurs in pelvic inflammatory disease. Pain and tenderness are common symptoms. The pain usually is more intense over the inflamed area. The person with peritonitis usually lies still because any movement aggravates the pain. Breathing often is shallow to prevent movement of the abdominal muscles. The abdomen usually is rigid and sometimes described as boardlike because of reflex muscle guarding. Vomiting is also common. Fever, an elevated white blood cell count, tachycardia, and hypotension are common. Paralytic ileus occurs shortly after the onset of widespread peritonitis and is accompanied by abdominal

distention. One of the most important manifestations of peritonitis is the translocation of extracellular fluid into the peritoneal cavity and into the bowel as a result of bowel obstruction. Nausea and vomiting cause further losses of fluid. The fluid loss may encourage development of hypovolemia and shock.

Treatment measures for peritonitis are directed toward preventing the extension of the inflammatory response, correcting the fluid and electrolyte imbalances that develop, and minimizing the effects of paralytic ileus and abdominal distention. Oral fluids are forbidden. Nasogastric suction, which entails the insertion of a tube placed through the nose into the stomach or intestine, is used to decompress the bowel and relieve the abdominal distention. Fluid and electrolyte replacement is essential. These fluids are prescribed on the basis of frequent blood chemistry determinations. Antibiotics are given to combat infection. Narcotics often are needed for pain relief. Surgical intervention may be needed to remove an acutely inflamed appendix or close the opening in a perforated peptic ulcer.

Disorders of Intestinal Absorption

Malabsorption is the failure to transport dietary constituents, such as fats, carbohydrates, proteins, vitamins, and minerals, from the lumen of the intestine into the extracellular fluid compartment for transport to the various parts of the body. It can selectively affect a single component, such as vitamin B_{12} or lactose, or its effects can extend to all the substances absorbed in a specific segment of the intestine.[7,8] When one segment of the intestine is affected, another may compensate. For example, the ileum may compensate for malabsorption in the proximal small intestine by absorbing substantial amounts of fats, carbohydrates, and amino acids. Similarly, the colon, which normally absorbs water, sodium, chloride, and bicarbonate, can compensate for small intestine malabsorption by absorbing additional end products of bacterial carbohydrate metabolism.

The conditions that impair one or more steps involved in digestion and absorption of nutrients can be divided into three broad categories: intraluminal maldigestion, disorders of transepithelial transport, and lymphatic obstruction. Intraluminal maldigestion involves a defect in processing of nutrients in the intestinal lumen. The most common causes are pancreatic insufficiency, hepatobiliary disease, and intraluminal bacterial growth. Disorders of transepithelial transport are caused by mucosal lesions that impair uptake and transport of available intraluminal nutrients across the mucosal surface of the intestine. They include disorders such as celiac disease and Crohn disease. Lymphatic obstruction interferes with the transport of the products of fat digestion to the systemic circulation after they have been absorbed by the intestinal mucosa. The process can be interrupted by congenital defects, neoplasms, trauma, and selected infectious diseases.

Malabsorption Syndrome

Persons with intestinal malabsorption usually have symptoms directly referable to the gastrointestinal tract that include diarrhea, steatorrhea, flatulence, bloating, abdominal pain, and cramps. Weakness, muscle wasting, weight loss, and abdominal distention often are present. Weight loss often occurs despite normal or excessive caloric intake. Steatorrheic stools contain excess fat. The fat content causes bulky, yellow-gray, malodorous stools.

Along with loss of fat in the stools, there is failure to absorb the fat-soluble vitamins. This can lead to easy bruising and bleeding (i.e., vitamin K deficiency), bone pain, a predisposition to the development of fractures and tetany (i.e., vitamin D and calcium deficiency), macrocytic anemia, and glossitis (i.e., folic acid deficiency). Neuropathy, atrophy of the skin, and peripheral edema may be present. Table 29-2 describes the signs and symptoms of impaired absorption of dietary constituents.

Celiac Disease

Celiac disease, also known as *celiac sprue* and *gluten-sensitive enteropathy,* is an immune-mediated disorder triggered by ingestion of gluten-containing grains (including wheat, barley, and rye).[56–59] Until recently, celiac disease was considered to be a rare malabsorption syndrome that manifested during early childhood, but today it is known to be one of the most common genetic diseases, with a mean prevalence of 1% in the general population. The disease is recognized not only in Europe and in countries populated by persons of European ancestry, but also in the Middle East, Asia, South America, and North Africa.

The disease results from an inappropriate T-cell–mediated immune response against the gliadin fraction of gluten contained in the diet of genetically predisposed people. Almost all persons with the disorder share the major histocompatibility complex class II allele HLA-DQ2 or HLA-DQ8. Several non-HLA genes that may influence susceptibility to the disease have been identified, but their role has not been confirmed. Persons with the disease have increased levels of antibodies to a variety of antigens, including transglutaminase, endomysium, and gliadin. The resultant immune response produces an intense inflammatory reaction that results in loss of absorptive villi from the small intestine. When the resulting lesions are extensive, they may impair absorption of macronutrients (i.e., proteins, carbohydrates, fats) and micronutrients (i.e., vitamins and minerals). Small-bowel involvement is most prominent in the proximal part of the small intestine, where the exposure to gluten is greatest.

There are a number of populations who are at higher risk for celiac disease. These include persons with type 1 diabetes mellitus, other autoimmune endocrine disorders such as autoimmune thyroid disorders and Addison disease, first- and second-degree relatives of persons with celiac disease, and individuals with Turner syndrome.[57] Various malignancies also appear to be a direct result of celiac disease, in that the increased incidence seen in persons with celiac disease returns to that of the general population after several years of a gluten-free diet. These malignancies include head and neck squamous cell carcinoma, small intestinal adenocarcinoma, and non-Hodgkin lymphoma.

TABLE 29-2 Sites of and Requirements for Absorption of Dietary Constituents and Manifestations of Malabsorption

Dietary Constituent	Site of Absorption	Requirements	Manifestations
Water and electrolytes	Mainly small bowel	Osmotic gradient	Diarrhea Dehydration Cramps
Fat	Upper jejunum	Pancreatic lipase Bile salts Functioning lymphatic channels	Weight loss Steatorrhea Fat-soluble vitamin deficiency
Carbohydrates			
Starch	Small intestine	Amylase Maltase Isomaltase α-dextrins	Diarrhea Flatulence Abdominal discomfort
Sucrose	Small intestine	Sucrase	
Lactose	Small intestine	Lactase	
Maltose	Small intestine	Maltase	
Fructose	Small intestine		
Protein	Small intestine	Pancreatic enzymes (e.g., trypsin, chymotrypsin, elastin)	Loss of muscle mass Weakness Edema
Vitamins			
A	Upper jejunum	Bile salts	Night blindness Dry eyes Corneal irritation
Folic acid	Duodenum and jejunum	Absorptive; may be impaired by some drugs (i.e., anticonvulsants)	Cheilosis Glossitis Megaloblastic anemia
B_{12}	Ileum	Intrinsic factor	Glossitis Neuropathy Megaloblastic anemia
D	Upper jejunum	Bile salts	Bone pain Fractures Tetany
E	Upper jejunum	Bile salts	Uncertain
K	Upper jejunum	Bile salts	Easy bruising and bleeding
Calcium	Duodenum	Vitamin D and parathyroid hormone	Bone pain Fractures Tetany
Iron	Duodenum and jejunum	Normal pH (hydrochloric acid secretion)	Iron-deficiency anemia Glossitis

The clinical manifestations of celiac disease vary greatly according to age group.[56,58] Infants and young children generally present with diarrhea, abdominal distention, failure to thrive, and, occasionally, severe malnutrition. Beyond infancy, the manifestations tend to be less dramatic. Older children may present with anemia, constitutional short stature, dental enamel defects, and constipation. Among adults, women constitute about 75% of newly diagnosed cases of celiac disease. The classic presentation in adults is diarrhea, which may be accompanied by abdominal pain or discomfort. It has been observed that fewer persons with celiac disease are presenting with the so-called "classic manifestations" of the disease. While diarrhea is still the most frequent mode of presentation, others include iron deficiency, osteoporosis, and recognition of mucosal changes in persons undergoing endoscopy for esophageal reflux or dyspepsia.[58] A prior diagnosis of irritable bowel is common.[56,58]

The diagnosis of celiac disease is based on clinical manifestations and confirmed by serologic tests and intestinal biopsy. Based on very high sensitivities, the best available tests are the immunoglobulin (Ig) A antihuman tissue transglutaminase (TTG) and IgA endomysial antibody immunofluorescence (EMA) tests.[56] Biopsies of the proximal small bowel are indicated in persons with a positive celiac disease antibody test. Usually, additional laboratory tests are done to determine if the disorder has resulted in nutritional disorders such as iron-deficiency anemia.

The primary treatment of celiac disease consists of removal of gluten and related proteins from the diet. Gluten is the primary protein in wheat, barley, and rye. Oat products, which are nontoxic, may be contaminated with wheat during processing. Many gluten-free types of bread, cereals, cookies, and other products are available.[59] Meats, vegetables, fruits, and dairy products are free of gluten as long as they are not contaminated during processing. Complete exclusion of dietary gluten generally results in rapid and complete healing of the intestinal mucosa.

Colorectal Neoplasms

Adenomatous Polyps

Adenomatous polyps (adenomas) are benign neoplasms that arise from the mucosal epithelium of the intestine. They are composed of neoplastic cells that have proliferated in excess of those needed to replace the cells that normally are shed from the mucosal surface. The most common and clinically important neoplastic polyps are colonic adenomas that are precursors in the majority of colorectal adenocarcinomas.

Adenomas can range in size from a barely visible nodule to a large, sessile mass. They can be classified as tubular, villous, or tubulovillous adenomas. *Tubular adenomas,* which constitute approximately 65% of benign large bowel adenomas, typically are smooth-surfaced spheres, usually less than 2 cm in diameter, that are attached to the mucosal surface by a stalk.[7] Although most tubular adenomas display little epithelial dysplasia, approximately 20% show a range of dysplastic changes, from mild nuclear changes to frank invasive carcinoma. *Villous adenomas* constitute 10% of adenomas of the colon.[7] They are found predominantly in the rectosigmoid colon. They typically are broad-based, elevated lesions, with a shaggy, cauliflower-like surface. In contrast to tubular adenomas, villous adenomas are more likely to contain malignant cells. When invasive carcinoma develops, there is no stalk to isolate the tumor and invasion is directly into the wall of the colon. *Tubulovillous adenomas* manifest both tubular and villous architecture. They are intermediate between tubular and villous adenomas in terms of invasive carcinoma risk.

The pathogenesis of adenoma formation involves neoplastic alterations in the replication of the colonic crypt cells (Fig. 29-14). There may be diminished apoptosis (see Chapter 2), persistence of cell replication, and failure of cell maturation and differentiation of the cells that migrate to the surface of the crypts. Normally, DNA synthesis ceases as the cells reach the upper two thirds of the crypts, after which they mature, migrate to the surface, and become senescent. They then become apoptotic and are shed from the surface.[7] Adenomas arise from a disruption in this sequence, such that the epithelial cells retain their proliferative ability throughout the entire length of the crypt. Aberrations in cell differentiation can lead to dysplasia and progression to the development of invasive adenocarcinoma.

Colorectal Cancer

Adenocarcinoma of the colon is the most common malignancy of the gastrointestinal tract and is the major cause of morbidity and mortality worldwide.[60,61] It affects approximately 150,000 Americans annually, approximately one third of whom die.[60] It affects approximately 250,000 persons annually in Europe and approximately 1 million persons worldwide.

Epidemiology. The incidence of colorectal cancer peaks at age 60 to 70 years of age, and fewer than 20% of cases occur before age 50.[7] Its incidence is increased among persons with a family history of cancer, persons with Crohn disease or ulcerative colitis, and those with familial adenomatous polyposis of the colon. Persons with a familial risk—those who have two or more first- or second-degree relatives (or both) with colorectal cancer—make up approximately 20% of all persons with colorectal cancer.[62] Familial adenomatous polyposis is a rare autosomal dominant trait linked to a mutation in the long arm of chromosome 5. Persons with the disorder develop multiple adenomatous polyps of the colon at an early age.[7] Carcinoma of the colon is inevitable, often by 40 years of age, unless a total colectomy is performed.

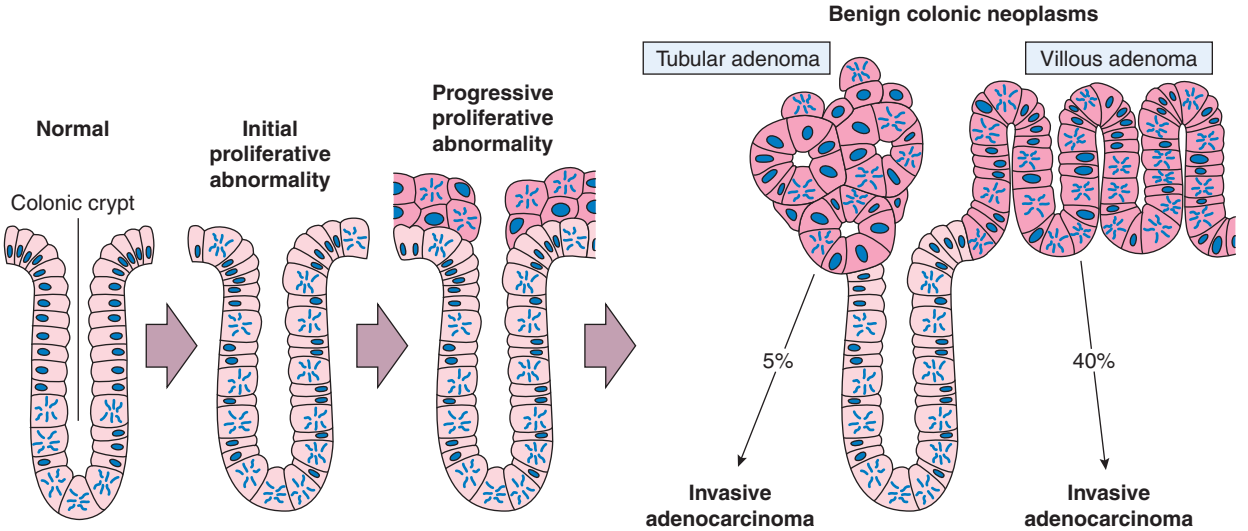


FIGURE 29-14. The histogenesis of adenomatous polyps of the colon. The initial proliferative abnormality of the colonic mucosa, the extension of the mitotic zone in the crypts, leads to accumulation of mucosal cells. The formation of adenomas may reflect epithelial–mesenchymal interactions. (From Mitos F.A., Rubin E. [2008]. The gastrointestinal tract. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathophysiology: Clinicopathologic foundations of medicine* [5th ed., p. 604]. Philadelphia: Lippincott Williams & Wilkins.)

Diet also is thought to play a role.[7] Attention has focused on dietary fat intake, refined sugar intake, fiber intake, and the adequacy of such protective micronutrients as vitamins A, C, and E in the diet. It has been hypothesized that a high level of fat in the diet increases the synthesis of bile acids in the liver, which may be converted to potential carcinogens by the bacterial flora in the colon. Bacterial organisms in particular are suspected of converting bile acids to carcinogens; their proliferation is enhanced by a high dietary level of refined sugars. Dietary fiber is thought to increase stool bulk and thereby dilute and remove potential carcinogens. Refined diets often contain reduced amounts of vitamins A, C, and E, which may act as oxygen free radical scavengers.

In addition to dietary modification, pharmacologic chemoprevention has become an area of great interest. Several studies indicate that aspirin or other NSAIDs may protect against colorectal cancer.[63] An analysis of the incidence of colorectal cancer in the Nurses' Health Study showed a decreased incidence of colorectal cancer among women who took four to six aspirins per week.[64] Although the mechanism of aspirin's action is unknown, it may be related to its effect on the synthesis of prostaglandins, one or more of which may be involved in signal systems that influence cell proliferation or tumor growth. Aspirin inhibits cyclooxygenase, the enzyme that catalyzes the conversion of arachidonic acid in cell membranes to prostaglandins. One form of cyclooxygenase, COX-2, promotes inflammation and cell proliferation, and colorectal cancers often overexpress this enzyme.

Clinical Features. Cancer of the colon is usually present for a long time before it produces symptoms.[60,61] Bleeding is a highly significant early symptom and usually is the one that causes persons to seek medical care. Other symptoms include a change in bowel habits, diarrhea or constipation, and sometimes a sense of urgency or incomplete emptying of the bowel. Pain usually is a late symptom.

Cancer of the colon may be detected with a high degree of reliability with barium enema or colonoscopy. Colonoscopy permits biopsy for pathologic confirmation. CT scans, pelvic magnetic resonance imaging (MRI), and ultrasonography may be used to determine the extent of the lesions and whether metastasis has occurred.

The only recognized treatment for cancer of the colon and rectum is surgical removal.[65] Preoperative radiation therapy may be used and has in some cases demonstrated increased 5-year survival rates. Postoperative adjuvant chemotherapy may be used. Radiation therapy and chemotherapy are used as palliative treatment methods.

The prognosis for persons with colorectal cancer depends largely on the stage of the cancer. Colorectal cancer commonly is classified into four TNM (tumor, node, and metastasis) stages.[65] In this system, a stage I tumor is limited to invasion of the mucosal and submucosal layers of the colon and has a 5-year survival rate of 90% to 100%. Stage IV (metastatic) tumors penetrate the serosa or adjacent organs and have a much poorer prognosis.

Screening. The single most important prognostic indicator of colorectal cancer is the extent (stage) of the tumor at the time of diagnosis. The challenge, therefore, is to discover the tumors at their earliest stages. Among the methods used for early detection of colorectal cancers are the digital rectal examination and the fecal occult blood test, usually done during routine physical examinations; x-ray studies using barium (e.g., barium enema); and flexible sigmoidoscopy and colonoscopy.[60,61]

Almost all cancers of the colon and rectum bleed intermittently, although the amount of blood is small and usually not apparent in the stools. It therefore is feasible to screen for colorectal cancers using commercially prepared tests for occult blood in the stool. The sensitivity of fecal occult blood tests is improved by performing stool tests on three different occasions. Digital rectal examinations are most helpful in detecting neoplasms of the rectum. Rectal examination should be considered a routine part of a good physical examination. Flexible sigmoidoscopy involves examination of the rectum and sigmoid colon with a hollow, lighted tube that is inserted through the rectum. The procedure is performed without sedation and is well tolerated. Approximately 40% of cancers and polyps are out of the reach of the sigmoidoscope, emphasizing the need for fecal occult blood tests. Polyps can be removed or tissue can be obtained for biopsy during the procedure.

Colonoscopy provides a means for direct visualization of the rectum and colon. The colonoscope consists of a flexible, 4-cm–diameter glass fiber bundle that contains approximately 250,000 glass fibers and has a lens at either end to focus and magnify the image. Light from an external source is transmitted by the fiberoptic viewing bundle. Instruments are available that afford direct examination of the sigmoid colon or the entire colon. This method is used for screening persons at high risk for development of cancer of the colon (e.g., those with ulcerative colitis) and for those with symptoms. Colonoscopy also is useful for obtaining a biopsy and for removing polyps. Although this method is one of the most accurate for detecting early colorectal cancers, it is not suitable for mass screening because it is expensive and time consuming and must be done by a person who is highly trained in the use of the instrument.

It is recommended that persons at average risk for colonic adenomatous polyps or cancer should undergo colonoscopy every 10 years or alternative screening tests at periodically prescribed intervals beginning at age 50.[61] Persons who are members of high-risk groups, such as those with a family history of adenomatous polyps or disorders that predispose to colon cancer (e.g., ulcerative colitis), should undergo periodic surveillance more frequently.

In summary, disorders of the small and large intestines include irritable bowel syndrome, inflammatory bowel disease, infectious enterocolitis, diverticular disease, appendicitis, disorders of motility (i.e., diarrhea, constipation, and intestinal obstruction), peritonitis, alterations in intestinal absorption, and colorectal cancer.

Irritable bowel syndrome is a functional disorder characterized by a variable combination of chronic and recurrent intestinal symptoms not explained by structural or biochemical abnormalities. The term *inflammatory bowel disease* is used to designate two inflammatory conditions: Crohn disease, which affects the small and large bowel, and ulcerative colitis, which affects the colon and rectum. Both are chronic diseases characterized by remissions and exacerbations of diarrhea, weight loss, fluid and electrolyte disorders, and systemic signs of inflammation.

Infectious forms of enterocolitis include viral (e.g., rotavirus) and bacterial (e.g., *C. difficile* and *E. coli* O157:H7) infections. Diverticular disease includes diverticulosis, which is a condition in which the mucosa and submucosa of the colon herniate through the muscularis layer, and diverticulitis, in which there is inflammation and gross or microscopic perforation of the diverticulum.

Diarrhea and constipation represent disorders of intestinal motility. Diarrhea is characterized by excessively frequent passage of stools. It can be acute or chronic and can be caused by infectious organisms, food intolerance, drugs, or intestinal disease. Acute diarrheas are predominantly caused by infectious agents and follow a self-limited course. Chronic diarrhea persists beyond 3 to 4 weeks and is caused by the presence of hyperosmotic luminal contents, increased intestinal secretory processes, inflammatory conditions, and infectious processes. Constipation can be defined as the infrequent passage of stools; it commonly is caused by failure to respond to the urge to defecate, inadequate fiber or fluid intake, weakness of the abdominal muscles, inactivity and bed rest, pregnancy, hemorrhoids, and gastrointestinal disease. Intestinal obstruction designates impairment in movement of intestinal contents as the result of mechanical or paralytic mechanisms. Peritonitis is an inflammatory response of the serous membrane that lines the abdominal cavity and covers the visceral organs. It can be caused by bacterial invasion or chemical irritation resulting from perforation of the viscera or abdominal organs.

Malabsorption results from the impaired absorption of nutrients and other dietary constituents from the intestine. It can involve a single dietary constituent, such as vitamin B_{12}, or extend to involve all of the substances absorbed in a particular part of the small intestine. Malabsorption can result from diseases of the small bowel and disorders that impair digestion and, in some cases, obstruction of lymph flow can interefere with the transport of fats into the general circulation. Celiac disease is an immune-mediated disorder triggered by ingestion of gluten-containing grains (including wheat, barley, and rye).

Colorectal cancer, the second most common fatal cancer, is seen most commonly in persons older than 50 years of age. Most, if not all, cancers of the colon and rectum arise in preexisting adenomatous polyps. Programs that provide careful follow-up for persons with adenomatous polyps and removal of all suspect lesions have substantially reduced the incidence of colorectal cancer.

REVIEW EXERCISES

1. A 40-year-old man reports to his health care provider complaining of "heartburn" that occurs after eating and also wakens him at night. He is overweight, admits to enjoying fatty foods, and usually lies down on the sofa and watches TV after dinner. He also complains that lately he has been having a cough and some wheezing. A diagnosis of GERD was made.

A. Explain the cause of heartburn and why it becomes worse after eating.
B. Persons with GERD are advised to lose weight, avoid eating fatty foods, remain sitting after eating, and sleep with their head slightly elevated. Explain the possible relationship between these situations and the occurrence of reflux.
C. Explain the possible relationship between GERD and the respiratory symptoms this man is having.

2. A 36-year-old woman who has been taking aspirin for back pain experiences a sudden episode of tachycardia and feeling faint, accompanied by the vomiting of a coffee-ground emesis and the passing of a tarry stool. She relates that she has not had any signs of a "stomach ulcer" such as pain or heartburn.

A. Relate the mucosal protective effects of prostaglandins to the development of peptic ulcer associated with aspirin or NSAID use.
B. Explain the apparent suddenness of the bleeding and the fact that the woman did not experience pain as a warning signal.
C. Among the results of her initial laboratory tests is an elevated blood urea nitrogen (BUN) level. Explain the reason for the elevated BUN.

3. A 29-year-old woman has been diagnosed with Crohn disease. Her medical history reveals that she began having symptoms of the disease at 24 years of age and that her mother died of complications of the disease at 54 years of age. She complains of diarrhea and chronic cramping abdominal pain.

A. Define the term *inflammatory bowel disease* and compare the pathophysiologic processes and manifestations of Crohn disease and ulcerative colitis.
B. Describe the possible association between genetic and environmental factors in the pathogenesis of Crohn disease.
C. Relate the use of the monoclonal antibody infliximab to the pathogenesis of the inflammatory lesions that occur in Crohn disease.

REFERENCES

1. Everhart J.F. (2008). *The burden of digestive diseases in the United States*. National Institute of Diabetes and Digestive Diseases. NIH publication no. 09-6443. [Online] Available: http://www3.niddk.nih.gov/Burden_of_Digestive_Diseases/index.shtml#Foreword/. Accessed July 21, 2009.
2. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 782–786, 817). Philadelphia: Elsevier Saunders.
3. Epstein R.K., Balaban D.H. (1997). The esophagogastric junction. *New England Journal of Medicine* 336(13), 924–932.
4. Saud B.M., Szyjkowski R. (2004). A diagnostic approach to dysphagia. *Gastroenterology* 6, 525–546.
5. Spieker M.R. (2000). Evaluating dysphagia. *American Family Physician* 61, 3639–3648.
6. Turner J.R. (2010). The gastrointestinal tract. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 763–831). Philadelphia: Saunders Elsevier.
7. Mitos F.A., Rubin E. (2008). The gastrointestinal tract. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathophysiology: Clinicopathologic foundations of medicine* (5th ed., pp. 557–576, 727–746). Philadelphia: Lippincott Williams & Wilkins.
8. McQuaid K.R. (2009). Gastrointestinal disorders. In McPhee S.J., Papadakis M. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 487–581). New York: McGraw-Hill.
9. Richter J.E. (2007). The many manifestations of gastrointestinal reflux disease: Presentation, evaluation, and treatment. *Gastroenterology Clinics of North America* 37, 577–599.
10. Cappell M.S. (2005). Clinical presentation, diagnosis, and management of gastroesophageal reflux disease. *Medical Clinics of North America* 84, 1137–1161.
11. Spechler S.J. (2002). Barrett's esophagus. *New England Journal of Medicine* 346, 836–842.
12. Mason D.B. (2000). Gastroesophageal reflux in children. *Nursing Clinics of North America* 35, 15–36.
13. Hassall E. (2005). Decisions in diagnosis and managing chronic gastroesophageal reflux disease in children. *Journal of Pediatrics* 146, S3–S12.
14. Gold B.D. (2005). Asthma and gastroesophageal reflux disease in children: Exploring the relationship. *Journal of Pediatrics* 146, S13–S20.
15. Enzinger P.C., Mayer R.J. (2003). Esophageal cancer. *New England Journal of Medicine* 349, 2241–2252.
16. Fromm D. (1987). Mechanisms involved in gastric mucosal resistance to injury. *Annual Review of Medicine* 38, 119.
17. Wolfe M.M., Lichtenstein D.R., Singh G. (1999). Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *New England Journal of Medicine* 340, 1888–1899.
18. Suerbaum S., Michetti P. (2002). *Helicobacter pylori* infections. *New England Journal of Medicine* 347, 1175–1186.
19. Vilaichone R-K., Mahachai V., Graham D.Y. (2006). *Helicobacter pylori* diagnosis and management. *Gastroenterology Clinics of North America* 35, 229–247.
20. Saad R.J., Scheiman J.M. (2004). Diagnosis and management of peptic ulcer disease. *Clinics in Family Practice* 6, 569–587.
21. Ramakrishnan K., Salinas R.C. (2007). Peptic ulcer disease. *American Family Physician* 76, 1005–1012.
22. Fass R. (1995). Zollinger-Ellison syndrome: Diagnosis and management. *Hospital Practice* 30(11), 73–80.
23. Ali T., Harty R.F. (2009). Stress-induced ulcer bleeding in critically ill patients. *Gastroenterology Clinics of North America* 38, 245–265.
24. Spirit M.J., Starily S. (2006). Update on stress ulcer prophylaxis in critically ill patients. *Critical Care Nurse* 26(1), 18–29.
25. Layke J.C., Lopez P.P. (2004). Gastric cancer: Diagnosis and treatment options. *American Family Physician* 69, 1133–1146.
26. Videlock E.J., Chang L. (2007). Irritable bowel syndrome: Current approach to symptoms, evaluation, and treatment. *Gastroenterology Clinics of North America* 36, 665–685.
27. Olden K.W. (2003). Irritable bowel syndrome: An overview of diagnosis and pharmacologic treatment. *Cleveland Clinic Journal of Medicine* 70(Suppl 2), S3–S17.
28. Hadley S.K., Gaarder S.M. (2005). Treatment of irritable bowel syndrome. *American Family Physician* 72, 2501–2506.
29. Podolsky D.K. (2002). Inflammatory bowel disease. *New England Journal of Medicine* 347, 417–429.
30. Thoreson R., Cullen J.J. (2007). Pathophysiology of inflammatory bowel disease: An overview. *Surgical Clinics of North America* 87, 575–585.
31. Bamias G., Nyce M.R., DeLaRue S.A., et al. (2005). New concepts of inflammatory bowel disease. *Annals of Internal Medicine* 143, 895–904.
32. Knutson D., Greenberg G., Cronau H. (2003). Management of Crohn's disease: A practical approach. *American Family Physician* 68, 707–714.
33. Kornbluth A., Sachar D.B. (2004). Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *American Journal of Gastroenterology* 99, 1371–1385.
34. Bass D.M. (2007). Rotaviruses, caliciviruses, and astroviruses. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1399–1401). Philadelphia: Saunders Elsevier.
35. Shatsky M. (2006). Rotavirus vaccine, live, oral, pentavalent (RotaTeq) for prevention of rotavirus gastroenteritis. *American Family Physician* 74, 1014–1016.
36. Mylonakis E., Ryan E.T., Claderswood S.B. (2001). *Clostridium difficile*-associated diarrhea: A review. *Archives of Internal Medicine* 161, 525–533.
37. Schroeder M.S. (2005). *Clostridium difficile*–associated diarrhea. *American Family Physician* 71, 921–928.
38. Tarr P.I., Neil M.A. (2001). *Escherichia coli* O157:H7. *Gastroenterology Clinics of North America* 30, 735–751.
39. Razzaq S. (2006). Hemolytic uremic syndrome. *American Family Physician* 74, 991–996.
40. Moake J.L. (2002). Thrombotic microangiopathies. *New England Journal of Medicine* 347, 589–600.
41. Stollman N., Raskin J.B. (2004). Diverticular disease of the colon. *Lancet* 363, 631–639.
42. Salzman H., Lillie D. (2005). Diverticular disease: Diagnosis and treatment. *American Family Physician* 72, 1229–1234.
43. Jacobs D.O. (2007). Diverticulitis. *New England Journal of Medicine* 357(20), 2057–2066.
44. Paulson E.K., Kalady M.F., Pappas T.N. (2003). Suspected appendicitis. *New England Journal of Medicine* 348, 236–242.
45. King C.K., Glass R., Brewer J.S., et al. (2003). Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *Morbidity and Mortality Weekly Report* 52(RR-16), 1–16.
46. Schiller L.R. (2000). Diarrhea. *Medical Clinics of North America* 84, 1259–1275.
47. Field M., Rao M.C., Chang E.B. (1989). Intestinal electrolyte transport and diarrheal disease (part 2). *New England Journal of Medicine* 321, 879–883.
48. Field M. (2003). Intestinal ion transport and the pathophysiology of diarrhea. *Journal of Clinical Investigation* 111, 931–943.
49. Dennehy P.H. (2005). Acute diarrheal disease in children: Epidemiology, prevention, treatment. *Infectious Disease Clinics* 19, 585–602.
50. Wald A. (2006). Constipation in the primary care setting. *American Journal of Medicine* 119, 736–739.

51. Hsieh C. (2005). Treatment of constipation in older adults. *American Family Physician* 72, 2277–2285.
52. Lembo A., Camilleri M. (2003). Chronic constipation. *New England Journal of Medicine* 349, 1360–1368.
53. Ramano S., Bartone G., Romano L. (2008). Ischemia and infarction of the intestine related to obstruction. *Radiology Clinics of North America* 46, 925–942.
54. Silen W. (2005). Acute intestinal obstruction, acute appendicitis, and peritonitis. In Kasper D.L., Braunwald E., Fauci A.S., et al. (Eds.), *Harrison's principles of internal medicine* (16th ed., pp. 1803–1808). New York: McGraw-Hill.
55. Wyllie R. (2004). Ileus, adhesions, intussusception, and closed-loop obstruction. In Berman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 1241–1243). Philadelphia: Elsevier Saunders.
56. Green P.H.R., Cellier C. (2007). Celiac disease. *New England Journal of Medicine* 357(17), 1731–1743.
57. Alaedini A., Green P.H.R. (2005). Narrative review: Celiac disease: Understanding a complex autoimmune disorder. *Annals of Internal Medicine* 142, 289–298.
58. Green P.H.R., Jabri B. (2006). Celiac disease. *Annual Review of Medicine* 57, 207–221.
59. Niewinski M.M. (2008). Advances in celiac disease and gluten-free diet. *Journal American Dietetic Association* 108, 661–672.
60. Cappell M.S. (2007). Pathophysiology, clinical presentation, and management of colon cancer. *Gastroenterology Clinics of North America* 37, 1–24.
61. Cappell M.S. (2005). The pathology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps. *Medical Clinics of North America* 89, 1–43.
62. Guttmacher A.E., de la Chapelle A. (2003). Hereditary colorectal cancer. *New England Journal of Medicine* 348, 919–932.
63. Chan A.T., Ogino S., Fuchs C.S. (2007). Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *New England Journal of Medicine* 356, 2131–2142.
64. Pasi J.A., Mayer R.J. (2000). Chemoprevention of colorectal cancer. *New England Journal of Medicine* 342, 1960–1966.
65. Rugo H.S. (2009). Cancer. In McPhee S.J., Papadakis M. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 1448–1455). New York: McGraw-Hill.

The Liver and Hepatobiliary System
Physiologic Functions of the Liver
Metabolic Functions
Bile Formation and Flow
Bilirubin Formation and Jaundice
Cholestasis
Tests of Hepatobiliary Function
Disorders of Hepatic and Biliary Function
Hepatitis
Viral Hepatitis
Autoimmune Hepatitis
Acute Fulminant Hepatitis
Intrahepatic Biliary Disorders
Primary Biliary Cirrhosis
Secondary Biliary Cirrhosis
Drug- and Alcohol-Induced Liver Disease
Drug Metabolism
Drug-Induced Liver Disease
Alcohol Metabolism
Alcohol-Induced Liver Disease
Nonalcoholic Fatty Liver Disease
Hepatic Syndromes
Cirrhosis
Portal Hypertension
Liver Failure
Cancer of the Liver
Primary Liver Cancers
Metastatic Tumors
Disorders of the Gallbladder and Exocrine Pancreas
Disorders of the Gallbladder
Cholelithiasis
Acute Cholecystitis
Chronic Cholecystitis
Diagnosis and Treatment of Gallbladder Disease
Choledocholithiasis and Cholangitis
Cancer of the Gallbladder
Disorders of the Exocrine Pancreas
Acute Pancreatitis
Chronic Pancreatitis
Cancer of the Pancreas

Chapter 30

Disorders of Hepatobiliary and Exocrine Pancreas Function

The liver, the gallbladder, and the exocrine pancreas are classified as accessory organs of the gastrointestinal tract. The liver produces and the gallbladder stores bile that is involved in the digestion of fats, and the exocrine pancreas secretes enzymes that are involved in the digestion of carbohydrates and proteins. In addition to producing digestive secretions, the liver and the pancreas have other metabolic functions. The liver plays an important role in the uptake, storage, and distribution of both nutrients and vitamins; synthesis of plasma proteins; and degradation and elimination of drugs and toxins. The endocrine pancreas functions in concert with the liver in controlling blood glucose levels and providing the nutrients needed for cell metabolism (Chapter 33). This chapter is divided into two parts: the first focuses on functions and disorders of the liver, and the second on disorders of the gallbladder, biliary tract, and pancreas.

The Liver and Hepatobiliary System

The liver is the largest visceral organ in the body, weighing approximately 1.5 kg (3.3 lb) in the adult.[1,2] It is located below the diaphragm and occupies much of the right hypochondrium (Fig. 30-1). The liver is anatomically divided into two large lobes (the right and left lobes) and two smaller lobes (the caudate and quadrate lobes). Except for the portion that is in the epigastric area, the liver is contained within the rib cage and cannot normally be palpated in healthy persons. With the exception of areas where the liver attaches to the diaphragm, the liver is completely enveloped by peritoneum, which forms a simple visceral covering for its fibrous tissue capsule (*Glisson capsule*). The liver is unusual in that its connective fibrous tissue components

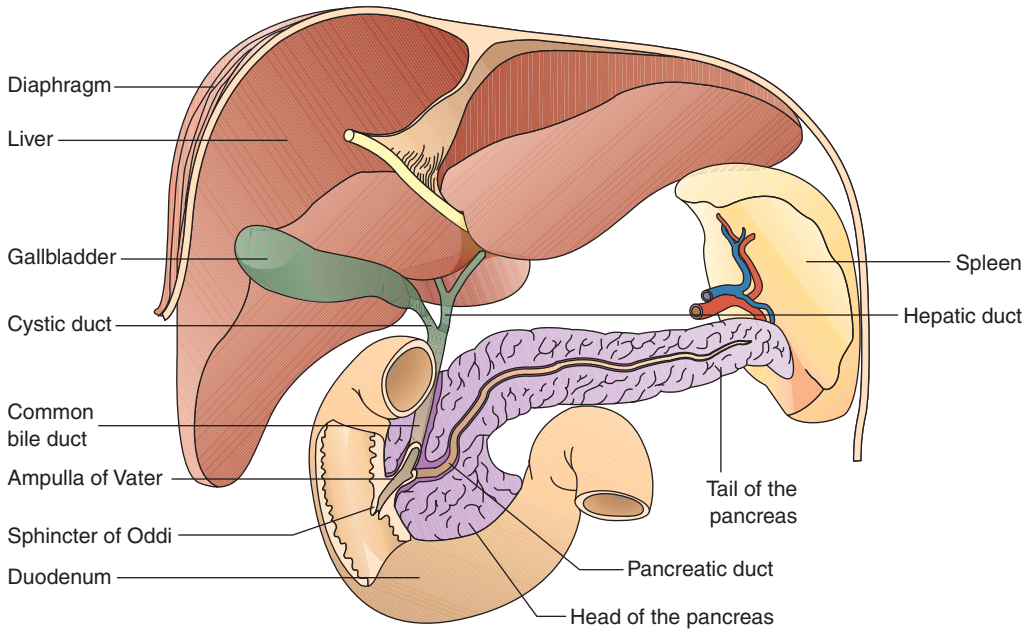


FIGURE 30-1. The liver and biliary system, including the gallbladder and bile ducts.

are normally sparse, with the bulk of its structure composed of uniform parenchymal cells, the *hepatocytes*.

The liver is unique among the abdominal organs in having a dual blood supply consisting of a venous (portal) supply through the hepatic portal vein and an arterial supply through the hepatic artery. Approximately 300 mL of blood per minute enters the liver through the hepatic artery; another 1050 mL/minute enters by way of the valveless portal vein.[1] The venous blood delivered by the hepatic portal vein comes from the digestive tract and major abdominal organs, including the pancreas and spleen (Fig. 30-2). The portal blood supply carries nutrient

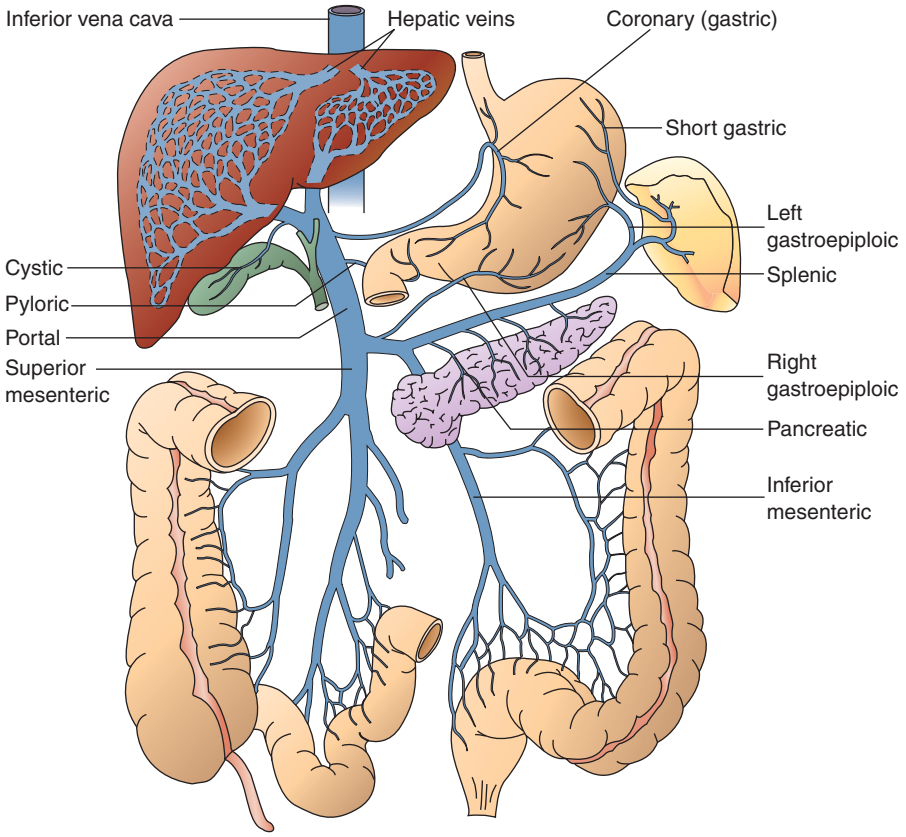


FIGURE 30-2. The portal circulation. Blood from the gastrointestinal tract, spleen, and pancreas travels to the liver through the portal vein before moving into the vena cava for return to the heart.

and toxic materials absorbed in the intestine, blood cells and their breakdown products from the spleen, and insulin and glucagon from the pancreas. Although the blood from the portal vein is incompletely saturated with oxygen, it supplies approximately 60% to 70% of the oxygen needs of the liver. The venous outflow from the liver is carried by the valveless hepatic veins, which empty into the inferior vena cava just below the level of the diaphragm. The pressure difference between the hepatic vein and the portal vein normally is such that the liver stores approximately 450 mL of blood.[1] This blood can be shifted back into the general circulation during periods of hypovolemia and shock. In right heart failure in which the pressure in the vena cava increases, blood backs up and accumulates in the liver.

The *lobules* are the functional units of the liver. The classic lobule consists of stacks of anastomosing plates of hepatocytes one cell thick.[2] Each lobule is organized around a central vein that empties into the hepatic veins and from there into the vena cava. The terminal bile ducts and small branches of the portal vein and hepatic artery are located at the periphery of the lobule. Plates of hepatic cells radiate centrifugally from the central vein like spokes on a wheel (Fig. 30-3). These hepatic plates are separated by wide, thin-walled vascular channels, called hepatic *sinusoids,* that extend from the periphery of the lobule to its central vein. The sinusoids are supplied by blood from the portal vein and hepatic artery. The sinusoids are in intimate contact with the hepatocytes and provide for the exchange of substances between the blood and liver cells.

The hepatic sinusoids are lined with two types of cells: the typical capillary endothelial cells and Kupffer cells. *Kupffer cells* (also called *reticuloendothelial cells*) are large resident macrophages, which are capable of removing and phagocytizing old and defective blood cells, bacteria, and other foreign material from the portal blood as it flows through the sinusoid. This phagocytic action removes enteric bacilli and other harmful substances that filter into the blood from the intestine.

The lobules also are supplied by small tubular channels, called *bile canaliculi,* which lie between the cell membranes of adjacent hepatocytes. The bile that is produced by the hepatocytes flows into the canaliculi and then to the periphery of the lobules, draining into progressively larger ducts, until it reaches the right and left hepatic ducts. The intrahepatic and extrahepatic bile ducts often are collectively referred to as the *hepatobiliary tree.* These ducts unite to form the bile duct (also called the common bile duct) (see Fig. 30-1). The common bile duct, which is approximately 10 to 15 cm long, descends and passes behind the pancreas and enters the descending duodenum. The pancreatic duct joins the bile duct at a short dilated tube called the *hepatopancreatic ampulla* (also called *ampulla of Vater*), which empties into the duodenum through the duodenal papilla. Muscle tissue at the junction of the papilla, sometimes called the *sphincter of Oddi,* regulates the flow of bile into the duodenum. When this sphincter is closed, bile moves back into the common duct and gallbladder.

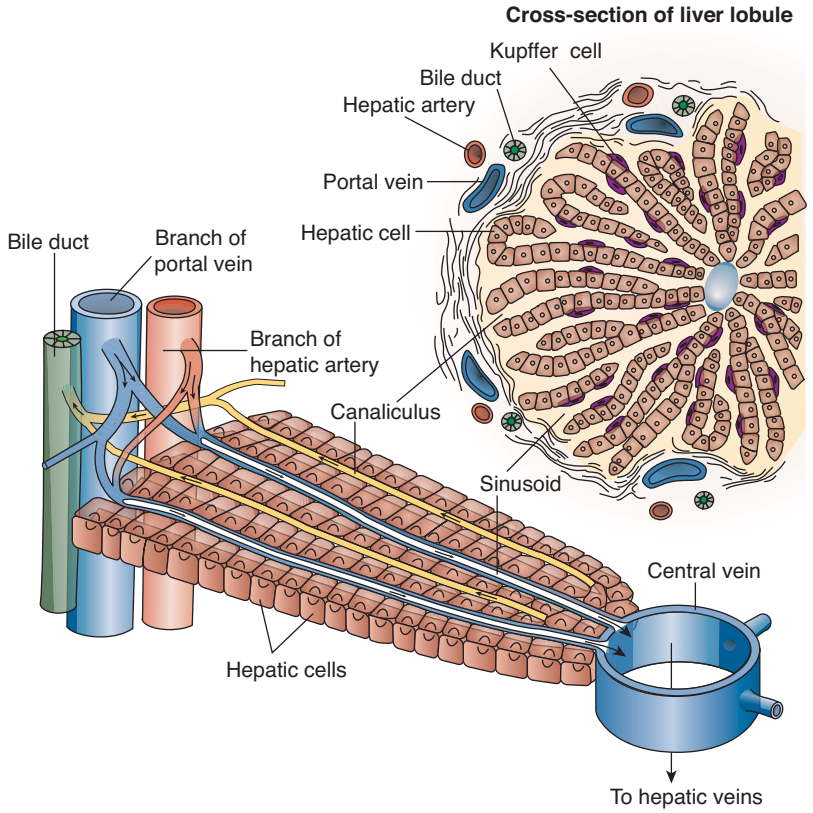


FIGURE 30-3. A section of liver lobule showing the location of the hepatic veins, hepatic cells, liver sinusoids, and branches of the portal vein and hepatic artery.

Physiologic Functions of the Liver

The liver is one of the most versatile and active organs in the body. It produces bile, metabolizes hormones and drugs, synthesizes plasma proteins and blood clotting factors, stores vitamins and minerals, maintains blood glucose levels, and regulates very–low-density lipoprotein (VLDL) levels. In its capacity for metabolizing drugs and hormones, the liver serves as an excretory organ. In this respect, the bile, which carries the end products of substances metabolized by the liver, is much like the urine, which carries the body wastes filtered by the kidneys. These functions, many of which are disrupted by the liver diseases discussed in this chapter, are summarized in Table 30-1.

Metabolic Functions

The liver is involved in many metabolic pathways including carbohydrate metabolism and maintenance of blood glucose, lipid metabolism, and protein synthesis and conversion of ammonia to urea. In addition to nutrients, several vitamins (e.g., A, D, K) are also taken up from the bloodstream and then stored or biochemically converted in the liver.

Carbohydrate Metabolism. The liver plays an essential role in carbohydrate metabolism and glucose homeostasis (Fig. 30-4A). It stores excess glucose as glycogen and synthesizes glucose from amino acids and other substrates as a means of maintaining blood glucose during periods of fasting or increased need. The liver also converts excess carbohydrates to triglycerides for storage in adipose tissue.

Pathways of Lipid Metabolism. Although most cells of the body metabolize fat, certain aspects of lipid metabolism occur mainly in the liver. These include the oxidation of free fatty acids to ketoacids; synthesis of cholesterol, phospholipids, and lipoproteins; and formation of triglycerides from carbohydrates and proteins (Fig. 30-4B). To derive energy from neutral fats (triglycerides), the molecule must first be split into glycerol and fatty acids, and then the fatty acids split into two-carbon acetyl-coenzyme A (acetyl-CoA units). Acetyl-CoA is readily channeled into the citric acid cycle to produce adenosine triphosphate ([ATP], see Chapter 1, Understanding Cell Metabolism). Because the liver cannot use all the acetyl-CoA that is formed, it converts the excess into acetoacetic acid, a highly soluble keto acid that is released into the bloodstream and transported to other tissues, where it is used for energy. The acetyl-CoA derived from fat metabolism is also used to synthesize cholesterol and bile acids. Cholesterol has several fates in the liver. It can be esterified and stored, exported bound to VLDLs, or converted to bile acids.

TABLE 30-1 Functions of the Liver and Manifestations of Altered Function

Function	Manifestations of Altered Function
Production of bile salts	Malabsorption of fat and fat-soluble vitamins
Elimination of bilirubin	Elevation in serum bilirubin and jaundice
Metabolism of steroid hormones	
Sex hormones	Disturbances in gonadal function, including gynecomastia in the male
Glucocorticoids	Signs of increased cortisol levels (i.e., Cushing syndrome)
Aldosterone	Signs of hyperaldosteronism (e.g., sodium retention and hypokalemia)
Metabolism of drugs	Decreased drug metabolism
	Decreased plasma binding of drugs owing to a decrease in albumin production
Carbohydrate metabolism	Hypoglycemia may develop when glycogenolysis and gluconeogenesis are impaired
Stores glycogen and synthesizes glucose from amino acids, lactic acid, and glycerol	Abnormal glucose tolerance curve may occur because of impaired uptake and release of glucose by the liver
Fat metabolism	
Formation of lipoproteins	Impaired synthesis of lipoproteins
Conversion of carbohydrates and proteins to fat	
Synthesis, recycling, and elimination of cholesterol	Altered cholesterol levels
Formation of ketones from fatty acid	
Protein metabolism	
Deamination of proteins	
Formation of urea from ammonia	Elevated blood ammonia levels
Synthesis of plasma proteins	Decreased levels of plasma proteins, particularly albumin, which contributes to edema formation
Synthesis of clotting factors (fibrinogen, prothrombin, factors V, VII, IX, X)	Bleeding tendency
Storage of minerals and vitamins	Signs of deficiency of fat-soluble and other vitamins that are stored in the liver
Filtration of blood and removal of bacteria and particulate matter by Kupffer cells	Increased exposure of the body to colonic bacteria and other foreign matter

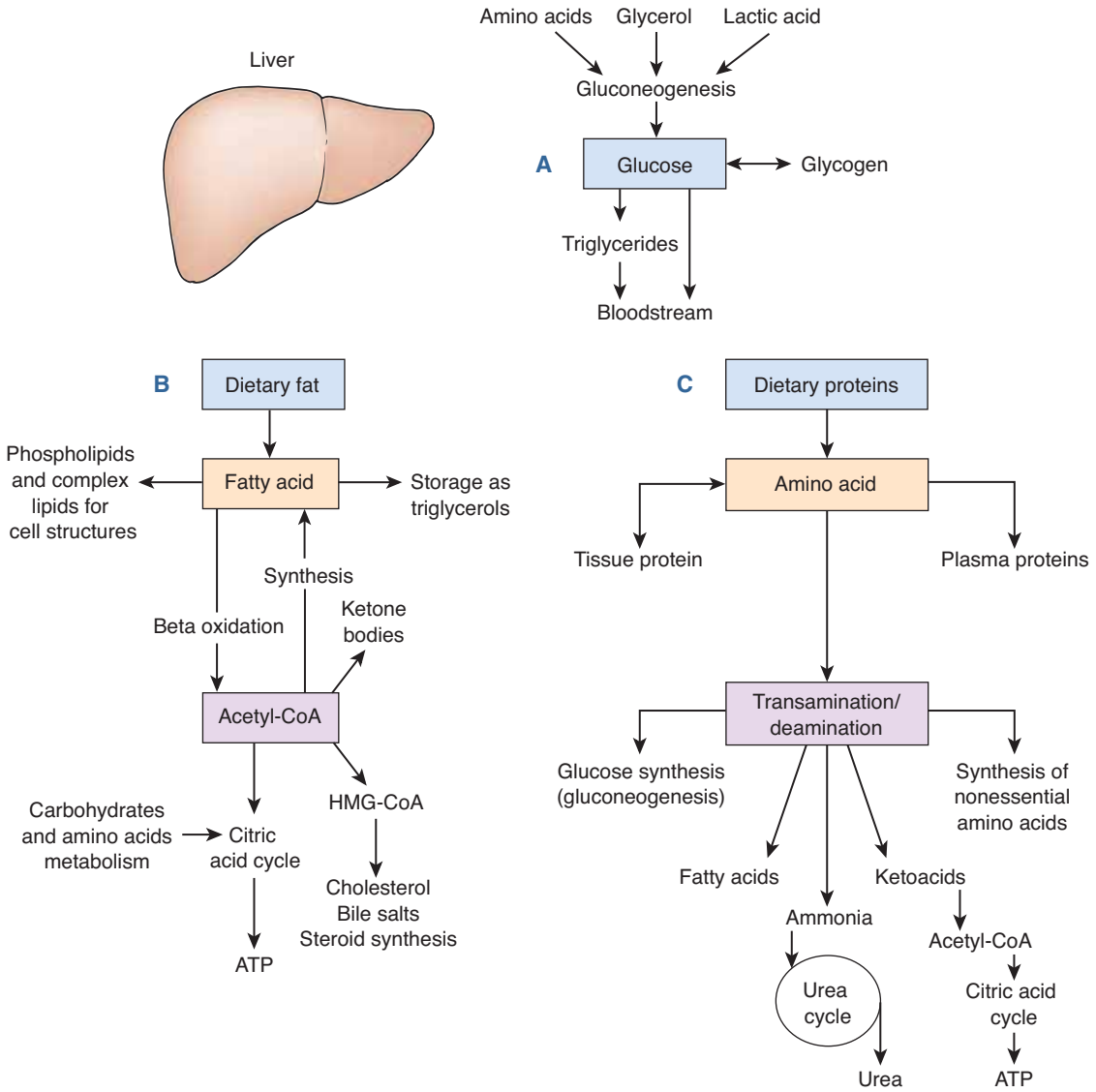


FIGURE 30-4. Hepatic pathways for **(A)** glucose metabolism, **(B)** lipid metabolism, and **(C)** protein metabolism and conversion of ammonia to urea.

Protein Synthesis and Conversion of Ammonia to Urea. In addition to its role in carbohydrate and lipid metabolism, the liver is also an important site for protein synthesis and degradation. It produces proteins for its own cellular needs, as well as secretory proteins (e.g., plasma proteins, fibrinogen, and coagulation factors) that are released into the circulation. One of the most important of these secretory proteins is albumin. Albumin contributes significantly to the plasma colloidal osmotic pressure (see Chapter 8) and to the binding and transport of numerous substances such as hormones, fatty acids, and bilirubin.

Proteins are made up of amino acids. Protein synthesis and degradation involves two major reactions: transamination and deamination[1] (Fig. 30-4C). In *transamination*, an amino group (NH_2) is transferred to an acceptor substance. As a result of transamination, amino acids can participate in the intermediary metabolism of carbohydrates and lipids. During periods of fasting or starvation, amino acids are used for producing glucose (i.e., gluconeogenesis). Most of the nonessential amino acids are synthesized in the liver by transamination.

The process of transamination is catalyzed by *aminotransferases*, enzymes that are found in high amounts in the liver. Oxidative *deamination* involves the removal of the amino groups from amino acids and conversion of amino acids to ketoacids and ammonia. This occurs mainly by transamination, in which the amino groups are removed and then transferred to another acceptor substance. The acceptor substance can then transfer the amino group to still another substance or release it as ammonia. Because ammonia is very toxic to body tissues, particularly neurons, the ammonia that is released during the deamination process is rapidly removed from the blood by the liver and converted to urea. Essentially all urea formed in the body is synthesized by the urea cycle in the liver and then excreted by the kidneys.

Although urea is mostly excreted by the kidneys, some diffuses into the intestine, where it is converted to ammonia by enteric bacteria. The intestinal production of ammonia also results from bacterial deamination of unabsorbed amino acids and proteins derived from the diet, exfoliated cells, or blood in the gastrointestinal tract. Ammonia produced in the intestine is absorbed into the portal circulation and transported to the liver, where it is converted to urea before being released into the systemic circulation. Intestinal production of ammonia is increased after ingestion of high-protein foods and gastrointestinal bleeding, a process that becomes impaired in persons with advanced liver disease.

Bile Formation and Flow

The secretion of bile is essential for digestion of dietary fats and absorption of fats and fat-soluble vitamins from the intestine. The liver produces approximately 600 to 1200 mL of yellow-green bile daily.[1] Bile contains water, bile salts, bilirubin, cholesterol, and certain by-products of metabolism. Of these, only bile salts, which are formed from cholesterol, are important in digestion. The other components of bile depend on the secretion of sodium, chloride, bicarbonate, and potassium by the bile ducts.

Bile salts serve an important function in digestion; they aid in emulsifying dietary fats, and they are necessary for the formation of the micelles that transport fatty acids and fat-soluble vitamins to the surface of the intestinal mucosa for absorption. Approximately 94% of bile salts that enter the intestine are reabsorbed into the portal circulation by an active transport process that takes place in the distal ileum. From the portal circulation, the bile salts move into the liver cells and are recycled. Normally, bile salts travel this entire circuit approximately 18 times before being expelled in the feces.[1] This system for recirculation of bile is called the *enterohepatic circulation.*

Bilirubin Formation and Jaundice

Bilirubin is the substance that gives bile its color. It is formed from senescent red blood cells. In the process of degradation, the hemoglobin from the red blood cell is broken down to form biliverdin, which is rapidly converted to free bilirubin (Fig. 30-5). Free bilirubin, which is insoluble in plasma, is transported in the blood attached to plasma albumin. Even when it is bound to albumin, this bilirubin is still called *free bilirubin,* to distinguish it from conjugated bilirubin. As it passes through the liver, free bilirubin is absorbed through the hepatocytes' cell membrane and released from its albumin carrier molecule. Once inside the hepatocytes, free bilirubin is converted to conjugated bilirubin, making it soluble in bile. Conjugated bilirubin is secreted as a constituent of bile, and in this form it passes through the bile ducts into the small intestine. In the intestine, approximately one half of the bilirubin is converted into a highly soluble substance called *urobilinogen* by the intestinal flora. Urobilinogen is either absorbed into the portal circulation or excreted in the feces. Most of the urobilinogen that is absorbed is returned to the liver

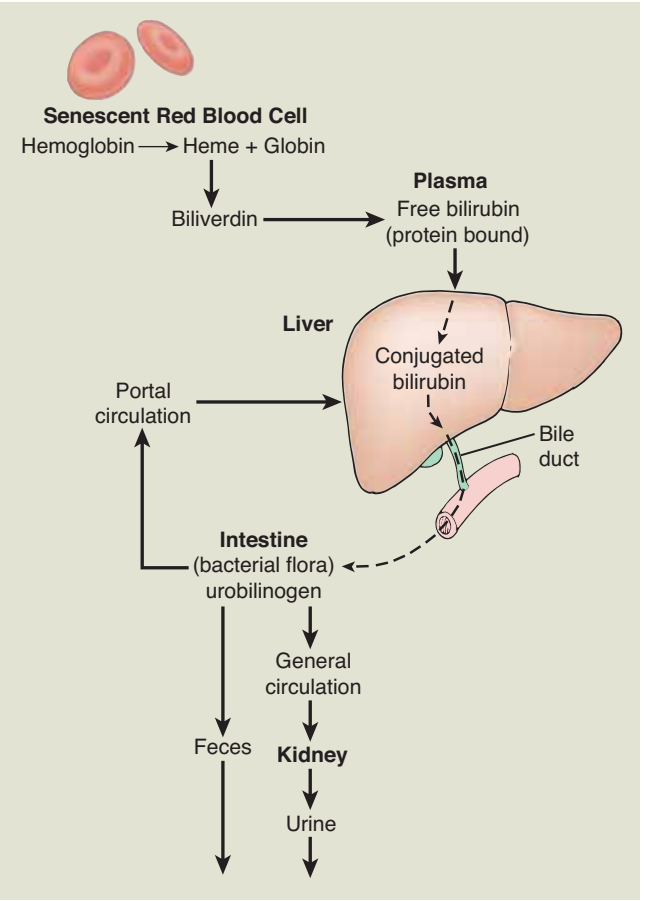


FIGURE 30-5. The process of bilirubin formation, circulation, and elimination.

to be reexcreted into the bile. A small amount of urobilinogen, approximately 5%, is absorbed into the general circulation and then excreted by the kidneys.

Usually, only a small amount of bilirubin is found in the blood; the normal level of total serum bilirubin is 0.1 to 1.2 mg/dL (2 to 21 μmol/L).[3] Laboratory measurements of bilirubin usually measure the free and the conjugated bilirubin as well as the total bilirubin. These are reported as the direct (conjugated) bilirubin and the indirect (unconjugated or free) bilirubin.

Jaundice. Jaundice (i.e., icterus) is a yellowish discoloration of the skin and deep tissues resulting from abnormally high levels of bilirubin in the blood. Jaundice becomes evident when the serum bilirubin levels rise above 2 to 2.5 mg/dL (34.2 to 42.8 μmol).[3,4] Because normal skin has a yellow cast, the early signs of jaundice often are difficult to detect, especially in persons with dark skin. Bilirubin has a special affinity for elastic tissue. The sclera of the eye, which contains a high proportion of elastic fibers, usually is one of the first structures in which jaundice can be detected (Fig. 30-6).

The four major causes of jaundice are excessive destruction of red blood cells, impaired uptake of bilirubin by the liver cells, decreased conjugation of bilirubin, and obstruction of bile flow in the canaliculi of the hepatic

FIGURE 30-6. Jaundice in a person with hepatitis A. (From Centers for Disease Control and Prevention. [2008]. Public Health Image Library. [Online] Available: http://phil.cdc.gov/phil/ home.asp.)

lobules or in the intrahepatic or extrahepatic bile ducts. From an anatomic standpoint, jaundice can be categorized as prehepatic, intrahepatic, and posthepatic. Chart 30-1 lists the common causes of prehepatic, hepatic, and posthepatic jaundice.

The major cause of *prehepatic jaundice* is excessive hemolysis of red blood cells. Hemolytic jaundice occurs when red blood cells are destroyed at a rate in excess of the liver's ability to remove the bilirubin from the blood. It may follow a hemolytic blood transfusion reaction or may occur in diseases such as hereditary spherocytosis, in which the red cell membranes are defective, or in hemolytic disease of the newborn. In prehepatic jaundice, there is mild jaundice, the unconjugated bilirubin is elevated, the stools are of normal color, and there is no bilirubin in the urine. Because the hepatic mechanisms for conjugating and excreting bilirubin are not fully mature during the first 2 weeks of life, many newborn infants develop a transient and mild unconjugated hyperbilirubinemia, termed *neonatal* or *physiologic jaundice of the newborn*.[3] Abnormally high or sustained levels of unconjugated bilirubin are abnormal, however, and require investigation and treatment (see Chapter 13).

CHART 30-1 Causes of Jaundice

Prehepatic (Excessive Red Blood Cell Destruction)
- Hemolytic blood transfusion reaction
- Hereditary disorders of the red blood cell
  - Sickle cell disease
  - Thalassemia
  - Spherocytosis
- Acquired hemolytic disorders
- Hemolytic disease of the newborn
- Autoimmune hemolytic anemias

Intrahepatic
- Decreased bilirubin uptake by the liver
- Decreased conjugation of bilirubin
- Hepatocellular liver damage
  - Hepatitis
  - Cirrhosis
  - Cancer of the liver
- Drug-induced cholestasis

Posthepatic (Obstruction of Bile Flow)
- Structural disorders of the bile duct
- Cholelithiasis
- Congenital atresia of the extrahepatic bile ducts
- Bile duct obstruction caused by tumors

Intrahepatic or *hepatocellular jaundice* is caused by disorders that directly affect the ability of the liver to remove bilirubin from the blood or conjugate it so it can be eliminated in the bile. Conjugation of bilirubin is impaired whenever liver cells are damaged, when transport of bilirubin into liver cells becomes deficient, or when the enzymes needed to conjugate the bile are lacking. Liver diseases such as hepatitis and cirrhosis are the most common causes of intrahepatic jaundice. Drugs such as the anesthetic agent halothane, oral contraceptives, estrogen, anabolic steroids, isoniazid, and chlorpromazine may also be implicated in this type of jaundice. Intrahepatic or hepatocellular jaundice usually interferes with all phases of bilirubin metabolism—uptake, conjugation, and excretion. Both conjugated bilirubin and unconjugated bilirubin are elevated, the urine often is dark because of bilirubin in the urine, and the serum alkaline phosphatase is slightly elevated. Gilbert syndrome is a relatively common, benign, inherited condition that results in a reduced removal of bilirubin from the blood. Affected persons have no symptoms other than a slightly elevated unconjugated bilirubin and mild jaundice.

Posthepatic or *obstructive jaundice*, also called *cholestatic jaundice,* occurs when bile flow is obstructed between the liver and the intestine, with the obstruction located at any point between the junction of the right or left hepatic duct and the point where the bile duct opens into the intestine. Among the causes are strictures of the bile duct, gallstones, and tumors of the bile duct or the pancreas. Conjugated bilirubin levels usually are elevated, the stools are clay colored because of the lack of bilirubin in the bile, the urine is dark, the levels of serum alkaline phosphatase are markedly elevated, and the aminotransferase levels are slightly increased. Blood levels of bile acids often are elevated in obstructive jaundice. As the bile acids accumulate in the blood, pruritus develops. A history of pruritus preceding jaundice is common in obstructive jaundice.

Cholestasis

Cholestasis represents a pathologic condition of impaired bile formation and bile flow, leading to accumulation of bile pigment in the parenchymal tissues of the liver. As a result, materials normally transferred to the bile, including bilirubin, cholesterol, and bile acids, accumulate in the blood.[3,4] The condition may be caused by intrinsic liver disease, in which case it is referred to as *intrahepatic*

cholestasis, or by obstruction of the large bile ducts, a condition known as *extrahepatic cholestasis.*

A number of mechanisms are implicated in the pathogenesis of cholestasis. Primary biliary cirrhosis and primary sclerosing cholangitis are caused by disorders of the small intrahepatic canaliculi and bile ducts. In the case of extrahepatic obstruction, which can be caused by conditions such as cholelithiasis, common duct strictures, or obstructing neoplasms, the effects begin with increased pressure in the large bile ducts. Genetic disorders involving the transport of bile into the canaliculi also can result in cholestasis.

The morphologic features of cholestasis depend on the underlying cause. Common to all types of obstructive and hepatocellular cholestasis is the accumulation of bile pigment in the liver. Elongated green-brown plugs of bile are visible in the dilated bile canaliculi. Rupture of the canaliculi leads to extravasation of bile and subsequent degenerative changes in the surrounding hepatocytes. Prolonged obstructive cholestasis leads not only to fatty changes in the hepatocytes but also to destruction of the supporting connective tissue, giving rise to bile lakes filled with cellular debris and pigment.[3] Unrelieved obstruction leads to biliary tract fibrosis and ultimately to end-stage biliary cirrhosis.

Pruritus is the most common presenting symptom in persons with cholestasis, probably related to an elevation in plasma bile acids. Skin xanthomas (focal accumulations of cholesterol) may occur as the result of hyperlipidemia and impaired excretion of cholesterol. A characteristic laboratory finding is an elevated serum alkaline phosphatase level, an enzyme present in the bile duct epithelium and canalicular membrane of hepatocytes. Other manifestations of reduced bile flow relate to intestinal absorption, including nutritional deficiencies of the fat-soluble vitamins A, D, and K.

Tests of Hepatobiliary Function

The history and physical examination, in most instances, provide clues about liver function. Diagnostic tests help to evaluate liver function and the extent of liver damage. Laboratory tests commonly are used to assess liver function and confirm the diagnosis of liver disease.

Liver function tests, including serum levels of liver enzymes, are used to assess injury to liver cells, the liver's ability to synthesize proteins, and the excretory functions of the liver.[5,6] Elevated serum enzyme test results usually indicate liver injury earlier than other indicators of liver function. The key enzymes are alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are present in liver cells. ALT is liver specific, whereas AST is derived from organs other than the liver. In most cases of liver damage, there are parallel rises in ALT and AST. The most dramatic rise is seen in cases of acute hepatocellular injury, as occurs with viral hepatitis, hypoxic or ischemic injury, acute toxic injury, or Reye syndrome. The liver's synthetic capacity is reflected in measures of serum protein levels and prothrombin time (i.e., synthesis of coagulation factors). Hypoalbuminemia due to depressed synthesis may complicate severe liver disease. Deficiencies of fibrinogen and coagulation factors (II, VII, IX, and X) may occur.

Serum bilirubin, γ-glutamyltransferase (GGT), and alkaline phosphatase measure hepatic excretory function.[6] Alkaline phosphatase is present in the membranes between liver cells and the bile duct and is released by disorders affecting the bile duct. GGT, which is thought to function in the transport of amino acids and peptides into liver cells, is a sensitive indicator of hepatobiliary disease. Measurement of GGT may be helpful in diagnosing alcohol abuse.

Ultrasonography provides information about the size, composition, and blood flow of the liver. It has largely replaced cholangiography in detecting stones in the gallbladder or biliary tree. Computed tomography (CT) scanning provides information similar to that obtained by ultrasonography. Magnetic resonance imaging (MRI) has proved to be useful in some disorders. Selective angiography of the celiac, superior mesenteric, or hepatic artery may be used to visualize the hepatic or portal circulation.

A liver biopsy affords a means of examining liver tissue without surgery. There are several methods for obtaining liver tissue: percutaneous liver biopsy, which uses a suction, cutting, or spring-loaded cutting needle; laparoscopic liver biopsy; and fine needle biopsy, which is performed under ultrasonographic or CT guidance.[7] The type of method used is based on the number of specimens needed and the amount of tissue required for evaluation. Laparoscopic liver biopsy provides the means for examining abdominal masses, evaluating ascites of unknown cause, and staging liver cancers.

In summary, the hepatobiliary system consists of the liver, gallbladder, and bile ducts. The liver is the largest and, in functions, one of the most versatile organs in the body. It is located between the gastrointestinal tract and the systemic circulation; venous blood from the intestine flows through the liver before it is returned to the heart. In this way, nutrients can be removed for processing and storage, and bacteria and other foreign matter can be phagocytosed and removed by Kupffer cells before the blood is returned to the systemic circulation.

The liver synthesizes plasma proteins, stores vitamins and minerals, maintains blood glucose levels and regulates circulating VLDL levels, and metabolizes and eliminates harmful toxins and drugs. Other important functions of the liver include the deamination of amino acids, conversion of ammonia to urea, and interconversion of amino acids and other compounds that are important to the metabolic processes of the body. Bile serves as an excretory vehicle for bilirubin, cholesterol, and certain products of metabolism and contains bile salts that are essential for digestion of fats and absorption of fat-soluble vitamins. The liver also removes bilirubin (i.e., a product of hemoglobin degradation) from the blood. Jaundice occurs when bilirubin accumulates in the blood. It can occur because of excessive red blood

cell destruction, failure of the liver to remove and conjugate the bilirubin, or obstructed biliary flow.

Liver function tests, including serum levels of liver enzymes (i.e., ALT and AST), are used to assess injury to liver cells. Plasma protein, especially serum albumin, and prothrombin levels provide information related to the liver's synthetic capacity. Serum bilirubin, GGT, and alkaline phosphatase are used as measures of hepatic excretory function. Ultrasonography, CT scans, and MRI are used to evaluate liver structures. Angiography may be used to visualize the hepatic or portal circulation, and a liver biopsy obtains tissue specimens for microscopic examination.

Disorders of Hepatic and Biliary Function

The structures of the hepatobiliary system are subject to many of the same pathologic conditions that affect other body systems. This section focuses on alterations in liver function due to viral and autoimmune hepatitis; intrahepatic biliary disorders; drug- and alcohol-induced liver disease; nonalcoholic fatty liver disease; the hepatic syndromes of cirrhosis, portal hypertension, and liver failure; and cancer of the liver.

Hepatitis

Hepatitis refers to the acute or chronic inflammation of the liver. Although hepatitis viruses account for many cases of chronic hepatitis, there are many other causes including chronic alcoholism, drug toxicities, and autoimmune disorders. The discussion in this section focuses on viral and autoimmune hepatitis.

Diseases of the Liver

- Diseases or injury of the liver can affect the liver cells (hepatocytes) or the biliary drainage system.
- Diseases of hepatocytes impair the metabolic and synthetic functions of the liver, causing disorders in carbohydrate, protein, and fat metabolism; metabolism and removal of drugs, hormones, toxins, ammonia, and bilirubin from the blood; and the interconversion of amino acids and synthesis of proteins. Elevations in serum aminotransferase levels signal the presence of hepatocyte damage.
- Diseases of the biliary drainage system obstruct the flow of bile and interfere with the elimination of bile salts and bilirubin, producing cholestatic liver damage because of the backup of bile into the lobules of the liver. Elevations in bilirubin and alkaline phosphatase signal the presence of cholestatic liver damage.

Viral Hepatitis

Viral hepatitis refers to hepatic infections due to a group of viruses known as *hepatotropic viruses* (hepatitis A [HAV], hepatitis B [HBV], hepatitis C [HCV], hepatitis D [HDV], and hepatitis E [HEV]) that are have a particular affinity for the liver.[3,4] Although all of the hepatotropic viruses cause hepatitis, they differ in terms of their mode of transmission and incubation period; mechanism, degree, and chronicity of liver damage; and ability to evolve to a carrier state. Acute hepatitis may also occur in the course of other viral infections such as infectious mononucleosis, caused by the Epstein-Barr virus; and cytomegalovirus infection, particularly in newborn or immunosuppressed persons. These other forms of hepatitis must be distinguished from hepatitis caused by hepatotropic viruses.

The clinical course of viral hepatitis can involve a number of syndromes, including acute asymptomatic hepatitis with only serologic evidence of infection, acute symptomatic hepatitis, chronic hepatitis, and the carrier state. Fulminant hepatic failure, a syndrome of hepatic insufficiency with rapid progression to liver failure, occurs in a small percentage (<1% to 3%) of persons with hepatitis A and B.

The manifestations of *acute symptomatic viral hepatitis* can be divided into three phases: the prodromal or preicterus period, the icterus period, and the convalescent period. The onset of the *prodromal period* may vary from abrupt to insidious, with general malaise, myalgia, arthralgia, easy fatigability, and severe anorexia out of proportion to the degree of illness. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea or constipation may occur. Abdominal pain is usually mild and felt on the right side. Chills and fever may mark an abrupt onset. In persons who smoke, there may be distaste for smoking that parallels the anorexia. Serum levels of AST and ALT show variable increases during the preicterus phase and precede a rise in bilirubin that accompanies the onset of the icterus or jaundice phase of infection. The *icterus phase*, if it occurs, usually follows the prodromal phase by 5 to 10 days. Jaundice is less likely to occur with HCV infection. The prodromal symptoms may become worse with the onset of jaundice, followed by progressive clinical improvement. Severe pruritus and liver tenderness are common during the icterus period. The *convalescent phase* is characterized by an increased sense of well-being, return of appetite, and disappearance of jaundice. The acute illness usually subsides gradually over a 2- to 3-week period, with complete clinical recovery by approximately 9 weeks in hepatitis A and 16 weeks in uncomplicated hepatitis B.

Chronic hepatitis is defined as "symptomatic, biochemical, or serological evidence of continuing or relapsing disease for more than 6 months."[3] Most cases of chronic hepatitis are due to HCV, with a small number being caused by HBV. The clinical features of chronic hepatitis are extremely variable and not predictive of outcome.

In some persons the only manifestation is a persistent elevation of serum aminotransferases. The most common symptoms are fatigue, followed by loss of appetite, and occasional bouts of jaundice. Persons with HCV infection often have mild or no symptoms. However, even persons with normal serum aminotransferase levels are at high risk for developing permanent liver damage.

Infection with HBV, HCV, and HDV can produce a *carrier state* in which the person does not have symptoms but harbors the virus and can therefore transmit the disease. There is no carrier state for HAV infection. There are two types of carriers: healthy carriers who have few or no ill effects and those with chronic disease who may or may not have symptoms. Factors that increase the risk of becoming a carrier are age at time of infection and immune status. The carrier state for infections that occur early in life, as in infants of HBV-infected mothers, may be as high as 90% to 95%, compared with 1% to 10% of infected adults.[3] Other persons at high risk of becoming carriers are those with impaired immunity, those who have received multiple transfusions or blood products, those who are on hemodialysis, and drug addicts.

Hepatitis A. Hepatitis A is usually a benign and self-limited disease caused by a small, nonenveloped, single-stranded ribonucleic acid (RNA) picornavirus. Lack of a lipid envelope confers resistance to lysis by bile acids in the intestine. The virus is hardy, surviving extended periods in seawater, fresh water, wastewater, and soil. Infection is contracted primarily by the fecal–oral route.[8]

Hepatitis A occurs throughout the world and is endemic in countries with substandard hygiene and sanitation. At special risk of infection are persons traveling abroad who have not been vaccinated or previously exposed to the virus. HAV has a brief incubation period (15 to 50 days), with an average of 25 to 30 days. The virus replicates in the liver, is excreted in the bile, and is shed in the stool. The fecal shedding of HAV occurs for 2 to 3 weeks before the development of symptoms and ends about 1 week after the onset of jaundice.[3] Because young children are asymptomatic, they play an important role in the spread of the disease. Oral behavior and lack of toilet training promote viral spread among children attending preschool day care centers, who then carry the virus home to older siblings and parents. Infected workers in food industries may also be a source of spread. Hepatitis A usually is not transmitted by transfusion of blood or plasma derivatives, presumably because its short period of viremia usually coincides with clinical illness, so that the disease is apparent and blood donations are not accepted.

The onset of symptoms usually is abrupt and includes fever, malaise, nausea, anorexia, abdominal discomfort, dark urine, and jaundice. The likelihood of having symptoms is related to age. Children younger than 6 years often are asymptomatic. The illness in older children and adults usually is symptomatic and jaundice occurs in approximately 70% of cases.[8] Symptoms usually last approximately 2 months but can last longer. HAV infection does not cause chronic hepatitis or induce a carrier state, and only rarely causes acute fulminant hepatitis.[3,8]

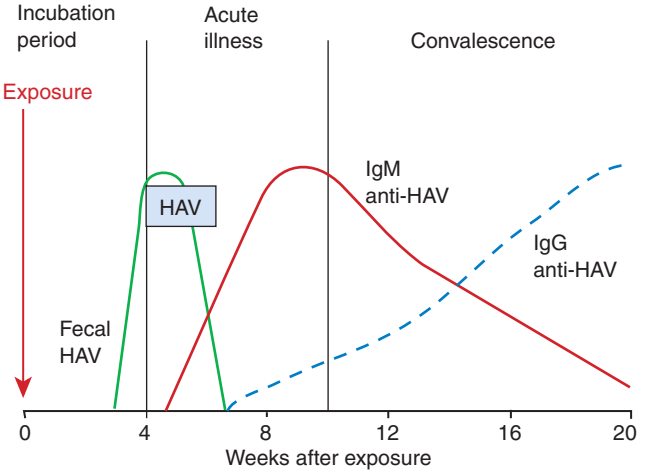


FIGURE 30-7. The sequence of fecal shedding of the hepatitis A virus (HAV), HAV viremia, and HAV antibody (IgM and IgG anti-HAV) changes in hepatitis A.

Antibodies to HAV (anti-HAV) appear early in the disease and tend to persist in the serum (Fig. 30-7). The immunoglobulin M (IgM) antibodies (see Chapter 15) usually appear during the first week of symptomatic disease and begin to decline in a few months.[3] Their presence coincides with a decline in fecal shedding of the virus. Peak levels of IgG antibodies occur after 1 month of illness and may persist for years; they provide long-term protective immunity against reinfection. The presence of IgM anti-HAV is indicative of acute hepatitis A, whereas IgG anti-HAV merely documents past infection.

A hepatitis A vaccine is available.[8,9] Immunization is intended to replace the use of immune globulin in persons at high risk for HAV exposure. These include international travelers to regions where sanitation is poor and endemic HAV infections are high, children living in communities with high rates of HAV infection, homosexually active men, and users of illicit drugs. Persons with preexisting chronic liver disease also may benefit from immunization. A public health benefit also may be derived from vaccinating persons with increased potential for transmitting the disease (e.g., food handlers). The Centers for Disease Control and Prevention (CDC) has recently recommended vaccination of children in states, counties, and communities with high rates of infection.[9] Persons who have been exposed to HAV are advised to receive postexposure prophylaxis with a single dose of HAV vaccine or immune globulin (IgG) as soon as possible. The immune globulin is preferred for persons older than 40 years or younger than 1 year of age and for those who are immunocompromised or have chronic liver disease.

Hepatitis B. Hepatitis is caused by a hepatotropic deoxyribonucleic acid (DNA)-containing *Hepadnavirus*. The complete hepatitis B virion, also called a *Dane particle,* consists of an outer envelope and an inner nucleocapsid that contains the viral DNA and viral polymerase that exhibits both DNA polymerase and reverse transcriptase activity (Fig. 30-8). HBV infection can produce acute hepatitis, chronic hepatitis, progression of chronic

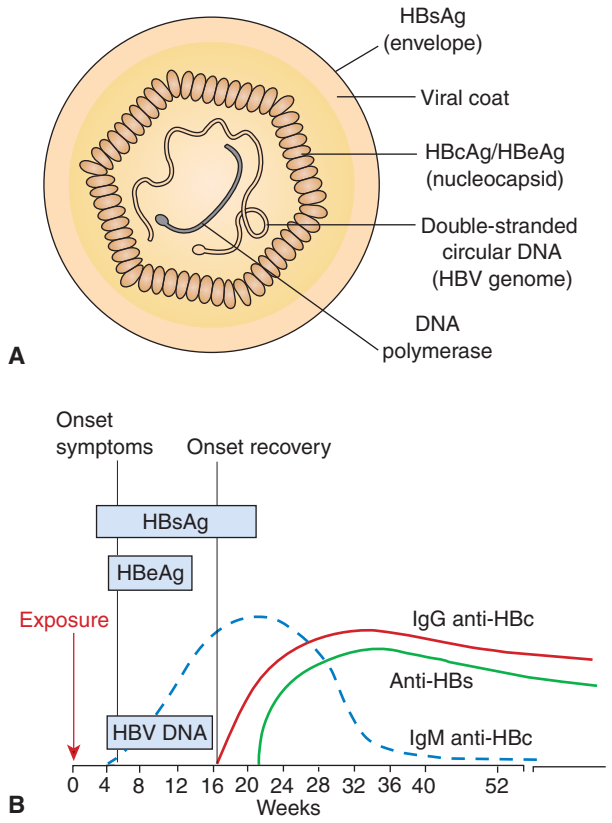


FIGURE 30-8. **(A)** The hepatitis B virus. **(B)** The sequence of hepatitis B virus (HBV) viral antigens (HBsAg, HBeAg), HBV DNA, and HBV antibody (IgM, IgG, anti-HBc, and anti-HBs) changes in acute resolving hepatitis B.

hepatitis to cirrhosis, fulminant hepatitis with massive hepatic necrosis, and the carrier state. It also participates in the development of hepatitis D (delta hepatitis).[3,4,10–12] The virus usually is transmitted through inoculation with infected blood or serum. However, the viral antigen can be found in most body secretions and can be spread by oral or sexual contact.

Hepatitis B has a longer incubation period and represents a more serious health problem than hepatitis A. More than 2 billion people—one third of the world's population—alive today have been infected with HBV, and of these 350 to 400 million remain infected.[3,11–13] The incidence of acute hepatitis B in the United States has dramatically declined since 1990, with the greatest declines in children and adolescents, coincident with hepatitis B vaccination in these age groups. Despite these advances, there continues to be an estimated 46,000 new infections per year with about 5000 acute symptomatic cases.[3] Worldwide, perinatal (vertical) transmission is the predominant mode of HBV transmission, whereas intravenous drug use and unprotected sexual intercourse are the main routes of transmission in low-prevalence areas such as the United States.[3] Although the virus can be spread through transfusion or administration of blood products, routine screening methods have appreciably reduced transmission through this route.

Three well-defined antigens are associated with the HBV virus: a core antigen, HBcAg; HBeAg, a precore protein; and a surface antigen, HBsAg. These HBV antigens evoke specific antibodies: anti-HBc, anti-HBe, and anti-HBs. The antigens and their antibodies serve as serologic markers for following the natural course of the disease[3,4] (see Fig. 30-8). HBsAg is the viral antigen measured most routinely in blood. It appears before onset of symptoms, peaks during overt disease, and then declines to undetectable levels in 3 to 6 months. Persistence beyond 6 months indicates continued viral replication, infectivity, and risk of chronic hepatitis. HBeAg appears in the serum soon after HBsAg and signifies active viral replication. IgM anti-HBc becomes detectable shortly before the onset of symptoms, concurrent with the onset of an elevation in serum transaminases. Over the months, the IgM antibody is replaced by IgG anti-HBc. Anti-HBe is detectable shortly after the disappearance of HBeAg and its appearance signals the onset of resolution of the acute illness. IgG anti-HBs, a specific antibody to HBsAg, occurs in most individuals after clearance of HBsAg. Development of anti-HBs signals recovery from HBV infection, noninfectivity, and protection from future HBV infection. Anti-HBs is the antibody present in persons who have been successfully immunized against HBV.

The presence of viral DNA (HBV DNA) in the serum is the most reliable indicator of hepatitis B infection. It is transiently present during the presymptomatic period and for a brief time during the acute illness. The presence of DNA polymerase, the enzyme used in viral replication, usually is transient but may persist for years in persons who are chronic carriers and is an indication of continued infectivity.

Hepatitis B can be prevented by vaccination and by the screening of donor blood, organs, and tissues. The vaccine, which is prepared from purified HBsAg produced in yeast, induces a protective antibody response in 95% of vaccinated infants, children, and adolescents.[3] The CDC recommends vaccination of all children 0 to 18 years of age as a means of preventing HBV transmission.[13] The vaccine also is recommended for all unvaccinated adults who are at high risk for infection by sexual exposure, percutaneous or mucosal exposure to blood, international travelers to regions with high or intermediate levels of endemic HBV infection, persons with human immunodeficiency virus (HIV) infection, and all other persons seeking protection from HBV infection.[9] It is also recommended that all pregnant women be routinely tested for HBsAg during an early prenatal visit and that infants born to HBsAg-positive mothers receive appropriate doses of hepatitis B immune globulin (HBIG) and hepatitis B vaccine.[9]

Hepatitis C. HCV, discovered in 1989, is a member the *Flaviviridae* family. It is a small, enveloped, single-stranded RNA virus.[3,4] The virus is genetically unstable, giving rise to multiple genotypes and subtypes. This allows a divergent population of closely related variants to circulate in infected persons.[3] Over time, dozens of these variant species can be detected and mapped as derivative strains of the original infecting HCV strain.

One of the HCV envelope proteins, the E2 protein, which is the target for anti-HCV antibodies, is the most variable region of the entire viral genome. It is likely that the wide diversity of genotypes contributes to the pathogenicity of the virus, allowing it to escape the actions of host immune mechanisms and antiviral medications, and to difficulties in developing a preventive vaccine.

Hepatitis C is the most common cause of chronic hepatitis, cirrhosis, and hepatocellular cancer in the world.[3,4,14–16] Before 1990, the main route of transmission of HCV was through contaminated blood transfusions or blood products. With implementation of HCV testing in blood banks, the risk of HCV infection from blood transfusion is almost nonexistent in the United States and other developed countries. However, unsafe medical procedures and unscreened blood transfusions may be the most important sources of HCV infections in less developed countries of the world. Currently, recreational injecting drug use is the most common mode of HCV transmission in the United States and Canada.[14,16] High-risk sexual behavior, defined as having sex with multiple sexual partners or sex with an HCV-infected partner, is currently the second most common risk factor in the United States. HCV also can be spread through exposure in the health care setting, primarily through needle-stick injuries. There also is concern that transmission of small amounts of blood during tattooing, acupuncture, and body piercing may facilitate the transmission of HCV.

The incubation period for HCV infection ranges from 2 to 26 weeks (average, 6 to 12 weeks).[3] Children and adults who acquire the infection usually are asymptomatic (60% to 70%) or have a nonspecific clinical disease characterized by fatigue, malaise, anorexia, and weight loss. A minority of persons develop sufficient elevations in bilirubin to produce overt jaundice or the development of dark urine. Only a few persons who are newly infected with HCV will clear the infection, with the majority going on to develop chronic hepatitis.[16] Factors associated with spontaneous clearing of HCV infection appear to include younger age, female sex, and certain histocompatibility genes. The most serious consequences of chronic HCV infection are progressive liver fibrosis leading to cirrhosis, end-stage liver disease, and hepatocellular cancer.

Both HCV RNA and anti-HCV antibody tests are available for detecting the presence of HCV infection (Fig. 30-9). False-negative results can occur in immunocompromised people and early in the course of the disease before antibodies develop. Direct measurement of HCV RNA in the serum remains the most accurate test for infection. The viral tests are highly sensitive and specific, but more costly than antibody tests. With newer antibody testing methods, infection often can be detected as early as 6 to 8 weeks after exposure, and as early as 1 to 2 weeks with viral tests that use polymerase chain reaction (PCR) methods (see Chapter 14). Unlike hepatitis A and B, antibodies to HCV are not protective, but they serve as markers for the disease.

Hepatitis D and E. Hepatitis D virus, or the delta hepatitis agent, is a defective RNA virus that requires concomitant infection with HBV for its own replication.[17] Acute hepatitis D occurs in two forms: coinfection that occurs simultaneously with acute hepatitis B, and a superinfection in which hepatitis D is imposed on chronic hepatitis B or the hepatitis B carrier state.[3,17] The delta agent often increases the severity of HBV infection.

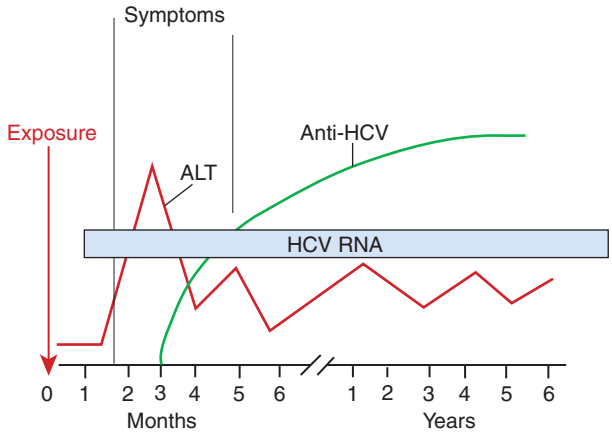


FIGURE 30-9. The sequence of serologic changes in chronic hepatitis C, with persistence of hepatitis C virus (HCV) RNA and exacerbations and remissions of clinical symptoms indicated by changes in serum alanine aminotransferase (ALT) levels.

The routes of transmission of hepatitis D are similar to those for hepatitis B. In the United States, infection is restricted largely to persons at high risk for HBV infection, particularly injecting drug users. The greatest risk is in HBV carriers; these persons should be informed about the dangers of HDV superinfection. Hepatitis D is diagnosed by detection of antibody to HDV (anti-HDV) in the serum or HDV RNA in the serum. There is no specific treatment for hepatitis D. Because the infection is linked to hepatitis B, prevention of hepatitis D should begin with prevention of hepatitis B through vaccination.

HEV is a nonenveloped, single-stranded RNA virus. It is transmitted by the fecal–oral route and causes manifestations of acute hepatitis that are similar to hepatitis A. It does not cause chronic hepatitis or the carrier state.[3] A distinguishing feature of HEV infection is the high mortality rate (approximately 20%) among pregnant women, owing to the development of fulminant hepatitis. The infection occurs primarily in developing areas such as India, other Southeast Asian countries, parts of Africa, and Mexico. The only reported cases in the United States have been in persons who have recently been in an endemic area.

Chronic Viral Hepatitis. Chronic hepatitis is defined as a chronic inflammatory reaction of the liver of more than 6 months' duration. It is characterized by persistently elevated serum aminotransferase levels and characteristic histologic findings on liver biopsy. Chronic viral hepatitis is the principal cause of chronic liver disease, cirrhosis, and hepatocellular cancer in the world and now ranks as the chief reason for liver transplantation in adults.[18] Of the hepatotropic viruses, only three are known to cause chronic hepatitis—HBV, HCV, and

HDV. Chronic HCV infection, which often smolders over a period of years, silently destroying liver cells, accounts for most cases of chronic viral hepatitis.

There are no simple and effective methods of treatment for chronic viral hepatitis. Drugs used in the treatment of chronic hepatitis B include the recombinant human interferon-2α or peginterferon and a nucleotide or nucleotide analog antiretroviral agent.[10,18] Persons with active viral replication may be treated with recombinant human interferon-2α and peginterferon. Peginterferons were developed by adding a polyethylene glycol (PEG) moiety to an interferon molecule (PEG-IFN), resulting in a prolonged serum half-life and the ability to administer the compound once weekly rather than three times a week. Up to 40% of treated patients respond with sustained normalization of liver enzyme levels, disappearance of HBeAg and HBV DNA from the serum, appearance of anti-HBe, and improved survival.[18] Nucleoside and nucleotide analogs (e.g., lamivudine, adefovir dipivoxil, entecavir) may be used instead of interferon for treatment of chronic HBV infection and are often better tolerated. Other antiviral agents are under study, and strategies using multiple drugs are likely to be investigated.

The current treatment for untreated persons with chronic hepatitis C is a combination of peginterferon (alfa-2b or alfa-2a) plus ribavirin (a nucleoside analog).[18,19] Treatment with peginterferon and ribavirin is costly, and side effects, which include flulike symptoms, are almost universal. More serious side effects, which include psychiatric symptoms (depression), thyroid dysfunction, and bone marrow depression, are less common. Although most persons with HCV infection are candidates for treatment, many have other health problems that are contraindications to therapy.

Liver transplantation is a treatment option for end-stage liver disease due to viral hepatitis. Liver transplantation has been more successful in persons with hepatitis C than those with hepatitis B. Although the graft often is reinfected, the disease seems to progress more slowly.

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic and progressive form of hepatitis of unknown origin that is associated with high levels of serum immunoglobulins, including autoantibodies.[3,4,20] Although the disorder is usually seen in young women, it can occur in either sex at any age.

Clinical and laboratory observations have led to the hypothesis that autoimmune hepatitis is a multifactorial disorder, with genetic and environmental factors playing important roles. Most knowledge about the genetics of the disease has focused on the human leukocyte antigen (HLA) genes that reside in the major histocompatibility complex (MHC), located on the short arm of chromosome 6 (see Chapter 15). The environmental agents assumed to induce autoimmune hepatitis have not been delineated, but include viral infections and certain drugs such as minocycline, methyldopa, atorvastatin, simvastatin, interferons, nitrofurantoin, and herbal products such as black cohash.[3,20]

Two distinct types of autoimmune hepatitis have been identified, based on the presence of circulating antibodies.[2,4,20] Type I autoimmune hepatitis, the most common form of the disease, is characterized by increased levels of anti–smooth muscle and antinuclear autoantibodies. Approximately 30% of cases occur in women younger than 40 years of age, a third of whom have other autoimmune diseases.[4] Type II autoimmune hepatitis, a rare disorder, occurs mainly in children 2 to 14 years of age and is characterized by the presence of antibody to liver and kidney microsomes and liver cytosol.[4] The disorder is often accompanied by other autoimmune disorders, especially type 1 diabetes mellitus and thyroiditis. The genetic component for this type of autoimmune hepatitis is less well defined than for type 1.

Clinical manifestations of the disorder cover a spectrum that extends from no apparent symptoms to the signs of liver failure. Physical examination may reveal no abnormalities, but may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease. In asymptomatic cases, the disorder may be discovered when abnormal serum enzyme levels are identified during performance of routine screening tests.

The differential diagnosis includes measures to exclude other causes of liver disease, including hepatitis B and C. A characteristic laboratory finding is that of a marked elevation in serum gamma globulins. A biopsy is used to confirm the diagnosis. Corticosteroid and immunosuppressant drugs are the treatment of choice for this type of hepatitis. Although some persons remain in remission after drug treatment is withdrawn, most require long-term maintenance treatment. Liver transplantation may be required for persons who are refractory to or intolerant of immunosuppressive therapy and in whom end-stage liver disease develops.

Acute Fulminant Hepatitis

Acute fulminant hepatitis or hepatic failure is hepatic insufficiency that progresses from onset of hepatitis symptoms to hepatic encephalopathy within 2 to 3 weeks in persons who do not have chronic liver disease.[3] Viral hepatitis is responsible for about 12% of cases of fulminant hepatitis, with about 8% of those being caused by HBV and the rest by HAV.[3,18] Acetaminophen (Tylenol) toxicity (to be discussed) is the most common cause, accounting for at least 45% of cases in the United States.[18] Other causes include idiosyncratic drug reactions (now the second most common cause), poisonous mushrooms, fatty liver of pregnancy, and other disorders of fatty acid oxidation.

Acute fulminant liver failure often presents with gastrointestinal symptoms, signs of the systemic inflammatory response (see Chapter 20), and hemorrhagic phenomenon. Jaundice may be absent or minimal early, but laboratory tests show severe hepatocellular damage. The blood ammonia level is typically elevated and correlates with the development of encephalopathy and cerebral edema. Survival of more than a week may permit replication of residual hepatocytes.

The treatment for acute liver failure is directed toward correcting the underlying liver abnormality and providing supportive care. Liver transplantation is the only option for persons who do not succumb to secondary infections or other organ failure. The mortality rate of fulminant hepatitis is about 85% without transplant and about 35% with transplant.[3]

Intrahepatic Biliary Disorders

Intrahepatic biliary diseases disrupt the flow of bile through the liver, causing cholestasis and biliary cirrhosis. Among the causes of intrahepatic biliary disease are primary biliary cirrhosis and secondary biliary cirrhosis.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is a chronic disease of the liver characterized by the autoimmune destruction of the medium-sized intrahepatic bile ducts with cholestasis and eventual development of cirrhosis and liver failure.[3,21–23] Cirrhosis develops only after many years; thus, the name *primary biliary cirrhosis* is somewhat misleading for persons diagnosed early in the precirrhotic stage.[3]

The disease is seen most commonly in women 40 to 60 years of age. Both the incidence and prevalence are increasing, and geographic clustering of the disease has been reported, suggesting genetic and environmental factors are important in its pathogenesis. Family members of persons with the disease have increased risk of developing the disease. The disease may be associated with other autoimmune disorders such as Sjögren syndrome (sicca complex of dry eyes and mouth), autoimmune thyroid disease, rheumatoid arthritis, Raynaud phenomenon, and celiac disease.

The disorder is characterized by an extremely insidious onset, and persons may be symptom-free for many years. Morphologically, there is progressive scarring and destruction of liver tissue. The liver becomes enlarged and takes on a green hue because of the accumulated bile. The earliest symptoms are unexplained pruritus or itching, weight loss, and fatigue, followed by dark urine and pale stools. Vitamin D malabsorption–related osteoporosis occurs in up to one third of persons with the disorder.[22] Jaundice is a late manifestation of the disorder, as are other signs of liver failure. Serum alkaline phosphatase levels are elevated in persons with primary biliary cirrhosis.

Treatment is largely symptomatic. Cholestyramine, a bile acid–binding drug, may prove beneficial for treatment of pruritus. There is no generally accepted treatment for the underlying disease. Ursodeoxycholic acid (ursodiol), a drug that increases bile flow and decreases the toxicity of bile contents, has been shown to decrease the rate of clinical deterioration. Colchicine, which acts to prevent leukocyte migration and phagocytosis, and methotrexate, a drug with immunosuppressive properties, has also resulted in reported benefits in terms of symptom relief. Liver transplantation, however, remains the only treatment for advanced disease. Primary biliary cirrhosis does not recur after liver transplantation if appropriate immunosuppression is used.

Secondary Biliary Cirrhosis

Secondary biliary cirrhosis results from prolonged obstruction of the extrabiliary tree.[3] The most common cause is cholelithiasis. Other causes of secondary biliary cirrhosis are malignant neoplasms of the biliary tree or head of the pancreas and strictures of the common duct caused by previous surgical procedures. Extrahepatic biliary cirrhosis may benefit from surgical procedures designed to relieve the obstruction.

Drug- and Alcohol-Induced Liver Disease

Drug Metabolism

By virtue of its many enzyme systems that are involved in biochemical processes, the liver has an important role in the metabolism of many drugs and chemical substances. The liver is particularly important in the metabolism of lipid-soluble substances that cannot be directly excreted by the kidney. There are two major types of reactions involved in the hepatic detoxification and metabolism of drugs and other chemicals: phase 1 and phase 2 reactions.[24–27] These reactions, often referred to as *biotransformations,* are important considerations in drug therapy.

Phase 1 reactions result in the chemical modification of reactive drug groups through oxidation, reduction, hydroxylation, or other chemical reactions. Many of these reactions involve drug-metabolizing enzymes that are located in lipophilic endoplasmic reticulum membranes of liver cells. One of the enzymes involved in phase 1 oxidation–reduction processes is the product of a gene superfamily that produces a hemoprotein called *cytochrome P450* (abbreviated CYP or CYP P450). Multiple isoforms of the CYP enzyme have been identified and traced to the metabolism of specific drugs and to potential interactions among drugs. Of these isoforms, the CYP3A4 enzyme accounts for approximately 30% of the liver's drug-metabolizing activity.[24]

Many gene members of the *CYP* enzyme system can have their activity induced or suppressed as they undergo the task of metabolizing drugs. For example, drugs such as alcohol and barbiturates can induce certain members to increase enzyme production, accelerating drug metabolism and decreasing the pharmacologic action of the drug and of coadministered drugs that use the same member of the CYP system. In the case of drugs metabolically transformed to reactive intermediates, enzyme induction may exacerbate drug-mediated tissue toxicity. Enzymes in the cytochrome system also can be inhibited by drugs. For example, the antibiotic erythromycin, antifungal agents (fluconazole, itraconazole, and ketoconazole), and grapefruit juice inhibit CYP3A4 enzyme activity, thereby decreasing the metabolism of drugs that use this enzyme system.[24]

Phase 2 reactions, which involve the conversion of lipid-soluble derivatives to water-soluble substances called *conjugates*, may follow phase 1 reactions or proceed independently. Conjugation, a process that couples

the drug with an activated endogenous compound such as glutathione, renders the drug more water soluble so it can be excreted in the bile or urine. Although many water-soluble drugs and endogenous substances are excreted unchanged in the urine or bile, lipid-soluble substances tend to accumulate in the body unless they are converted to less active compounds or water-soluble metabolites. Because the endogenous substrates used in the conjugation process are obtained from the diet, nutrition plays a critical role in phase 2 reactions.

In addition to its role in metabolism of drugs and chemicals, the liver also is responsible for hormone inactivation or modification. Insulin and glucagon are inactivated by proteolysis or deamination. Thyroxine and triiodothyronine are metabolized by reactions involving deiodination. Steroid hormones such as the glucocorticoids are first inactivated by a phase 1 reaction and then conjugated by phase 2 reactions.

Drug-Induced Liver Disease

Many of the widely used therapeutic drugs, including over-the-counter "natural" products, can cause hepatic injury.[25,26] Drug-related hepatotoxicity is the leading cause of acute liver failure in the United States. The most common cause for drug-induced liver injury is acetaminophen, with half the cases reported to be unintentional overdoses.[27] Unintentional overdoses may occur when people unknowingly take several over-the-counter preparations that contain acetaminophen (e.g., an acetaminophen-containing cold preparation and acetaminophen pain medication). Numerous host factors contribute to the susceptibility to drug-induced liver disease, including genetic predisposition, age, underlying chronic liver disease, diet and alcohol consumption, and the use of multiple interacting drugs.

Drugs and chemicals can exert their effects by causing hepatocyte injury and death or by cholestatic liver damage due to injury of biliary drainage structures. Drug reactions can be acute or chronic, and predictable based on the drug's chemical structure and metabolites or unpredictable (idiosyncratic) based on individual characteristics of the person receiving the drug.

Direct Predictable Injury. Some drugs are known to have toxic effects on the liver based on their chemical structure and the way they are metabolized in the liver. Direct hepatic damage often is age and dose dependent. Direct hepatotoxic reactions usually are a recognized characteristic of certain drugs. They usually result from drug metabolism and the generation of toxic metabolites. Because of the greater activity of the drug-metabolizing enzymes in the central zones of the liver, these agents typically cause centrilobular necrosis. Examples of drugs that cause direct hepatotoxicity are acetaminophen, isoniazid, and phenytoin. The injury is characterized by marked elevations in ALT and AST values with minimally elevated alkaline phosphatase. Bilirubin levels invariably are increased, and the prognosis often is worse when hepatocellular necrosis is accompanied by jaundice.

Idiosyncratic Reactions. In contrast to direct predictable drug reactions, idiosyncratic reactions are unpredictable, not related to dose, and sometimes accompanied by features suggesting an allergic reaction. Drugs are relatively small molecules and, therefore, unlikely to evoke an immune response. However, in the process of biotransformation, drugs may combine with enzymes that are large enough to serve as immune targets that induce the formation of antibodies (antibody-mediated cytotoxicity) or produce direct cytolytic T-cell responses. In some cases, the reaction results directly from a metabolite that is produced only in certain persons based on a genetic predisposition. For example, certain people are capable of rapid acetylation of isoniazid, an antituberculosis drug.

Cholestatic Reactions. Cholestatic drug reactions result in decreased secretion of bile or obstruction of the biliary tree. Acute intrahepatic cholestasis is one of the most frequent types of idiosyncratic drug reactions. Among the drugs credited with causing cholestatic drug reactions are estradiol; chlorpromazine, an antipsychotic drug; and some of the antibiotics, including amoxicillin/clavulanic acid, erythromycin, and nafcillin. Typically, cholestatic drug reactions are characterized by an early onset of jaundice and pruritus, with little alteration in the person's general feeling of well-being. Most instances of acute drug-induced cholestasis subside once the drug is withdrawn.

Chronic Hepatitis. Some drugs produce a more indolent form of liver damage that closely resembles autoimmune hepatitis. Early identification of drug-related chronic hepatitis often is difficult; cirrhosis may develop before the hepatitis is diagnosed. Identifying the responsible drug that caused the liver damage may be difficult retrospectively if the person has been consuming alcohol or taking several drugs.

Alcohol Metabolism

Alcohol is readily absorbed from the stomach and intestine. It is then distributed to all of the tissues and fluids in the body in direct proportion to the blood level. Most of the alcohol that a person drinks (80% and 90%) is metabolized by the liver. In the liver, alcohol metabolism proceeds simultaneously by two major pathways: the alcohol dehydrogenase (ADH) system and the microsomal ethanol-oxidizing system (MEOS).[27–29]

The main enzyme system involved in alcohol metabolism is ADH, an enzyme located in the cytosol of hepatocytes. In the ADH-mediated oxidation of alcohol, both acetaldehyde and hydrogen (H^+) are produced. The reaction involves a reduction in the adenine dinucleotide (NAD–to–nicotinamide adenine dinucleotide (NADH) ratio (see Chapter 1, Understanding Cell Metabolism), with a consequent decrease in NAD and increase in NADH. Since NAD is required for fatty acid oxidation, its deficiency is a main cause of the accumulation of fat in the liver of alcoholics. It also causes lactic acidosis in alcoholics.

Metabolism of alcohol by the MEOS system involves the CYP drug-metabolizing enzymes, located in the smooth endoplasmic reticulum. One of these metabolizing enzymes also oxidizes a number of other compounds, including various drugs (e.g., acetaminophen, isoniazid), toxins (e.g., carbon tetrachloride, halothane), industrial solvents, and carcinogenic agents (e.g., aflatoxin, nitrosamines). Induction of this system by alcohol enhances the susceptibility of alcoholics to the hepatotoxic effects of these and other compounds metabolized by the same system.[29]

The metabolic end products of alcohol metabolism (e.g., acetaldehyde, free radicals) are responsible for a variety of metabolic alterations that can cause liver injury. Acetaldehyde, for example, has multiple toxic effects on liver cells and liver function. Age and sex play a role in metabolism of alcohol and production of harmful metabolites. The ADH system is depressed by testosterone. Thus, women tend to produce greater amounts of acetaldehyde and are more predisposed to alcohol-induced liver damage than men.[29] Age also appears to affect the alcohol-metabolizing abilities of the liver and the resistance to hepatotoxic effects. Furthermore, genetic factors may influence the severity of alcohol-induced liver disease.

Alcohol-Induced Liver Disease

About 2 million people in the United States are suspected of having alcoholic liver disease, and 14,000 die each year of cirrhosis.[30] Most deaths from alcoholic cirrhosis are attributable to liver failure, bleeding esophageal varices, or kidney failure. It has been estimated that there are 14 million alcoholics in the United States. Only approximately 10% to 15% of alcoholics develop cirrhosis, however, suggesting that other conditions such as genetic and environmental factors contribute to its occurrence.[3]

The spectrum of alcoholic liver disease includes fatty liver disease, alcoholic hepatitis, and cirrhosis.[3,4] *Fatty liver disease* is characterized by the accumulation of fat in hepatocytes, a condition called *steatosis* (Fig. 30-10). The liver becomes yellow and enlarges owing to excessive fat accumulation. The pathogenesis of fatty liver is not completely understood and can depend on the amount of alcohol consumed, dietary fat content, body stores of fat, hormonal status, and other factors. There is evidence that ingestion of large amounts of alcohol can cause fatty liver changes even with an adequate diet. For example, young, nonalcoholic volunteers had fatty liver changes after 2 days of consuming an excess amount of alcohol, even though adequate carbohydrates, fats, and proteins were included in the diet.[31] The fatty changes that occur with ingestion of alcohol usually do not produce symptoms and are reversible after the alcohol intake has been discontinued.

Alcoholic hepatitis is the intermediate stage between fatty changes and cirrhosis. Alcoholic hepatitis is characterized by inflammation and necrosis of liver cells.[3,4,32] The cardinal sign of alcoholic hepatitis is rapid onset of jaundice. Other manifestations include fever, hepatic tenderness, pain, anorexia, nausea, ascites, and liver failure. Persons with severe hepatic hepatitis may have encephalopathy. The condition is always serious and sometimes fatal. The immediate prognosis correlates with severity of liver cell injury. In some cases, the disease progresses rapidly to liver failure and death. The mortality rate in the acute stage is about 10%.[4] In persons who survive and continue to drink, the acute phase often is followed by persistent alcoholic hepatitis with progression to cirrhosis in a matter of 1 to 2 years.

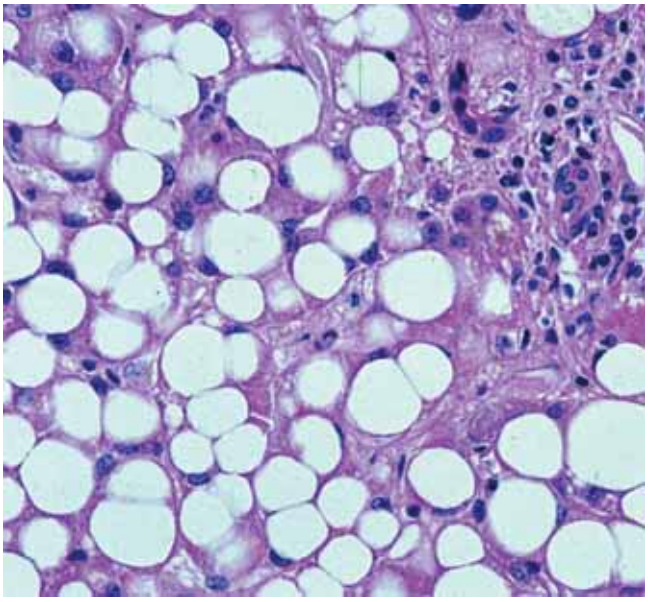


FIGURE 30-10. Alcoholic fatty liver. A photomicrograph shows the cytoplasm of almost all hepatocytes distended by fat that displaces the nucleus to the periphery. (From Rubin R., Rubin E. [2008]. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 646]. Philadelphia: Lippincott Williams & Wilkins.)

Alcoholic cirrhosis is the end result of repeated bouts of drinking-related hepatocyte injury and regeneration and designates the onset of end-stage alcoholic liver disease. The gross appearance of the early cirrhotic liver is one of fine, uniform nodules on its surface (Fig. 30-11A). The condition has traditionally been called *micronodular* or *Laennec cirrhosis*. Initially, the developing fibrous septa extend through the sinusoids from the central to the portal regions and the entrapped hepatocytes generate uniform micronodules (Fig 30-11B). With more advanced cirrhosis, regenerative processes cause the nodules to become larger and more irregular in size and shape. As this occurs, the nodules cause the liver to become relobulized through the formation of new portal tracts and venous outflow channels. The nodules may compress the hepatic veins, curtailing blood flow out of the liver and producing portal hypertension, extrahepatic portosystemic shunts, and cholestasis.

Nonalcoholic Fatty Liver Disease

The term *nonalcoholic fatty liver disease* (NAFLD) is often used to describe fatty liver disease with the potential for progression to cirrhosis and end-stage liver disease arising from causes other than alcohol.[33–35] The condition can range from simple steatosis (fatty infiltration of the liver)

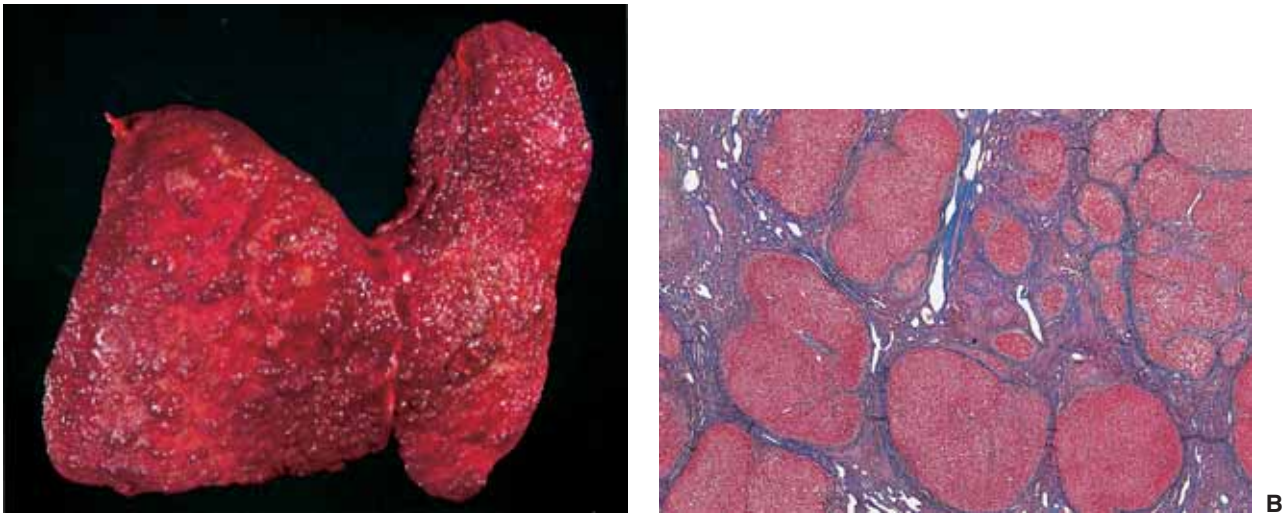


FIGURE 30-11. Alcoholic cirrhosis. **(A)** The surface of the liver displays innumerable small, regular nodules. **(B)** A photomicrograph shows small, regular nodules surrounded by uniform blue-staining fibrous septa. (From Rubin R., Rubin E. [2008]. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 648]. Philadelphia: Lippincott Williams & Wilkins.)

to nonalcoholic steatohepatitis (steatosis with inflammation and hepatocyte necrosis). Although steatosis alone does not appear to be progressive, approximately 20% of persons with nonalcoholic steatohepatitis progress to cirrhosis over the course of a decade.[35] Obesity, type 2 diabetes, the metabolic syndrome, and hyperlipidemia are coexisting conditions frequently associated with fatty liver disease (see Chapter 33). The condition is also associated with other nutritional abnormalities, surgical conditions, drugs, and occupational exposure to toxins. Both rapid weight loss and parenteral nutrition may lead to NAFLD.

The pathogenesis of NAFLD is thought to involve both lipid accumulation within hepatocytes and formation of free radicals, in a manner similar to that which occurs with alcohol metabolism. The primary metabolic abnormalities leading to lipid accumulation are poorly understood but are thought to include alterations in the pathways for uptake, synthesis, degradation, or secretion of hepatic lipids resulting from insulin resistance. Obesity increases the synthesis and reduces the oxidation of free fatty acids. Type 2 diabetes or insulin resistance also increases adipose tissue lipolysis and the subsequent production of free fatty acids.[36] When the capacity of the liver to export triglyceride is exceeded, excess fatty acids contribute to the development of steatosis and fatty liver disease. Both ketones and free fatty acids are inducers of previously described CYP P450 enzymes of the MEOS pathway, which results in free radical formation, including hydrogen peroxide and superoxide. Abnormal lipid peroxidation ensues, followed by direct hepatocyte injury, release of toxic byproducts, inflammation, and fibrosis.

NAFLD is usually asymptomatic, although fatigue and discomfort in the right upper quadrant of the abdomen may be present. Mildly to moderately elevated serum levels of AST, ALT, or both are the most common and often the only abnormal laboratory findings. Other abnormalities, including hypoalbuminemia, a prolonged prothrombin time, and hyperbilirubinemia, may be present in persons with cirrhotic-stage liver disease. The diagnosis of NAFLD requires liver biopsy and exclusion of alcohol as a cause of the disorder.

The aim of treatment is to slow progression of NAFLD and to prevent liver-related illness. Both weight loss and exercise improve insulin resistance and are recommended in conjunction with treatment of associated metabolic disturbances. Alcohol use should be avoided. Disease progression is slow and the magnitude of disease-related morbidity and mortality is uncertain. Liver transplantation is an alternative for some persons with end-stage liver disease, but NAFLD may recur or develop after liver transplantation.[35]

Hepatic Syndromes

As with other organ systems, the liver responds to a number of injurious insults with similar cellular and tissue responses, including hepatocyte degeneration, necrosis and apoptosis, and fibrosis. Clinically, these changes commonly lead to a few syndromes including cirrhosis, portal hypertension, and liver failure.

Cirrhosis

Cirrhosis represents the end stage of chronic liver diseases in which much of the functional liver tissue has been replaced by fibrous tissue. Although cirrhosis usually is associated with alcoholism, it can develop in the course of other disorders, including viral hepatitis, nonalcoholic liver disease, and biliary disease. Cirrhosis also accompanies metabolic disorders that cause the deposition of minerals in the liver. Two of these disorders are hemochromatosis (i.e., iron deposition) and Wilson disease (i.e., copper deposition).

Cirrhosis is characterized by diffuse fibrosis and conversion of normal liver architecture into nodules containing proliferating hepatocytes encircled by fibrosis. The formation of nodules, which vary in size from very small (<3 mm, micronodules) to large (several centimeters, macronodules), represents a balance between regenerative activity and constrictive scarring.[3,4] The fibrous tissue that replaces normally functioning liver tissue forms constrictive bands that disrupt flow in the vascular channels and biliary duct systems of the liver. The disruption of vascular channels predisposes to portal hypertension and its complications; obstruction of biliary channels and exposure to the destructive effects of bile stasis; and loss of liver cells, leading to liver failure.

The manifestations of cirrhosis are variable, ranging from asymptomatic hepatomegaly to hepatic failure (Fig. 30-12). Often there are no symptoms until the disease is far advanced.[37] The most common signs and symptoms of cirrhosis are weight loss (sometimes masked by ascites), weakness, and anorexia. Diarrhea frequently is present, although some persons may complain of constipation. Hepatomegaly and jaundice also are common signs of cirrhosis. There may be abdominal pain because of liver enlargement or stretching of the liver's fibrous tissue capsule. This pain is located in the epigastric area or in the upper right quadrant and is described as dull, aching, and causing a sensation of fullness.

The late manifestations of cirrhosis are related to portal hypertension and liver cell failure. Splenomegaly, ascites, and portosystemic shunts (i.e., esophageal varices, hemorrhoids, and caput medusae) result from portal hypertension.[38] Other complications include bleeding due to decreased clotting factors, thrombocytopenia due to splenomegaly, gynecomastia and a feminizing pattern of pubic hair distribution in men because of testicular atrophy, spider angiomas, palmar erythema, and encephalopathy with asterixis and neurologic signs.

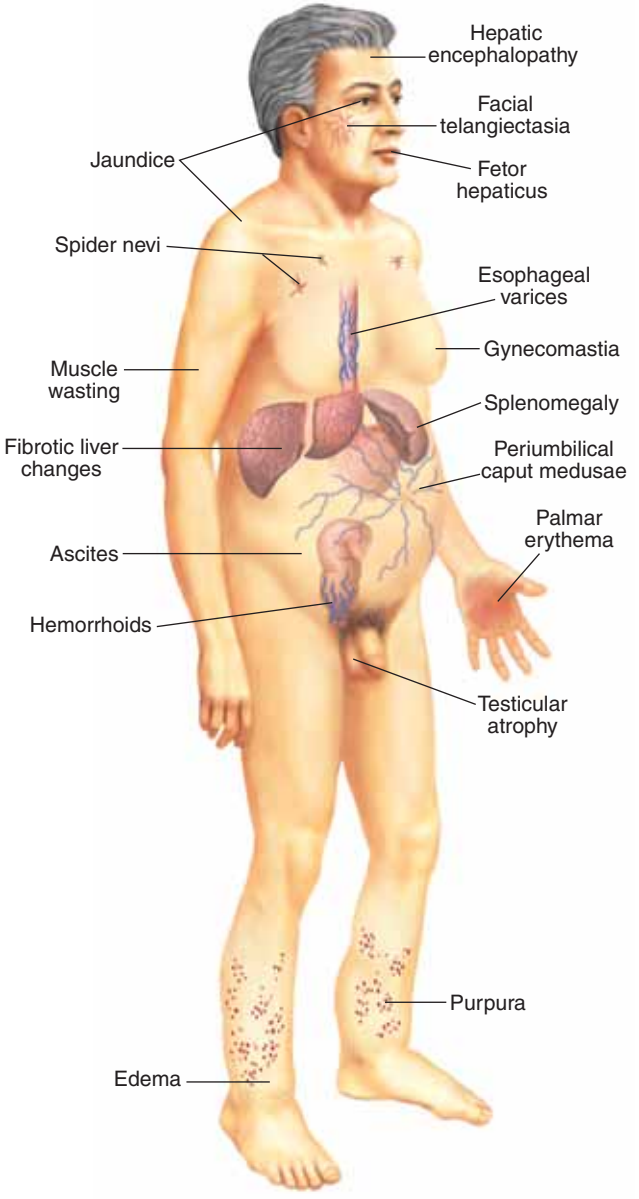


FIGURE 30-12. Clinical manifestations of cirrhosis.

Portal Hypertension

Portal hypertension is characterized by increased resistance to flow in the portal venous system and sustained increase in portal venous pressure.[3,4,39] Normally, venous blood returning to the heart from the abdominal organs collects in the portal vein and travels through the liver before entering the vena cava (see Fig. 30-2). Portal hypertension can be caused by a variety of conditions that increase resistance to hepatic blood flow, including prehepatic, posthepatic, and intrahepatic obstructions.[3,4] *Prehepatic* causes of portal hypertension include obstructive thrombosis, narrowing of the portal vein before it enters the liver, and massive splenomegaly with increased splenic blood flow. The main *posthepatic* causes are right-sided heart failure and hepatic vein outflow obstruction. The dominant *intrahepatic* cause of portal hypertension is cirrhosis, in which bands of fibrous tissue and fibrous nodules distort the architecture of the liver and increase the resistance to blood flow.

Portal Hypertension

- Venous blood from the gastrointestinal tract empties into the portal vein and travels through the liver before moving into the general venous circulation.
- Obstruction of blood flow in the portal vein produces an increase in the hydrostatic pressure within the peritoneal capillaries, contributing to the development of ascites, splenic engorgement with sequestration and destruction of blood cells and platelets, and shunting of blood to collateral venous channels causing varicosities of the hemorrhoidal and esophageal veins.

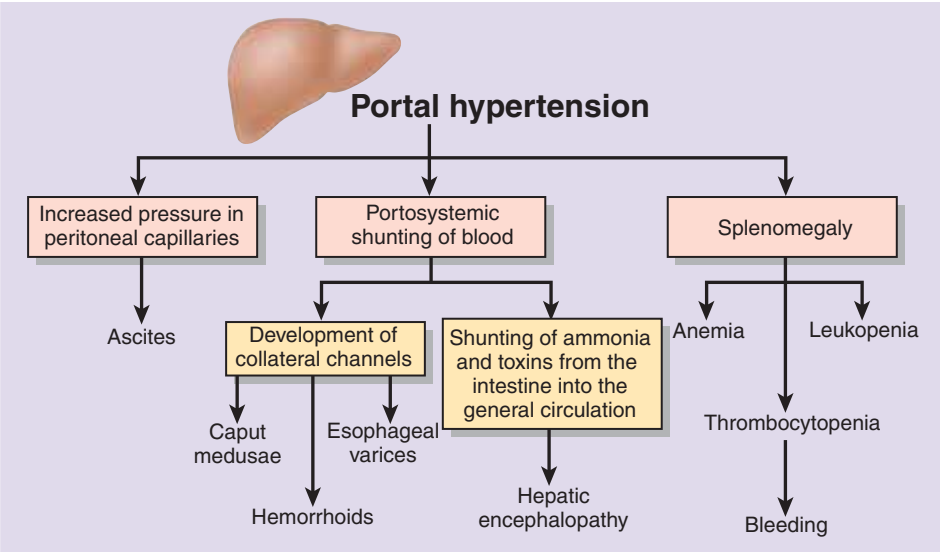


FIGURE 30-13. Mechanisms of disturbed liver function related to portal hypertension.

The major clinical consequences of portal hypertension arise from the increased pressure and dilation of the venous channels behind the obstruction. In addition, collateral channels open that connect the portal circulation with the systemic venous circulation. The complications of the increased portal vein pressure and the opening of collateral channels are ascites, congestive splenomegaly, and the formation of portosystemic shunts with bleeding from esophageal varices (Fig. 30-13).

Ascites. Ascites occurs when the amount of fluid in the peritoneal cavity is increased and is a late-stage manifestation of cirrhosis and portal hypertension.[3,4,40] Ascites usually becomes clinically evident when at least 500 mL of fluid has accumulated. However, the amount may be so great (frequently several liters) that it not only distends the abdomen, but also interferes with breathing. The fluid is generally serous, having less than 3 g of protein (largely albumin) and a concentration of solutes (glucose, sodium, and potassium) similar to that in the blood.

Although the mechanisms responsible for the development of ascites are not completely understood, several factors appear to contribute to fluid accumulation, including an increase in hydrostatic pressure due to portal hypertension, salt and water retention by the kidney, and decreased colloidal osmotic pressure due to impaired synthesis of albumin by the liver. Diminished blood volume (i.e., underfill theory) and excessive blood volume (i.e., overfill theory) have been used to explain the increased salt and water retention by the kidney. According to the underfill theory, a contraction in the effective blood volume causes the kidney to retain salt and water. The effective blood volume may be reduced because of loss of fluid into the peritoneal cavity or because of vasodilation caused by the presence of circulating vasodilating substances. The overfill theory proposes that the initial event in the development of ascites is renal retention of salt and water caused by disturbances in the liver itself. These disturbances include failure of the liver to metabolize aldosterone, causing an increase in salt and water retention by the kidney. Another likely contributing factor in the pathogenesis of ascites is a decreased colloidal osmotic pressure, which limits reabsorption of fluid from the peritoneal cavity (see Chapter 8).

Treatment of ascites usually focuses on dietary restriction of sodium and administration of diuretics.[18,40] Water intake also may need to be restricted. Because of the many limitations in sodium restriction, the use of diuretics has become the mainstay of treatment for ascites. Two classes of diuretics are used: a diuretic that acts in the distal part of the nephron to inhibit aldosterone-dependent sodium reabsorption and a loop diuretic such as furosemide (see Chapter 24). Oral potassium supplements often are given to prevent hypokalemia. Large-volume paracentesis (removal of 5 L or more of ascitic fluid) may be done in persons with massive ascites and pulmonary compromise.[18] Because the removal of fluid produces a decrease in vascular volume along with increased plasma renin activity and aldosterone-mediated sodium and water reabsorption by the kidneys, a volume expander such as albumin usually is administered to maintain the effective circulating volume. A transjugular intrahepatic portosystemic shunt may be inserted in persons with refractory ascites (to be discussed).[18]

Spontaneous bacterial peritonitis is a potential complication in persons with both cirrhosis and ascites. The infection is serious and carries a high mortality rate even when treated with antibiotics. Presumably, the peritoneal fluid is seeded with bacteria from the blood or lymph or from passage of bacteria through the bowel wall. Symptoms include fever and abdominal pain. Other symptoms include worsening of hepatic encephalopathy, diarrhea, hypothermia, and shock. It is diagnosed by a neutrophil count of 250/mm^3 or higher and a protein concentration of 1 g/dL or less in the ascitic fluid.[18]

Splenomegaly. The spleen enlarges progressively in portal hypertension because of shunting of blood into the splenic vein.[3] The enlarged spleen often gives rise to sequestering of significant numbers of blood elements

and development of a syndrome known as *hypersplenism*. Hypersplenism is characterized by a decrease in the life span of all the formed elements of the blood and a subsequent decrease in their numbers, leading to anemia, thrombocytopenia, and leukopenia. The decreased life span of the blood elements is thought to result from an increased rate of removal because of the prolonged transit time through the enlarged spleen.

Portosystemic Shunts and Esophageal Varices. With the gradual obstruction of venous blood flow in the liver, the pressure in the portal vein increases, and large collateral channels develop between the portal and systemic veins that supply the lower rectum and esophagus and the umbilical veins of the falciform ligament that attaches to the anterior wall of the abdomen.[3,4] The collaterals between the inferior and internal iliac veins may give rise to hemorrhoids. In some persons, the fetal umbilical vein is not totally obliterated; it forms a channel on the anterior abdominal wall. Dilated veins around the umbilicus are called *caput medusae*. Portopulmonary shunts also may develop and cause blood to bypass the pulmonary capillaries, interfering with blood oxygenation and producing cyanosis.

Clinically, the most important collateral channels are those connecting the portal and coronary veins that lead to reversal of flow and formation of thin-walled varicosities in the submucosa of the esophagus[3,4,39,41] (Fig. 30-14). These thin-walled *esophageal varices* are subject to rupture, producing massive and sometimes fatal hemorrhage. Impaired hepatic synthesis of coagulation factors and decreased platelet levels (i.e., thrombocytopenia) due to splenomegaly may further complicate the control of esophageal bleeding.

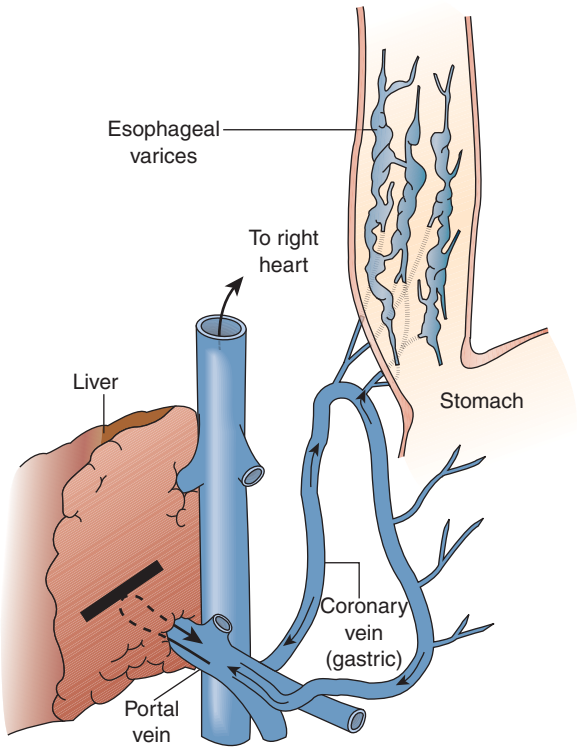


FIGURE 30-14. Obstruction of blood flow in the portal circulation, with portal hypertension and diversion of blood flow to other venous channels, including the gastric and esophageal veins.

Treatment of portal hypertension and esophageal varices is directed at prevention of initial hemorrhage, management of acute hemorrhage, and prevention of recurrent hemorrhage. Pharmacologic therapy is used to lower portal venous pressure and prevent initial hemorrhage. Nonselective β-adrenergic blocking drugs (propranolol, nadolol) commonly are used for this purpose.[39] These agents reduce portal venous pressure by decreasing splanchnic blood flow and thereby decreasing blood flow in collateral channels.

Several methods are used to control acute hemorrhage, including pharmacologic therapy, balloon tamponade, and emergent endoscopic therapy.[39,41] Pharmacologic methods include the administration of octreotide, a long-acting synthetic analog of somatostatin. Somatostatin, which is normally produced by enteric cells in the gastrointestinal tract, by delta cells in the endocrine pancreas, and from the hypothalamus, reduces splanchnic and hepatic blood flow and portal pressures in persons with cirrhosis. The drug, which is given intravenously, provides control of variceal bleeding in up to 80% of cases.[41] Balloon tamponade provides compression of the varices and is accomplished through the insertion of a tube with inflatable gastric and esophageal balloons. After the tube has been inserted, the balloons are inflated; the esophageal balloon compresses the bleeding esophageal veins, and the gastric balloon helps to maintain the position of the tube. Emergent endoscopic procedures include sclerotherapy, in which the varices are injected with a sclerosing solution that obliterates the vessel lumen, and ligation, in which a band is inserted around the bleeding vessel.

Prevention of recurrent hemorrhage focuses on lowering portal venous pressure and diverting blood flow away from the easily ruptured collateral channels.[39] Two procedures may be used for this purpose: the surgical creation of a portosystemic shunt or a transjugular intrahepatic portosystemic shunt (TIPS). *Surgical portosystemic shunt* procedures involve the creation of an opening between the portal vein and a systemic vein. These shunts have a considerable complication rate, and TIPS has evolved as the preferred treatment for refractory portal hypertension. The TIPS procedure involves insertion of an expandable metal stent between a branch of the hepatic vein and the portal vein using a catheter inserted through the internal jugular vein. A limitation of the procedure is that stenosis and thrombosis of the stent occur in most cases over time, with consequent risk of rebleeding. A complication that is associated with the creation of a portosystemic shunt is hepatic encephalopathy, which is thought to result when ammonia and other neurotoxic substances from the gut pass directly into the systemic circulation without going through the liver.

Liver Failure

The most severe clinical consequence of liver disease is hepatic failure.[3,4] It may result from sudden and massive

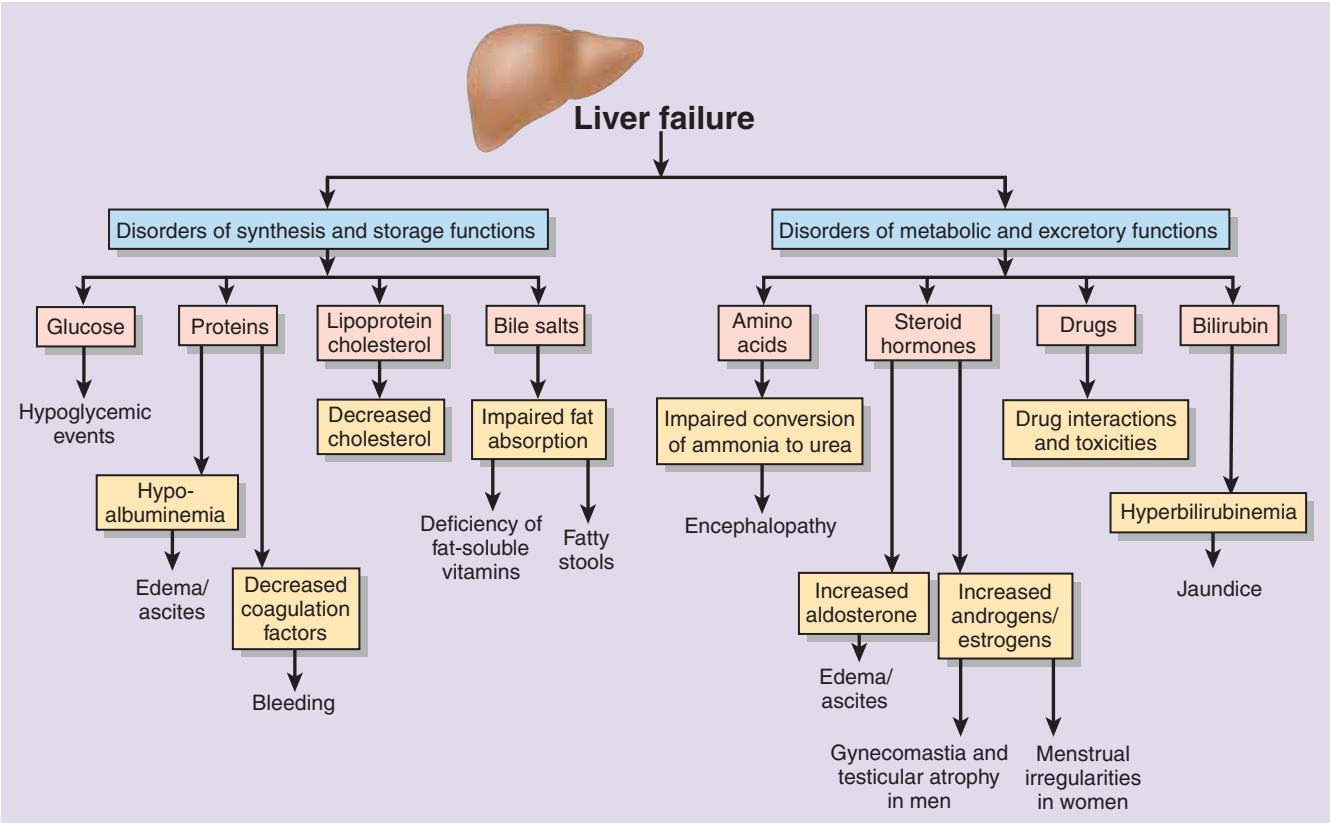


FIGURE 30-15. Alterations in liver function and manifestations of liver failure.

liver destruction, as in fulminant hepatitis, or be the result of progressive damage to the liver, as occurs in alcoholic cirrhosis. Whatever the cause, 80% to 90% of hepatic functional capacity must be lost before hepatic failure occurs.[3] In many cases, the progressive decompensating effects of the disease are hastened by intercurrent conditions such as gastrointestinal bleeding, systemic infection, electrolyte disturbances, or superimposed diseases such as heart failure.

Manifestations. The manifestations of liver failure reflect the various synthesis, storage, metabolic, and elimination functions of the liver (Fig. 30-15). *Fetor hepaticus* refers to a characteristic musty, sweetish odor of the breath in the patient in advanced liver failure, resulting from the metabolic by-products of the intestinal bacteria.

Liver failure can cause *anemia*, *thrombocytopenia*, *coagulation defects*, and *leukopenia*. Anemia may be caused by blood loss, excessive red blood cell destruction, and impaired formation of red blood cells. A folic acid deficiency may lead to severe megaloblastic anemia. Changes in the lipid composition of the red blood cell membrane increase hemolysis. Because factors V, VII, IX, and X; prothrombin; and fibrinogen are synthesized by the liver, their decline in liver disease contributes to bleeding disorders. Malabsorption of the fat-soluble vitamin K contributes further to the impaired synthesis of these clotting factors. Thrombocytopenia often occurs as the result of splenomegaly. The person with liver failure is subject to purpura, easy bruising, hematuria, and abnormal menstrual bleeding and is vulnerable to bleeding from the esophagus and other segments of the gastrointestinal tract.

Endocrine disorders, particularly disturbances in gonadal (sex hormone) function, are common accompaniments of cirrhosis and liver failure. Women may have menstrual irregularities (usually amenorrhea), loss of libido, and sterility. In men, testosterone levels usually fall, the testes atrophy, and loss of libido, impotence, and gynecomastia occur. A decrease in aldosterone metabolism may contribute to salt and water retention by the kidney, along with a lowering of serum potassium resulting from increased elimination of potassium.

Liver failure also brings on numerous *skin disorders*. These lesions, called variously *vascular spiders, telangiectases, spider angiomas,* and *spider nevi,* are seen most often in the upper half of the body. They consist of a central pulsating arteriole from which smaller vessels radiate. Palmar erythema is redness of the palms, probably caused by increased blood flow from higher cardiac output. Clubbing of the fingers may be seen in persons with cirrhosis. Jaundice usually is a late manifestation of liver failure.

The *hepatorenal syndrome* refers to a functional renal failure sometimes seen during the terminal stages of liver failure with ascites.[42] It is characterized by progressive azotemia, increased serum creatinine levels, and oliguria. Although the basic cause is unknown, a decrease in renal blood flow is believed to play a part. Ultimately, when

renal failure is superimposed on liver failure, azotemia and elevated levels of blood ammonia occur; this condition is thought to contribute to hepatic encephalopathy and coma.

Hepatic encephalopathy refers to the totality of central nervous system manifestations of liver failure.[3,43] It is characterized by neural disturbances ranging from a lack of mental alertness to confusion, coma, and convulsions. A very early sign of hepatic encephalopathy is a flapping tremor called *asterixis*. Various degrees of memory loss may occur, coupled with personality changes such as euphoria, irritability, anxiety, and lack of concern about personal appearance and self. Speech may be impaired, and the person may be unable to perform certain purposeful movements. The encephalopathy may progress to decerebrate rigidity and then to a terminal deep coma.

Although the cause of hepatic encephalopathy is unknown, the accumulation of neurotoxins, which appear in the blood because the liver has lost its detoxifying capacity, is believed to be a factor. Hepatic encephalopathy develops in approximately 10% of persons with portosystemic shunts. One of the suspected neurotoxins is ammonia. A particularly important function of the liver is the conversion of ammonia, a by-product of protein and amino acid metabolism, to urea. The ammonium ion is produced in abundance in the intestinal tract, particularly in the colon, by the bacterial degradation of luminal proteins and amino acids. Normally, these ammonium ions diffuse into the portal blood and are transported to the liver, where they are converted to urea before entering the general circulation. When the blood from the intestine bypasses the liver or the liver is unable to convert ammonia to urea, ammonia moves directly into the general circulation and from there to the cerebral circulation. Hepatic encephalopathy may become worse after a large protein meal or gastrointestinal tract bleeding. Narcotics and tranquilizers are poorly metabolized by the liver, and administration of these drugs may contribute to central nervous system depression and precipitate hepatic encephalopathy.

A nonabsorbable antibiotic, such as neomycin, may be given to eradicate bacteria from the bowel and thus prevent this cause of ammonia production. Another drug that may be used is lactulose. It is not absorbed from the small intestine but moves directly to the large intestine, where it is broken down by colonic bacteria to small organic acids that cause production of large, loose stools with a low pH. The low pH favors the conversion of ammonia to ammonium ions, which are not absorbed by the blood. The acid pH also inhibits the intestinal degradation of amino acids, proteins, and blood.

Treatment. The treatment of liver failure is directed toward eliminating alcohol intake when the condition is caused by alcoholic cirrhosis; preventing infections; providing sufficient carbohydrates and calories to prevent protein breakdown; correcting fluid and electrolyte imbalances, particularly hypokalemia; and decreasing ammonia production in the gastrointestinal tract by controlling protein intake. In many cases, liver transplantation remains the only effective treatment.

Liver transplantation rapidly is becoming a realistic form of treatment for many persons with irreversible chronic liver disease, fulminant liver failure, primary biliary cirrhosis, chronic active hepatitis, sclerosing cholangitis, and certain metabolic disorders that result in end-stage liver disease. Currently, 1-year survival rates approach 90%, and a 3-year survival rate of 80% is achieved at many transplantation centers in the United States.[44] In addition to longer survival, many liver recipients are now experiencing improved quality of life, including return to active employment. Unfortunately, the shortage of donor organs severely limits the number of transplantations that are done, and many persons die each year while waiting for a transplant. During the past several years a number of innovative methods have been developed to deal with the shortage, including split liver transplantation, in which a cadaver liver is split into two pieces and transplanted into two recipients, and living donor transplantation, in which a segment or lobe from the liver from a living donor is resected and grafted into a recipient.[44]

Cancer of the Liver

Primary Liver Cancers

There are two major types of primary liver cancer: hepatocellular carcinoma, which arises from the liver cells, and cholangiocarcinoma, which is a primary cancer of bile duct cells.[3,4] Although primary tumors of the liver are relatively rare in developed countries of the world, the liver shares with the lung the distinction of being the most common site of metastatic tumors.

Hepatocellular Carcinoma. Hepatocellular cancer, the most common form of liver cancer, is the fifth most common cancer and third leading cause of cancer-related mortality worldwide.[45,46] In East Asia and sub-Saharan Africa, the incidence is 15 cases per 100,000. In Europe, Australia, and the United States, the incidence is approximately 3 cases per 100,000.[46] There has been an increased incidence, however, in developed countries as a consequence of chronic HCV infection.[45,46]

Among the factors identified as etiologic agents in liver cancer are chronic viral hepatitis (i.e., HBV, HCV, HDV), chronic alcoholism, nonalcoholic fatty liver disease, long-term exposure to environmental agents such as aflatoxin, and drinking water contaminated with arsenic. Just how these etiologic agents contribute to the development of liver cancer is still unclear. With HBV and HCV, both of which become integrated into the host DNA, repeated cycles of cell death and regeneration afford the potential for development of cancer-producing mutations. Aflatoxins, produced by food spoilage molds in certain areas endemic for hepatocellular carcinoma, are particularly potent carcinogenic agents.[3,46] They are activated by hepatocytes and their products incorporated into the host DNA with the potential for developing cancer-producing mutations.

The manifestations of hepatocellular cancer often are insidious in onset and masked by those related to cirrhosis

or chronic hepatitis. The initial symptoms include weakness, anorexia, weight loss, fatigue, bloating, a sensation of abdominal fullness, and a dull, aching abdominal pain.[46,47] Ascites, which often obscures weight loss, is common. Jaundice, if present, usually is mild. There may be a rapid increase in liver size and worsening of ascites in persons with preexisting cirrhosis. Usually, the liver is enlarged when these symptoms appear. Various paraneoplastic syndromes (e.g., disturbances due to ectopic hormone or growth factor production by the tumor [see Chapter 7]) have been associated with hepatocellular cancer, including erythrocytosis (erythropoietin), hypoglycemia (insulin-like growth factor), and hypercalcemia (parathyroid-related protein). Serum α-fetoprotein, which is present during fetal life but barely detectable in the serum after the age of 2 years, is present in 50% of persons with hepatocellular carcinoma.[3] However, the test lacks specificity and is not very useful as a surveillance or diagnostic tool. Diagnostic methods include ultrasonography, CT scans, and MRI. Liver biopsy may be used to confirm the diagnosis.

Primary cancers of the liver are often far advanced at the time of diagnosis. The treatment of choice is subtotal hepatectomy, if conditions permit. Chemotherapy and radiation therapy are largely palliative. Although liver transplantation may be an option for people with well-compensated cirrhosis and small tumors, it often is impractical because of the shortage of donor organs.

Cholangiocarcinoma. Cholangiocarcinoma is a malignancy of the biliary tree, arising from bile ducts within and outside the liver. It accounts for 7.6% of cancer deaths worldwide and 3% of cancer deaths in the United States.[3] The etiology, clinical features, and prognosis vary considerably with the part of the biliary tree that is the site of origin. Cholangiocarcinoma is not associated with the same risk factors as hepatocellular carcinoma. Instead, most of the risk factors revolve around long-standing inflammation and injury of the bile duct epithelium. Cholangiocarcinoma often presents with pain, weight loss, anorexia, and abdominal swelling or awareness of a mass in the right hypochondrium. Tumors affecting the central or distal bile ducts may present with jaundice.

Metastatic Tumors

Metastatic tumors of the liver are much more common than primary tumors.[3,4] Common sources include colorectal cancer and those spread from breast, lung, or urogenital cancer. In addition, tumors of neuroendocrine origin spread to the liver. It often is difficult to distinguish primary from metastatic tumors with the use of CT scans, MRI, or ultrasonography. Usually the diagnosis is confirmed by biopsy.

In summary, the liver is subject to most of the disease processes that affect other body structures, such as infections, autoimmune disorders, toxic injury, metabolic diseases, and neoplasms. Hepatitis is characterized by inflammation of the liver. Acute viral hepatitis is caused by hepatitis viruses A, B, C, D, and E. Although all these viruses cause acute hepatitis, they differ in terms of mode of transmission, incubation period, mechanism, degree and chronicity of liver damage, and the ability to evolve to a carrier state. HBV, HCV, and HDV infections have the potential for progression to the carrier state, chronic hepatitis, and hepatocellular carcinoma. Autoimmune hepatitis involves the immune destruction of hepatocytes. Intrahepatic biliary diseases disrupt the flow of bile through the liver, causing cholestasis and biliary cirrhosis. Among the causes of intrahepatic biliary diseases are primary biliary cirrhosis, primary sclerosing cholangitis, and secondary biliary cirrhosis.

As the major drug-metabolizing and detoxifying organ in the body, the liver is subject to potential damage from an enormous array of pharmaceutical and environmental chemicals. Drugs and chemicals can exert their effects by causing hepatocyte injury and death or by cholestatic liver damage due to injury of biliary drainage structures. Drug reactions can be predictable based on the drug's chemical structure and metabolites, or unpredictable (idiosyncratic) based on individual characteristics of the person receiving the drug. Early identification of drug-induced liver disease is important because withdrawal of the drug is curative in most cases. Because alcohol competes for use of intracellular cofactors normally needed by the liver for other metabolic processes, it tends to disrupt the metabolic functions of the liver. The spectrum of alcoholic liver disease includes fatty liver disease, alcoholic hepatitis, and cirrhosis.

Portal hypertension, cirrhosis, and liver failure represent clinical syndromes common to a number of liver diseases. Portal hypertension is characterized by increased resistance to flow and increased pressure in the portal venous system; the pathologic consequences of the disorder include ascites, the formation of collateral bypass channels (e.g., esophageal varices) from the portosystemic circulation, and splenomegaly. Cirrhosis represents the end stage of chronic liver disease in which much of the functional liver tissue has been replaced by fibrous tissue. The fibrous tissue forms constrictive bands that disrupt flow in the vascular channels and biliary duct systems of the liver. The disruption of vascular channels predisposes to portal hypertension and its complications, loss of liver cells, and eventual liver failure. Liver failure represents the end stage of a number of liver diseases and occurs when less than 10% of liver tissue is functional. The manifestations of liver failure reflect the various functions of the liver, including hematologic disorders, disruption of endocrine function, skin disorders, hepatorenal syndrome, and hepatic encephalopathy.

There are two types of primary cancers of the liver: hepatocellular (the most common form, derived from hepatocytes and their precursors) and cholangiocarcinoma (bile duct cancer, arising from biliary epithelium). Hepatocellular carcinoma, which is associated with HBV

and HCV infection, alcoholic cirrhosis, and food contaminants (e.g., aflatoxins), is the fifth most common cancer and third leading cause of cancer-related mortality worldwide. Cholangiocarcinoma occurs primarily in older persons with a history of chronic disorders of the bile ducts. Although primary tumors of the liver are relatively rare in developed countries of the world, the liver shares with the lung the distinction of being the most common site of metastatic tumors.

Disorders of the Gallbladder and Exocrine Pancreas

The so-called hepatobiliary system consists of the gallbladder; the left and right hepatic ducts, which come together to form the common hepatic duct; the cystic duct, which extends to the gallbladder; and the bile duct, which is formed by the union of the common hepatic duct and the cystic duct[2] (Fig. 30-16). The bile duct descends posteriorly to the first part of the duodenum, where it comes in contact with the main pancreatic duct. These ducts unite to form the hepatopancreatic ampulla. The circular muscle around the distal end of the bile duct is thickened to form the sphincter of the bile duct.

The pancreas lies transversely in the posterior part of the upper abdomen (see Fig. 30-1). The head of the pancreas is at the right of the abdomen; it rests against the curve of the duodenum in the area of the hepatopancreatic ampulla and its entrance into the duodenum. The body of the pancreas lies beneath the stomach. The tail touches the spleen. The pancreas is virtually hidden because of its posterior position; unlike many other organs, it cannot be palpated. Because of the position of the pancreas and its large functional reserve, symptoms from conditions such as cancer of the pancreas do not usually appear until the disorder is far advanced.

The pancreas is both an endocrine and exocrine organ. Its function as an endocrine organ is discussed in Chapter 33. The exocrine pancreas is made up of lobules that consist of acinar cells, which secrete digestive enzymes into a system of microscopic ducts. These ducts empty into the main pancreatic duct, which extends from left to right through the substance of the pancreas. The main pancreatic duct and the bile duct unite to form the hepatopancreatic ampulla, which empties into the duodenum. The sphincter of the pancreatic duct controls the flow of pancreatic secretions into the bile duct (see Fig. 30-16).

Disorders of the Gallbladder

The gallbladder is a distensible, pear-shaped muscular sac located on the ventral surface of the liver.[2] It has an outer serous peritoneal layer, a middle smooth muscle layer, and an inner mucosal layer that is continuous with the lining of the bile duct. The function of the gallbladder is to store and concentrate bile. Bile contains bile salts, cholesterol, bilirubin, lecithin, fatty acids, water, and the electrolytes normally found in the plasma. The cholesterol found in bile has no known

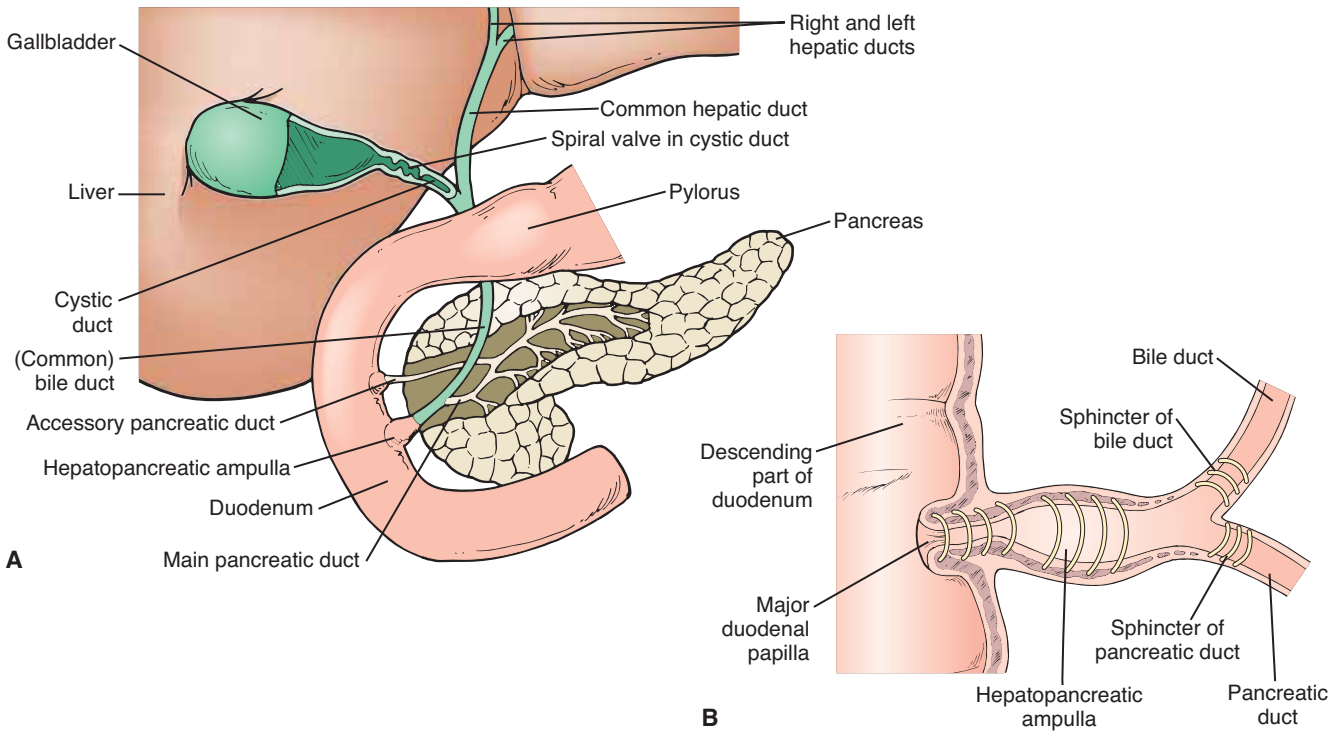


FIGURE 30-16. **(A)** Extrahepatic bile passages, gallbladder, and pancreatic ducts. **(B)** Entry of bile duct and pancreatic duct into the hepatopancreatic ampulla, which opens into the duodenum.

function; it is assumed to be a by-product of bile salt formation, and its presence is linked to the excretory function of bile. Normally insoluble in water, cholesterol is rendered soluble by the action of bile salts and lecithin, which combine with it to form micelles. In the gallbladder, water and electrolytes are absorbed from the liver bile, causing the bile to become more concentrated. Because neither lecithin nor bile salts are absorbed in the gallbladder, their concentration increases along with that of cholesterol; in this way, the solubility of cholesterol is maintained.

Entrance of food into the intestine causes the gallbladder to contract and the sphincter of the bile duct to relax, such that bile stored in the gallbladder moves into the duodenum. The stimulus for gallbladder contraction is primarily hormonal. Products of food digestion, particularly lipids, stimulate the release of a gastrointestinal hormone called *cholecystokinin* from the mucosa of the duodenum. Cholecystokinin provides a strong stimulus for gallbladder contraction. The role of other gastrointestinal hormones in bile release is less clearly understood.

Passage of bile into the intestine is regulated largely by the pressure in the common duct. Normally, the gallbladder regulates this pressure. It collects and stores bile as it relaxes and the pressure in the common bile duct decreases, and it empties bile into the intestine as the gallbladder contracts, producing an increase in common duct pressure. After gallbladder surgery, the pressure in the common duct changes, causing the common duct to dilate. The flow of bile then is regulated by the sphincters in the common duct.

Two common disorders of the biliary system are cholelithiasis (i.e., gallstones) and inflammation of the gallbladder (cholecystitis) or common bile duct (cholangitis). At least 10% of adults have gallstones.[3,4] There is an increased prevalence with age, and approximately twice as many white women as men have gallstones.[3] In both circumstances, hypersecretion of biliary cholesterol appears to play a major role.

Cholelithiasis

Cholelithiasis or gallstones is caused by precipitation of substances contained in bile, mainly cholesterol and bilirubin. Approximately 80% of gallstones are composed primarily of cholesterol; the other 20% are black or brown pigment stones consisting of calcium salts with bilirubin.[3] Pigment stones containing bilirubin are seen in persons with hemolytic disease (e.g., sickle cell disease) and hepatic cirrhosis. Many stones have a mixed composition. Figure 30-17 shows a gallbladder with numerous cholesterol gallstones.

Three factors contribute to the formation of gallstones: abnormalities in the composition of bile, stasis of bile, and inflammation of the gallbladder.[3,4] The formation of cholesterol stones is associated with obesity and occurs more frequently in women, especially women who have had multiple pregnancies or who are taking oral contraceptives. All of these factors cause the liver to excrete more cholesterol into the bile. Estrogen reduces the synthesis of bile acid in women. Gallbladder sludge

FIGURE 30-17. Cholesterol gallstones. The gallbladder has been opened to reveal numerous yellow cholesterol gallstones. (From Rubin R., Rubin E. [2008]. The liver and biliary system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 668]. Philadelphia: Lippincott Williams & Wilkins.)

(thickened gallbladder mucoprotein with tiny trapped cholesterol crystals) is thought to be a precursor of gallstones. Sludge frequently occurs with pregnancy, starvation, and rapid weight loss. Drugs that lower serum cholesterol levels, such as clofibrate, also cause increased cholesterol excretion into the bile. Malabsorption disorders stemming from ileal disease or intestinal bypass surgery tend to interfere with the absorption of bile salts, which are needed to maintain the solubility of cholesterol. Inflammation of the gallbladder alters the absorptive characteristics of the mucosal layer, allowing excessive absorption of water and bile salts. Cholesterol gallstones are extremely common among Native Americans, which suggests that a genetic component may have a role in gallstone formation.

Many persons with gallstones have no symptoms. Gallstones cause symptoms when they obstruct bile flow.[47,48] Small stones (i.e., <8 mm in diameter) pass into the common duct, producing symptoms of indigestion and biliary colic. Larger stones are more likely to obstruct flow and cause jaundice. The pain of biliary colic is usually located in the upper right quadrant or epigastric area and may be referred to the upper back, right shoulder, or midscapular region. Typically the pain is abrupt in onset, increases steadily in intensity, persists for 2 to 8 hours, and is followed by soreness in the upper right quadrant.

Acute Cholecystitis

Acute cholecystitis is a diffuse inflammation of the gallbladder, usually secondary to obstruction of the gallbladder outlet. Most cases of acute cholecystitis (85% to

90%) are associated with the presence of gallstones (calculous cholecystitis).[3,4,48–50] The remaining cases (acalculous cholecystitis) are associated with sepsis, severe trauma, or infection of the gallbladder. Acute acalculous cholecystitis, which involves ischemic rather than inflammatory changes associated with stones, can rapidly progress to gangrene and perforation.[48]

Acute *calculous* cholecystitis occurs when a stone becomes impacted in the cystic duct and inflammation develops behind the obstruction. It has been theorized that obstruction of the cystic duct leads to the release of mucosal phospholipase from the epithelium of the gallbladder. These lipases, in turn, lead to disruption of the normal glycoprotein mucous layer, exposing the mucosal epithelium to the destructive action of concentrated bile salts.[3,4] Acute *acalculous* cholecystitis is thought to result from ischemia. The cystic artery is an end artery with essentially no collateral circulation.[3] Contributing factors may include inflammation and edema of the gallbladder wall, stasis of bile, and conditions that lead to cystic duct obstruction in the absence of frank stone formation. Risk factors for acute acalculous cholecystitis include sepsis with hypotension and multisystem organ failure, immunosuppression, major trauma and burns, diabetes mellitus, and infections.[3,48]

Persons with acute cholecystitis usually experience an acute onset of upper right quadrant or epigastric pain, frequently associated with mild fever, anorexia, nausea, vomiting.[48–50] Whereas in biliary colic the cystic duct obstruction is transient, in acute cholecystitis it is persistent. Persons with calculous cholecystitis usually, but not always, have experienced previous episodes of biliary pain. The pain may appear with remarkable suddenness and constitute a surgical emergency. In the absence of medical attention, the attack usually subsides in 7 to 10 days and frequently within 24 hours. In persons who recover, recurrence is common. The onset of acalculous cholecystitis tends to be more insidious because the manifestations are obscured by the underlying conditions precipitating the attack. In the severely ill patient, early recognition is crucial because a delay in treatment can prove life-threatening. Persons with acute cholecystitis usually have an elevated white blood cell count and many have mild elevations in AST, ALT, alkaline phosphatase, and bilirubin.

Chronic Cholecystitis

Chronic cholecystitis results from repeated episodes of acute cholecystitis or chronic irritation of the gallbladder by stones.[3,4] It is characterized by varying degrees of chronic inflammation. Gallstones almost always are present. Cholelithiasis with chronic cholecystitis may be associated with acute exacerbations of gallbladder inflammation, common duct stones, pancreatitis, and, rarely, carcinoma of the gallbladder.

The manifestations of chronic cholecystitis are more vague than those of acute cholecystitis. There may be intolerance to fatty foods, belching, and other indications of discomfort. Often, there are episodes of colicky pain with obstruction of biliary flow caused by gallstones. The gallbladder, which in chronic cholecystitis usually contains stones, may be enlarged, shrunken, or of normal size.

Diagnosis and Treatment of Gallbladder Disease

The methods used to diagnose gallbladder disease include ultrasonography, cholescintigraphy (nuclear scanning), and CT scans.[48–50] Ultrasonography is widely used in diagnosing gallbladder disease and has largely replaced the oral cholecystogram in most medical centers. It can detect stones as small as 1 to 2 cm, and its overall accuracy in detecting gallbladder disease is high. In addition to stones, ultrasonography can detect wall thickening, which indicates inflammation. It also can rule out other causes of right upper quadrant pain such as tumors. Cholescintigraphy, also called a *gallbladder scan,* relies on the ability of the liver to extract a rapidly injected radionuclide, technetium-99m, bound to one of several iminodiacetic acids, that is excreted into the bile ducts. Serial scanning images are obtained within several minutes of the injection of the tracer and every 10 to 15 minutes during the next hour. The gallbladder scan is highly accurate in detecting acute cholecystitis. Although CT is not as accurate as ultrasonography in detecting gallstones, it can show thickening of the gallbladder wall or pericholecystic fluid associated with acute cholecystitis.

Gallbladder disease usually is treated by removing the gallbladder. The gallbladder stores and concentrates bile, and its removal usually does not interfere with digestion. Laparoscopic cholecystectomy has become the treatment of choice for symptomatic gallbladder disease.[48] The procedure involves insertion of a laparoscope through a small incision near the umbilicus, and surgical instruments are inserted through several stab wounds in the upper abdomen. Although the procedure requires more time than the older open surgical procedure, it usually requires only 1 night in the hospital. A major advantage of the procedure is that patients can return to work in 1 to 2 weeks, compared with 4 to 6 weeks after open cholecystectomy.

Choledocholithiasis and Cholangitis

Choledocholithiasis refers to stones in the common duct and *cholangitis* to inflammation of the common duct.[3,48] Common duct stones usually originate in the gallbladder, but can form spontaneously in the common duct.

The manifestations of choledocholithiasis are similar to those of gallstones and acute cholecystitis. There is a history of acute biliary colic and right upper abdominal pain, with chills, fever, and jaundice associated with episodes of abdominal pain. Bilirubinuria and an elevated serum bilirubin are present if the common duct is obstructed. Complications include acute suppurative cholangitis accompanied by pus in the common duct. It is characterized by the presence of an altered sensorium, lethargy, and septic shock.[3] Acute suppurative cholangitis represents an endoscopic or surgical emergency. Common duct stones also can obstruct the outflow of the pancreatic duct, causing a secondary pancreatitis.

Ultrasonography, CT scans, and radionuclide imaging may be used to demonstrate dilation of bile ducts and impaired blood flow. Endoscopic ultrasonography and magnetic resonance cholangiography are used for detecting common duct stones. Both percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) provide a direct means for determining the cause, location, and extent of obstruction. PTC involves the injection of dye directly into the biliary tree. It requires the insertion of a thin, flexible needle through a small incision in the skin with advancement into the biliary tree. ERCP involves the passage of an endoscope into the duodenum and the passage of a catheter into the hepatopancreatic ampulla. ERCP can be used to enlarge the opening of the sphincter of the bile duct, which may allow the lodged stone to pass, or an instrument may be inserted into the bile duct to remove the stone.

Common duct stones in persons with cholelithiasis usually are treated by stone extraction followed by laparoscopic cholecystectomy. Antibiotic therapy, with an agent that enters the bile, is used to treat the infection. Emergency decompression of the common duct, usually by ERCP, may be necessary for persons who are septic or fail to improve with antibiotic treatment.

Cancer of the Gallbladder

Cancer of the gallbladder is the fifth most common cancer of the gastrointestinal tract. It is slightly more common in women and occurs more often in the seventh decade of life. The onset of symptoms usually is insidious, and they resemble those of cholecystitis; the diagnosis often is made unexpectedly at the time of gallbladder surgery. About 80% to 85% of persons with gallbladder cancer have cholelithiasis.[51] Because of its ability to produce chronic irritation of the gallbladder mucosa, it is believed that cholelithiasis plays a role in the development of gallbladder cancer. It is seldom resectable at the time of diagnosis, and the mean 5-year survival rate has remained a dismal 1% for many years.[3]

Disorders of the Exocrine Pancreas

The pancreas is both an endocrine organ (see Chapter 33) and exocrine organ. The exocrine pancreatic secretions contain proteolytic enzymes that break down dietary proteins, including trypsin, chymotrypsin, carboxypolypeptidase, ribonuclease, and deoxyribonuclease. The pancreas also secretes pancreatic amylase, which breaks down starch, and lipases, which hydrolyze neutral fats into glycerol and fatty acids. The pancreatic enzymes are secreted in the inactive form and become activated in the intestine. This is important because the enzymes would digest the tissue of the pancreas itself if they were secreted in the active form. The acinar cells secrete a trypsin inhibitor, which prevents trypsin activation. Because trypsin activates other proteolytic enzymes, the trypsin inhibitor prevents subsequent activation of the other enzymes.

Two types of pancreatic disease are discussed in this chapter: acute and chronic pancreatitis and cancer of the pancreas.

Acute Pancreatitis

Acute pancreatitis represents a reversible inflammatory process of the pancreatic acini brought about by premature activation of pancreatic enzymes.[52–56] Although the disease process may be limited to pancreatic tissue, it also can involve peripancreatic tissues or those of more distant organs.

The pathogenesis of acute pancreatitis involves the autodigestion of pancreatic tissue by inappropriately activated pancreatic enzymes. The process is thought to begin with the activation of trypsin. Once activated, trypsin can then activate a variety of digestive enzymes that cause pancreatic injury, resulting in an intense inflammatory response. The acute inflammatory response itself causes substantial tissue damage and may progress beyond the pancreas to produce a systemic inflammatory response syndrome and multiorgan failure (see Chapter 20). Although a number of factors are associated with the development of acute pancreatitis, most cases result from gallstones (stones in the common duct) or alcohol abuse.[52–55] In the case of biliary tract obstruction due to gallstones, pancreatic duct obstruction or biliary reflux is believed to activate the enzymes in the pancreatic duct system. The precise mechanisms whereby alcohol exerts its action are largely unknown. Alcohol is known to be a potent stimulator of pancreatic secretions, and it also is known to cause partial obstruction of the sphincter of the pancreatic duct. Acute pancreatitis also is associated with hyperlipidemia, hypercalcemia, infections (particularly viral), abdominal and surgical trauma, and drugs such as thiazide diuretics.

Clinical Features. The manifestations of acute pancreatitis can range from mild with minimal organ dysfunction to severe and life-threatening. Overall, about 20% of persons with acute pancreatitis have a severe course, and 10% to 30% of those with severe pancreatitis die.[54,55] Abdominal pain is a cardinal manifestation of acute pancreatitis. The pain is usually located in the epigastric or periumbilical region and may radiate to the back, chest, or flank areas. Physical examination findings are variable and include fever, tachycardia, hypotension, severe abdominal tenderness, respiratory distress, and abdominal distention. Recognized markers of severe disease include laboratory values that measure the inflammatory response (e.g., C-reactive protein), scoring systems that assess inflammation or organ failure, and findings on imaging studies. Clinical findings such as thirst, poor urine output, progressive tachycardia, tachypnea, hypoxemia, agitation, confusion, a rising hematocrit level, and lack of improvement in symptoms within the first 48 hours are warning signs of impending severe disease. Complications include the systemic inflammatory response, acute respiratory distress syndrome, acute tubular necrosis, and organ failure. An important disturbance related to acute pancreatitis is the loss of a large volume of fluid into the retroperitoneal and peripancreatic spaces and the abdominal cavity. Signs of hypocalcemia may develop, probably as a result

of the precipitation of serum calcium in the areas of fat necrosis.

Serum amylase and serum lipase are the laboratory markers most commonly used to establish a diagnosis of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. However, the level of elevation of the serum amylase or lipase does not correlate with the severity of the disorder. The white blood cell count may be increased, and hyperglycemia and an elevated serum bilirubin level may be present. Determination of the cause is important in guiding the immediate management and preventing recurrence. Abdominal ultrasonography is usually performed to assess for gallstones. CT scans and dynamic contrast-enhanced CT of the pancreas are used to detect necrosis and fluid accumulation.

Treatment measures depend on the severity of the disease. Persons who present with persistent or severe pain, vomiting, dehydration, or signs of impending severe acute pancreatitis require hospitalization. Treatment measures are directed at pain relief, "putting the pancreas to rest" by withholding oral foods and fluids, and restoration of lost plasma volume. Meperidine rather than morphine usually is given for pain relief because it causes fewer spasms of the sphincter of the pancreatic duct. Gastric suction is instituted to treat distention of the bowel and prevent further stimulation of the secretion of pancreatic enzymes. Intravenous fluids and electrolytes are administered to replace those lost from the circulation and to combat hypotension and shock. Intravenous colloid solutions are given to replace the fluid that has become sequestered in the abdomen and retroperitoneal space.

Complications. Sequelae in persons surviving an episode of severe acute pancreatitis include fluid collections and infection.[54] In 40% to 60% of persons with acute necrotizing pancreatitis, the necrotic debris becomes infected, usually by gram-negative organisms from the alimentary canal, further complicating the condition.[52] Fluid collections with a high level of pancreatic enzymes are usually associated with pancreatic duct disruptions and may eventually form pseudocysts (a collection of pancreatic fluid enclosed in a layer of inflammatory tissue). A pseudocyst most often is connected to a pancreatic duct, so that it continues to increase in mass. The symptoms depend on its location; for example, jaundice may occur when a cyst develops near the head of the pancreas, close to the common duct. Pseudocysts may resolve or, if they persist, may require surgical intervention.

Chronic Pancreatitis

Chronic pancreatitis is characterized by progressive and permanent destruction of the exocrine pancreas, fibrosis, and, in the later stages, destruction of the endocrine pancreas.[3,4,57,58] Most factors that cause acute pancreatitis can also cause chronic pancreatitis. However, the chief distinction between the two conditions is the irreversibility of pancreatic function that is characteristic of chronic pancreatitis. By far the most common cause of chronic pancreatitis is long-term alcohol abuse. Less common causes are long-standing obstruction of the pancreatic duct by pseudocysts, calculi, or neoplasms; autoimmune chronic pancreatitis, which occurs in association with autoimmune disorders such as Sjögren syndrome, primary sclerosing cholangitis, and inflammatory bowel disease; idiopathic chronic pancreatitis, associated with cystic fibrosis (discussed in Chapter 23); and hereditary pancreatitis, a rare autosomal dominant disorder that is associated with both acute and chronic pancreatitis.

Clinical Features. Chronic pancreatitis is manifested in episodes that are similar, albeit of lesser severity, to those of acute pancreatitis. Patients have persistent, recurring episodes of epigastric and upper left quadrant pain; the attacks often are precipitated by alcohol abuse or overeating. Anorexia, nausea, vomiting, constipation, and flatulence are common. Eventually the disease progresses to the extent that endocrine and exocrine pancreatic functions become deficient. At this point, signs of diabetes mellitus and the malabsorption syndrome (e.g., weight loss, fatty stools [steatorrhea]) become apparent.

Treatment consists of measures to treat coexisting biliary tract disease. A low-fat diet usually is prescribed. The signs of malabsorption may be treated with pancreatic enzymes. When diabetes is present, it is treated with insulin. Alcohol is forbidden because it frequently precipitates attacks. Because of the frequent episodes of pain, narcotic addiction is a potential problem in persons with chronic pancreatitis. Surgical intervention sometimes is needed to relieve the pain and usually focuses on relieving any obstruction that may be present.

Cancer of the Pancreas

Pancreatic cancer is now the fourth leading cause of death from cancer in the United States, preceded only by lung, colon, and breast cancer.[52] Considered to be one of the most deadly malignancies, pancreatic cancer is associated with a 5-year survival rate of only 4% to 5%.[52,53,60,61] The incidence of pancreatic cancer seems to be increasing in all countries studied and has tripled in the United States over the past 50 years.[53]

The cause of pancreatic cancer is unknown. Age is a major risk factor. Pancreatic cancer rarely occurs in persons younger than 50 years of age, and the risk increases with age. The most significant and reproducible environmental risk factor is cigarette smoking.[52,53,59–61] The incidence of pancreatic cancer is twice as high among smokers than nonsmokers. Diabetes and chronic pancreatitis also are associated with pancreatic cancer, although neither the nature nor the sequence of the possible cause-and-effect relation has been established. There has been a recent focus on the molecular genetics of pancreatic cancer, and more insights into the genetic mechanisms involved in pancreatic cancer undoubtedly will be forthcoming.

Clinical Features. Almost all pancreatic cancers are adenocarcinomas of the ductal epithelium, and symptoms are primarily caused by mass effect rather than disruption of exocrine or endocrine function. The clinical

manifestations depend on the size and location of the tumor as well as its metastasis. Pain, jaundice, and weight loss constitute the classic presentation of the disease. The most common pain is a dull epigastric pain often accompanied by back pain, often worse in the supine position, and relieved by sitting forward. Although the tumor can arise anywhere in the pancreas, the most frequent site is the head (60%), followed by the body (10%) and tail (5%). The pancreas is diffusely involved in the remaining 25%.[53] Because of the proximity of the pancreas to the common duct and the hepatopancreatic ampulla, cancer of the head of the pancreas tends to obstruct bile flow. Jaundice frequently is the presenting symptom of a person with cancer of the head of the pancreas, and it usually is accompanied by complaints of pain and pruritus. Cancer of the body of the pancreas usually impinges on the celiac ganglion, causing pain. The pain usually worsens with ingestion of food or assumption of the supine position. Cancer of the tail of the pancreas usually has metastasized before symptoms appear.

Migratory thrombophlebitis (deep vein thrombosis) develops in about 10% of persons with pancreatic cancer, particularly when the tumor involves the body or tail of the pancreas.[53] Thrombi develop in multiple veins, including the deep veins of the legs, the subclavian vein, the inferior and superior mesentery veins, and even the vena cava. It is not uncommon for the migratory thrombophlebitis to provide the first evidence of pancreatic cancer, although it may present in other cancers as well. The mechanism responsible for the hypercoagulable state is largely unclear, but may relate to activation of clotting factors by proteases released from the tumor cells.[53]

Patient history, physical examination, and elevated serum bilirubin and alkaline phosphate levels may suggest the presence of pancreatic cancer but are not diagnostic.[59–61] The serum cancer antigen (CA) 19-9, a Lewis blood group antigen, may help confirm the diagnosis in symptomatic patients and may help predict prognosis and recurrence after resection. However, CA 19-9 lacks the sensitivity and specificity to screen asymptomatic patients effectively.[60] Ultrasonography and CT scanning are the most frequently used diagnostic methods to confirm the disease. Intravenous and oral contrast–enhanced spiral CT is the preferred method for imaging the pancreas. Percutaneous fine needle aspiration cytology of the pancreas has been one of the major advances in the diagnosis of pancreatic cancer. Unfortunately, the smaller and more curable tumors are most likely to be missed by this procedure. ERCP may be used for evaluation of persons with suspected pancreatic cancer and obstructive jaundice.

Most cancers of the pancreas have metastasized at the time of diagnosis. Surgical resection of the tumor is done when the tumor is localized or as a palliative measure. Radiation therapy may be useful when the disease is localized but not resectable. The use of irradiation and chemotherapy for pancreatic cancer continues to be investigated. Pain control is one of the most important aspects in the management of persons with end-stage pancreatic cancer.

In summary, the biliary tract serves as a passageway for the delivery of bile from the liver to the intestine. This tract consists of the bile ducts and gallbladder. The most common causes of biliary tract disease are cholelithiasis and cholecystitis. Three factors contribute to the development of cholelithiasis: abnormalities in the composition of bile, stasis of bile, and inflammation of the gallbladder. Cholelithiasis predisposes to obstruction of bile flow, causing biliary colic and acute or chronic cholecystitis. Cancer of the gallbladder, which has a poor 5-year survival rate, occurs in 2% of persons with biliary tract disease.

The pancreas is an endocrine and exocrine organ. The exocrine pancreas produces digestive enzymes that are secreted in an inactive form and transported to the small intestine through the main pancreatic duct, which usually empties into the hepatopancreatic ampulla and then into the duodenum through the sphincter of the bile duct. The most common diseases of the exocrine pancreas are acute and chronic forms of pancreatitis and cancer. Acute and chronic pancreatitis are associated with biliary reflux and chronic alcoholism. Acute pancreatitis is an inflammatory condition of the pancreas due to inappropriate activation of pancreatic enzymes, with manifestations that can range from mild to severe and life-threatening. Chronic pancreatitis causes progressive destruction of the endocrine and exocrine pancreas. It is characterized by episodes of pain and epigastric distress that are similar to but less severe than those that occur with acute pancreatitis. Cancer of the pancreas is the fourth leading cause of cancer death in the United States. It usually is far advanced at the time of diagnosis, and the 5-year survival rate is 4% to 5%.

REVIEW EXERCISES

1. A 24-year-old woman reports to her health care professional with complaints of a yellow discoloration of her skin, loss of appetite, and a feeling of upper gastric discomfort. She denies use of intravenous drugs and has not received blood products. She cannot recall eating uncooked shellfish or drinking water that might have been contaminated. She has a daughter who attends day care.

A. What tests could be done to confirm a diagnosis of hepatitis A?
B. What is the most common mode of transmission for hepatitis A? It is suggested that the source might be through the day care center that her daughter attends. Explain.
C. What methods could be used to protect other family members from getting the disease?

2. A 56-year-old man with a history of heavy alcohol consumption and a previous diagnosis of alcoholic cirrhosis and portal hypertension is admitted to the

emergency department with acute gastrointestinal bleeding due to a tentative diagnosis of bleeding esophageal varices and signs of circulatory shock.

A. Relate the development of esophageal varices to portal hypertension in persons with cirrhosis of the liver.
B. Many persons with esophageal varices have blood coagulation problems. Explain.
C. What are the possible treatment measures for this man, both in terms of controlling the current bleeding episode and preventing further bleeding episodes?

3. A 40-year-old woman presents in the emergency department with a sudden episode of vomiting and severe right epigastric pain that developed after eating a fatty evening meal. Although there is no evidence of jaundice in her skin, the sclera of her eyes is noted to have a yellowish discoloration. Palpation reveals tenderness of the upper right quadrant with muscle splinting and rebound pain. Right upper quadrant abdominal ultrasonography confirms the presence of gallstones. The woman is treated conservatively with pain and antiemetic medications. She is subsequently scheduled for a laparoscopic cholecystectomy.

A. Relate this woman's signs and symptoms to gallstones and their effect on gallbladder function.
B. Explain the initial appearance of jaundice in the eyes as opposed to the skin. Which of the two laboratory tests for bilirubin would you expect to be elevated—direct (conjugated) or indirect (unconjugated or free)?
C. What effect will removal of the gallbladder have on the storage and release of bile into the intestine, particularly as it relates to meals?

REFERENCES

1. Guyton A., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 799–804). Philadelphia: Elsevier Saunders.
2. Ross M.H., Pawlina W. (2006). *Histology: A test and atlas* (5th ed., pp. 576–609). Philadelphia: Lippincott Williams & Wilkins.
3. Crawford J.M., Liu C. (2010). Liver and biliary tract. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 833–890). Philadelphia: Saunders Elsevier.
4. Rubin R., Rubin E. (2008). The liver and biliary system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathophysiology: Clinicopathologic foundations of medicine* (5th ed., pp. 617–673). Philadelphia: Lippincott Williams & Wilkins.
5. Pratt D.S., Kaplan M.M. (2000). Evaluation of abnormal liver-enzyme results in asymptomatic patients. *New England Journal of Medicine* 342, 1266–1271.
6. Giannini E.G., Testa R., Savarino V. (2005). Liver enzyme alteration: A guide for clinicians. *Canadian Medical Association Journal* 172, 367–379.
7. Bravo A., Sheth S.G., Chopra S. (2001). Liver biopsy. *New England Journal of Medicine* 344, 495–500.
8. Brundage S., Fitzpatrick A. (2006). Hepatitis A. *American Family Physician* 73, 2162–2170.
9. Nguyen C.T., Tran T.T. (2009). Hepatitis vaccination and prophylaxis. *Clinics in Liver Disease* 13, 317–329.
10. Dienstag J.L. (2008). Hepatitis B infection. *New England Journal of Medicine* 359(14), 1486–1500.
11. Ghany M.G., Doo E.C. (2006). Assessment and management of chronic hepatitis B. *Infectious Disease Clinics of North America* 20, 63–69.
12. Elgouhari H.M., Tamini T.I., Carey W.D. (2008). Hepatitis B infection: Understanding its epidemiology, course, and diagnosis. *Cleveland Clinic Journal of Medicine* 75(12), 881–889.
13. Mast E.E., Margolis H.S., Fiore A.E., et al. (2005). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practice (ACIP) part I: Immunization of infants, children, and adolescents. *Morbidity and Mortality Weekly Report* 54(RR-16), 1–39.
14. Bialek S.R., Terrault N.A. (2006). The changing epidemiology and natural history of hepatitis C virus infection. *Clinics in Liver Disease* 10, 697–715.
15. Wong T., Lee S.S. (2006). Hepatitis C: A review for primary care physicians. *Canadian Medical Association Journal* 174, 649–659.
16. Blackard J.T., Shata M.T., Shira N.J., et al. (2008). Acute hepatitis C: A chronic problem. *Hepatology* 27(1), 321–331.
17. Hoofnagle J.H. (1989). Type D (delta) hepatitis. *Journal of the American Medical Association* 261, 1321–1325.
18. Friedman S. (2009). Liver, biliary tract and pancreas. In Tierney L.M., McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (47th ed., pp. 582–629). New York: McGraw-Hill.
19. American Gastroenterological Association. (2006). American Gastroenterological Association medical position statement on management of hepatitis C. *Gastroenterology* 130, 225–230.
20. Krawitt E.L. (2006). Autoimmune hepatitis. *New England Journal of Medicine* 354, 54–66.
21. Talwalker J.A. (2003). Primary biliary cirrhosis. *Lancet* 362, 53–61.
22. Kaplan M.M., Gershwin M.E. (2005). Primary biliary cirrhosis. *New England Journal of Medicine* 353, 1261–1273.
23. Jones D.E.J. (2008). Pathogenesis of primary biliary cirrhosis. *Clinics in Liver Disease* 12, 303–301.
24. Katzung B.G. (2007). *Basic and clinical pharmacology* (10th ed., pp. 50–63). New York: McGraw-Hill Medical.
25. Lee W.M. (2003). Drug-induced hepatotoxicity. *New England Journal of Medicine* 349(5), 474–485.
26. Pugh A.J., Ashutosh J.B., Falkner K., et al. (2009). Drug-induced hepatotoxicity or drug-induced liver injury. *Clinics in Liver Disease* 13, 277–294.
27. Kumar V., Abbas A.K., Fausto N., et al. (Eds.). (2010). Environmental and nutritional diseases. In *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 412–420). Philadelphia: Saunders Elsevier.
28. Wakim-Fleming J., Mullen K.D. (2005). Long-term management of alcoholic liver disease. *Clinics in Liver Disease* 9, 135–149.
29. Lieber C.S. (2000). Alcohol: Its metabolism and interaction with nutrients. *Annual Review of Nutrition* 20, 395–430.
30. Lieber C.S. (2005). Metabolism of alcohol. *Clinics in Liver Disease* 9, 1–35.
31. Rubin E., Lieber C.S. (1968). Alcohol-induced hepatic injury in non-alcoholic volunteers. *New England Journal of Medicine* 278, 869–876.
32. Lucey M.R., Mthurin P., Morgan T.P. (2009). Alcoholic hepatitis. *New England Journal of Medicine* 360(26), 2758–2769.
33. Bayard M., Hot J., Boroughs E. (2006). Nonalcoholic fatty liver disease. *American Family Physician* 73, 1961–1969.
34. Adams L.A., Angulo P., Lindor K.D. (2005). Nonalcoholic fatty liver disease. *Canadian Medical Association Journal* 172, 899–904.

35. Angulo P. (2002). Nonalcoholic fatty liver disease. *New England Journal of Medicine* 346, 1221–1231.
36. Utzschneider K.M., Kahn S.E. (2006). Review: The role of insulin resistance in nonalcoholic fatty liver disease. *Journal of Clinical Endocrinology and Metabolism* 91, 4753–4761.
37. Heilelbaugh J.J., Bruderly M. (2006). Cirrhosis and chronic liver failure: Part I. Diagnosis and management. *American Family Physician* 74, 756–781.
38. Heilelbaugh J.J., Sherbondy M. (2006). Cirrhosis and chronic liver failure: Part II. Complications and treatment. *American Family Physician* 74, 756–781.
39. Toubia N., Sanyal A.J. (2008). Portal hypertension and variceal hemorrhage. *Medical Clinics of North America* 92, 351–374.
40. Sandhu B.S., Sanyal A.J. (2005). Management of ascites in cirrhosis. *Clinics in Liver Disease* 9, 715–732.
41. McQuaid K.R. (2009). Esophageal varices. In Tierney L.M., McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (47th ed., pp. 523–526). New York: McGraw-Hill.
42. Brigalia A.E., Anania F.A. (2002). Hepatorenal syndrome: Definition, pathophysiology, and intervention. *Critical Care Clinics* 18, 345–373.
43. Sundaram V. (2009). Hepatic encephalopathy: Pathophysiology and emerging therapies. *Medical Clinics of North America* 93, 819–836.
44. Weimer R.H., Rakela J., Ishitani M.B., et al. (2003). Recent advances in liver transplantation. *Mayo Clinic Proceedings* 78, 197–210.
45. Parikh S., Hyman D. (2007). Hepatocellular cancer: A guide for the internist. *American Journal of Medicine* 120, 194–202.
46. Ahn J., Flamm S.L. (2004). Hepatocellular carcinoma. *Disease of the Month* 50, 556–573.
47. Sherman M. (2004). Pathophysiology and screening for hepatocellular carcinoma. *Clinics in Liver Disease* 8, 419–443.
48. Vogt D.P. (2002). Gallbladder disease. *Cleveland Clinic Journal of Medicine* 69, 977–984.
49. Strasberg S.M. (2008). Acute calculous cholecystitis. *New England Journal of Medicine* 358(26), 2804–2811.
50. Bellows C.F., Berger D.H., Crass R.A. (2005). Management of gallstones. *American Family Physician* 72, 637–642.
51. Gourgiotis S., Kocher H.M., Solaini L., et al. (2008). Gallbladder cancer. *American Journal of Surgery* 196, 252–264.
52. Hruban R.H., Iacobuzio-Donahue C. (2010). The pancreas. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 891–904). Philadelphia: Saunders Elsevier.
53. Lauwers G.Y., Mino-Kenudson M., Rubin R. (2008). The pancreas. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathophysiology: Clinicopathologic foundations of medicine* (5th ed., pp. 675–689). Philadelphia: Lippincott Williams & Wilkins.
54. Whitcomb D.C. (2006). Acute pancreatitis. *New England Journal of Medicine* 354, 2142–2150.
55. Carroll J.K., Herrick B., Gipson T., et al. (2007). Acute pancreatitis: Diagnosis, prognosis, and treatment. *American Family Physician* 75, 1513–1520.
56. Banks P.A., Freeman M.L., and the Practice Parameters Committee of the American College of Gastroenterologists. (2006). Practice guidelines for acute pancreatitis. *American Journal of Gastroenterology* 101, 2379–2400.
57. Nair R.J., Lawler L. (2007). Chronic pancreatitis. *American Family Physician* 76, 1679–1688.
58. Isla A.M. (2000). Chronic pancreatitis. *Hospital Medicine* 61, 386–389.
59. Freelove R., Walling A.D. (2006). Pancreatic cancer: Diagnosis and management. *American Family Physician* 73, 485–492.
60. Brand R. (2004). Pancreatic cancer. *Disease of the Month* 50, 545–555.
61. Lillemoe K.D. (2000). Pancreatic cancer: State-of-the-art care. *CA: A Cancer Journal for Clinicians* 50, 241–268.

UNIT 9

Endocrine System

The Endocrine System
- *Hormones*
  - Paracrine and Autocrine Actions
  - Eicosanoids and Vitamins
  - Structural Classification
  - Synthesis and Transport
  - Metabolism and Elimination
  - Mechanisms of Action
- *Control of Hormone Levels*
  - Hypothalamic-Pituitary Regulation
  - Feedback Regulation
- *Diagnostic Tests*
  - Blood Tests
  - Urine Tests
  - Stimulation and Suppression Tests
  - Genetic Tests
  - Imaging

Chapter 31

Mechanisms of Endocrine Control

The endocrine system is involved in all of the integrative aspects of life, including growth, sex differentiation, metabolism, and adaptation to an ever-changing environment. This chapter focuses on general aspects of endocrine function, organization of the endocrine system, hormone receptors and hormone actions, and regulation of hormone levels.

The Endocrine System

The endocrine system uses chemical messengers called *hormones* as a means of controlling the flow of information between different cells and tissues. Although the endocrine system once was thought to be the sole source of chemical messengers, it is now known that a number of other tissues release chemical messengers that modulate body processes. The functions of the endocrine system are closely linked with those of the nervous system and the immune system. For example, neurotransmitters such as epinephrine can act as neurotransmitters or as hormones. The functions of the immune system also are closely linked with those of the endocrine system. The immune system responds to foreign agents by means of chemical messengers (cytokines, such as interleukins; interferons) and complex receptor mechanisms (see Chapter 15). The immune system also is extensively regulated by hormones such as the adrenal corticosteroid hormones.

Hormones

- Hormones function as chemical messengers, moving through the blood to distant target sites of action, or acting more locally as paracrine or autocrine messengers that incite more local effects.
- Most hormones are present in body fluids at all times, but in greater or lesser amounts depending on the needs of the body.
- Hormones exert their actions by interacting with high-affinity receptors, which in turn are linked to one or more effector systems in the cell. Some hormone receptors are located on the surface of the cell and act through second messenger mechanisms, and others are located in the cell, where they modulate the synthesis of enzymes, transport proteins, or structural proteins.

Hormones

Hormones generally are thought of as chemical messengers that are transported in body fluids. They are highly specialized organic molecules produced by endocrine organs that exert their action on specific target cells. Hormones do not initiate reactions but function as modulators of cellular and systemic responses. Most hormones are present in body fluids at all times, but in greater or lesser amounts depending on the needs of the body.

A characteristic of hormones is that a single hormone can exert various effects in different tissues or, conversely, a single function can be regulated by several different hormones. For example, estradiol, which is produced by the ovary, can act on the ovarian follicles to promote their maturation, on the uterus to stimulate its growth and maintain the cyclic changes in the uterine mucosa, on the mammary gland to stimulate ductal growth, on the hypothalamic-pituitary system to regulate the secretion of gonadotropins and prolactin, on the bone to maintain skeletal integrity, and on general metabolic processes to affect adipose tissue distribution. Lipolysis, which is the release of free fatty acids from adipose tissue, is an example of a single function that is regulated by several hormones, including the catecholamines, insulin, and glucagon, but also by the cytokine tumor necrosis factor-α. Table 31-1 lists the major actions and sources of body hormones.

Paracrine and Autocrine Actions

In the past, hormones were described as chemical substances that were released into the bloodstream and transported to distant target sites, where they exerted their action. Although many hormones travel by this mechanism, some hormones and hormonelike substances never enter the bloodstream but instead act locally in the vicinity in which they are released (Fig. 31-1). When they act locally on cells other than those that produced the hormone, the action is called *paracrine*. The action of sex steroids on the ovary is a paracrine action. Hormones also can exert an *autocrine* action on the cells from which they were produced. For example, the release of insulin from pancreatic beta cells can inhibit its release from the same cells.

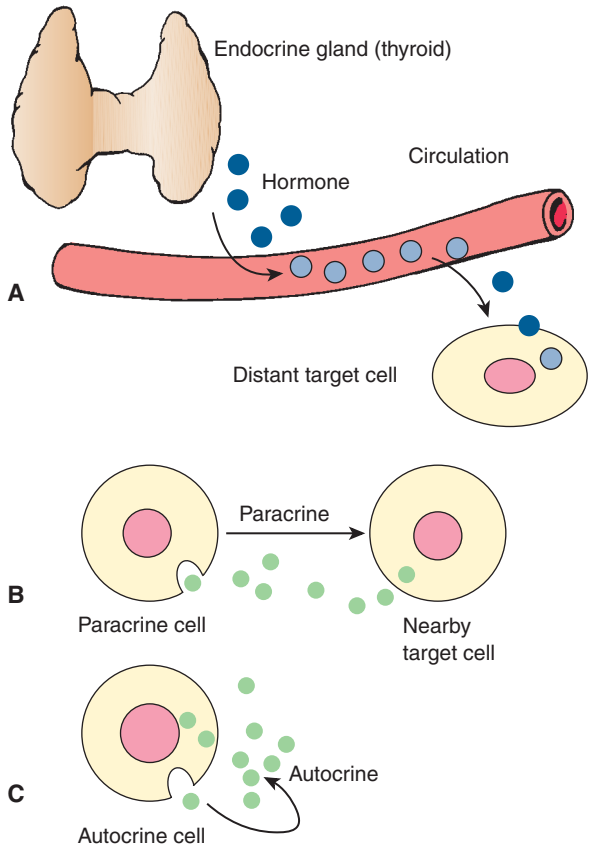


FIGURE 31-1. Examples of endocrine **(A)**, paracrine **(B)**, and autocrine **(C)** secretions.

Eicosanoids and Vitamins

A group of compounds that have a hormonelike action are the eicosanoids, which are derived from polyunsaturated fatty acids in the cell membrane. Among these, *arachidonic acid* is the most important and abundant precursor of the various eicosanoids (see Chapter 3, Fig. 3-4). The most important of the eicosanoids are the prostaglandins, leukotrienes, and thromboxanes. These fatty acid derivatives are produced by most body cells, are rapidly cleared from the circulation, and are thought to act mainly by paracrine and autocrine mechanisms. Eicosanoid synthesis often is stimulated in response to hormones, and they serve as mediators of hormone action.

Vitamins are essential substances derived from the diet. They are required in small amounts and are utilized by the body as cofactors and modulators of body function.

TABLE 31-1 Major Action and Source of Selected Hormones

Source	Hormone	Major Action
Hypothalamus	Releasing and inhibiting hormones Corticotropin-releasing hormone (CRH) Thyrotropin-releasing hormone (TRH) Growth hormone-releasing hormone (GHRH) Gonadotropin-releasing hormone (GnRH)	Controls the release of pituitary hormones
	Somatostatin	Inhibits GH and TSH
Anterior pituitary	Growth hormone (GH)	Stimulates growth of bone and muscle, promotes protein synthesis and fat metabolism, decreases carbohydrate metabolism
	Adrenocorticotropic hormone (ACTH)	Stimulates synthesis and secretion of adrenal cortical hormones
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormone
	Follicle-stimulating hormone (FSH)	Female: stimulates growth of ovarian follicle, ovulation Male: stimulates sperm production
	Luteinizing hormone (LH)	Female: stimulates development of corpus luteum, release of oocyte, production of estrogen and progesterone Male: stimulates secretion of testosterone, development of interstitial tissue of testes
	Prolactin	Prepares female breast for breast-feeding
Posterior pituitary	Antidiuretic hormone (ADH)	Increases water reabsorption by kidney
	Oxytocin	Stimulates contraction of pregnant uterus, milk ejection from breasts after childbirth
Adrenal cortex	Mineralocorticosteroids, mainly aldosterone	Increases sodium absorption, potassium loss by kidney
	Glucocorticoids, mainly cortisol	Affects metabolism of all nutrients; regulates blood glucose levels, affects growth, has anti-inflammatory action, and decreases effects of stress
	Adrenal androgens, mainly dehydroepiandrosterone (DHEA) and androstenedione	Have minimal intrinsic androgenic activity; they are converted to testosterone and dihydrotestosterone in the periphery
Adrenal medulla	Epinephrine Norepinephrine	Serve as neurotransmitters for the sympathetic nervous system
Thyroid (follicular cells)	Thyroid hormones: triiodothyronine (T_3), thyroxine (T_4)	Increase the metabolic rate; increase protein and bone turnover; increase responsiveness to catecholamines; necessary for fetal and infant growth and development
Thyroid C cells	Calcitonin	Lowers blood calcium and phosphate levels
Parathyroid glands	Parathyroid hormone (PTH)	Regulates serum calcium
Pancreatic islet cells	Insulin	Lowers blood glucose by facilitating glucose transport across cell membranes of muscle, liver, and adipose tissue
	Glucagon	Increases blood glucose concentration by stimulation of glycogenolysis and glyconeogenesis
	Somatostatin	Delays intestinal absorption of glucose
Kidney	1,25-Dihydroxyvitamin D	Stimulates calcium absorption from the intestine
Ovaries	Estrogen	Affects development of female sex organs and secondary sex characteristics
	Progesterone	Influences menstrual cycle; stimulates growth of uterine wall; maintains pregnancy
Testes	Androgens, mainly testosterone	Affect development of male sex organs and secondary sex characteristics; aid in sperm production

The body also produces hormonelike molecules that are described as "vitamins." Vitamin D, for example, is produced in individuals who are exposed to sunlight, and supplementation is required only when there is inadequate exposure to sunlight. Further, ingested vitamin D is converted to its active form in the liver and kidneys. Vitamins also act in ways that resemble hormones. For example, vitamin D and the retinoids (e.g., retinoic acid), which are made from vitamin A, act through nuclear receptors (to be discussed).

Structural Classification

Hormones, which have diverse structures ranging from single amino acids to complex proteins and lipids, are divided into three categories: (1) amines and amino

TABLE 31-2 Classes of Hormones Based on Structure

Amines and Amino Acids	Peptides, Polypeptides, and Proteins	Steroids
Dopamine	Corticotropin-releasing hormone (CRH)	Aldosterone
Epinephrine	Growth hormone–releasing hormone (GHRH)	Glucocorticoids
Norepinephrine	Thyrotropin-releasing hormone (TRH)	Estrogens
Thyroid hormone	Adrenocorticotropic hormone (ACTH)	Testosterone
	Follicle-stimulating hormone (FSH)	Progesterone
	Luteinizing hormone (LH)	Androstenedione
	Thyroid-stimulating hormone (TSH)	1,25-Dihydroxyvitamin D
	Growth hormone (GH)	Dihydrotestosterone (DHT)
	Antidiuretic hormone (ADH)	Dehydroepiandrosterone (DHEA)
	Oxytocin	
	Insulin	
	Glucagon	
	Somatostatin	
	Calcitonin	
	Parathyroid hormone (PTH)	
	Prolactin	

acids; (2) peptides, polypeptides, proteins, and glycoproteins; and (3) steroids (Table 31-2). The first category, the amines, includes norepinephrine and epinephrine, which are derived from a single amino acid (i.e., tyrosine), and the thyroid hormones, which are derived from two iodinated tyrosine amino acid residues. The second category, the peptides, polypeptides, proteins, and glycoproteins, can be as small as thyrotropin-releasing hormone (TRH), which contains 3 amino acids, and as large and complex as growth hormone (GH) and follicle-stimulating hormone (FSH), which have approximately 200 amino acids. Glycoproteins are large peptide hormones associated with a carbohydrate (e.g., FSH). The third category consists of the steroid hormones, which are derivatives of cholesterol.

Synthesis and Transport

The mechanisms for hormone synthesis and release vary with hormone structure. Protein and polypeptide hormones are synthesized and stored in vesicles in the cytoplasm of the cell until secretion is required. Other hormones, such as the lipid-soluble steroid hormones are released as they are synthesized.

The protein and polypeptide hormones comprise the most prominent class of hormones whose synthesis and release is vesicle mediated. These hormones are synthesized in the rough endoplasmic reticulum of the endocrine cell in a manner similar to the synthesis of other proteins (see Chapter 1). The appropriate amino acid sequence is dictated by messenger ribonucleic acids (mRNAs) from the nucleus. Usually, synthesis involves the production of a precursor hormone, which is modified by the addition of peptides or sugar units. These precursor hormones often contain extra peptide units that ensure proper folding of the molecule and insertion of essential linkages. If extra amino acids are present, as in insulin, the precursor hormone is called a *prohormone*. After synthesis and sequestration in the endoplasmic reticulum, the protein and peptide hormones move into the Golgi complex, where they are packaged in vesicles. It is in the Golgi complex that prohormones are converted into hormones. Stimulation of the endocrine cell causes the vesicles to move to the cell membrane and release their hormones. The vesicle-mediated pathway is also used for secretion of a number of nonpolypeptide hormones and neurotransmitters such as the catecholamines (dopamine, epinephrine, and norepinephrine). However, these small molecules do not pass through the full range of intracellular mechanisms seen in the synthesis and secretion of the larger protein and polypeptide hormones.

Hormones synthesized by non–vesicle-mediated pathways include the glucocorticoids, androgens, estrogens, and mineralocorticoids—all steroids derived from cholesterol. These hormones are synthesized in the smooth endoplasmic reticulum, and steroid-secreting cells can be identified by their large amounts of smooth endoplasmic reticulum. Certain steroids serve as precursors for the production of other hormones. In the adrenal cortex, for example, progesterone and other steroid intermediates are enzymatically converted into aldosterone, cortisol, or androgens (see Chapter 32). The release of hormones synthesized by non–vesicle-mediated pathways is not fully understood. Historically it was thought to occur by simple diffusion. In recent years, however, specific transporters have been implicated in directing some of these classes of hormones out of the cell. Whether all hormones produced by non–vesicle-mediated pathways depend on transporters for their secretion remains a subject for further investigation.

Hormones that are released into the bloodstream circulate as either free or unbound molecules or as hormones attached to transport carriers (Fig. 31-2). Peptide hormones and protein hormones are water soluble and usually circulate unbound in the blood. Steroid hormones and thyroid hormone are carried by specific carrier proteins synthesized in the liver. The extent of carrier binding influences the rate at which hormones leave the blood and enter the cells. The half-life of a hormone—the

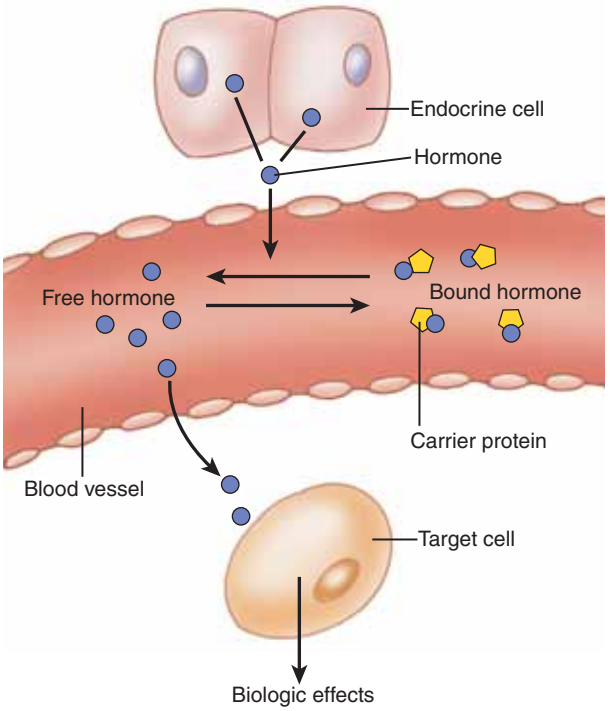


FIGURE 31-2. Relationship of free and carrier-bound hormones.

time it takes for the body to reduce the concentration of the hormone by one half—is positively correlated with its percentage of protein binding. Thyroxine, which is more than 99% protein bound, has a half-life of 6 days. Aldosterone, which is only 15% bound, has a half-life of only 25 minutes. Drugs that compete with a hormone for binding with transport carrier molecules increase hormone action by increasing the availability of the active unbound hormone. For example, aspirin competes with thyroid hormone for binding to transport proteins; when this drug is administered to persons with excessive levels of circulating thyroid hormone, such as during thyroid crisis, serious effects may occur due to the dissociation of free hormone from the binding proteins.

Metabolism and Elimination

Hormones secreted by endocrine cells must be inactivated continuously to prevent their accumulation. Intracellular and extracellular mechanisms participate in the termination of hormone function. Most peptide hormones and catecholamines are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood or tissues and then excreted by the kidneys and liver. For example, the catecholamines are rapidly degraded by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). Because of their short half-life, their production is measured by some of their metabolites. In general, peptide hormones also have a short life span in the circulation. Their major mechanism of degradation is through binding to cell surface receptors, with subsequent uptake and degradation by peptide-splitting enzymes in the cell membrane or inside the cell.

Steroid hormones are bound to protein carriers for transport and are inactive in the bound state. Their activity depends on the availability of transport carriers. Unbound adrenal and gonadal steroid hormones are conjugated in the liver, which renders them inactive, and then excreted in the bile or urine. Thyroid hormones also are transported by carrier molecules. The free hormone is rendered inactive by the removal of amino acids (i.e., deamination) in the tissues, and the hormone is conjugated in the liver and eliminated in the bile.

Mechanisms of Action

Hormones produce their effects through interaction with high-affinity receptors, which in turn are linked to one or more effector systems within the cell. These mechanisms involve many of the cell's metabolic activities, ranging from ion transport at the cell surface to stimulation of nuclear transcription of complex molecules. The rate at which hormones react depends on their mechanism of action. The neurotransmitters, which control the opening of ion channels, have a reaction time of milliseconds. Thyroid hormone, which functions in the control of cell metabolism and synthesis of intracellular signaling molecules, requires days for its full effect to occur.

Receptors. Hormone receptors are complex molecular structures that are located either on the surface or inside target cells. The function of these receptors is to recognize a specific hormone and translate the hormonal signal into a cellular response. The structure of these receptors varies in a manner that allows target cells to respond to one hormone and not to others. For example, receptors in the thyroid are specific for thyroid-stimulating hormone, and receptors on the gonads respond to the gonadotropic hormones.

The response of a target cell to a hormone varies with the *number* of receptors present and with the *affinity* of these receptors for hormone binding. A variety of factors influence the number of receptors that are present on target cells and their affinity for hormone binding.

The number of hormone receptors on a cell may be altered for any of several reasons. Antibodies may destroy or block the receptor proteins. Increased or decreased hormone levels often induce changes in the activity of the genes that regulate receptor synthesis. For example, decreased hormone levels often produce an increase in receptor numbers by means of a process called *up-regulation;* this increases the sensitivity of the body to existing hormone levels. Likewise, sustained levels of excess hormone often bring about a decrease in receptor numbers by *down-regulation,* producing a decrease in hormone sensitivity. In some instances, the reverse effect occurs, and an increase in hormone levels appears to recruit its own receptors, thereby increasing the sensitivity of the cell to the hormone. The process of up-regulation and down-regulation of receptors is regulated largely by inducing or repressing the transcription of receptor genes.

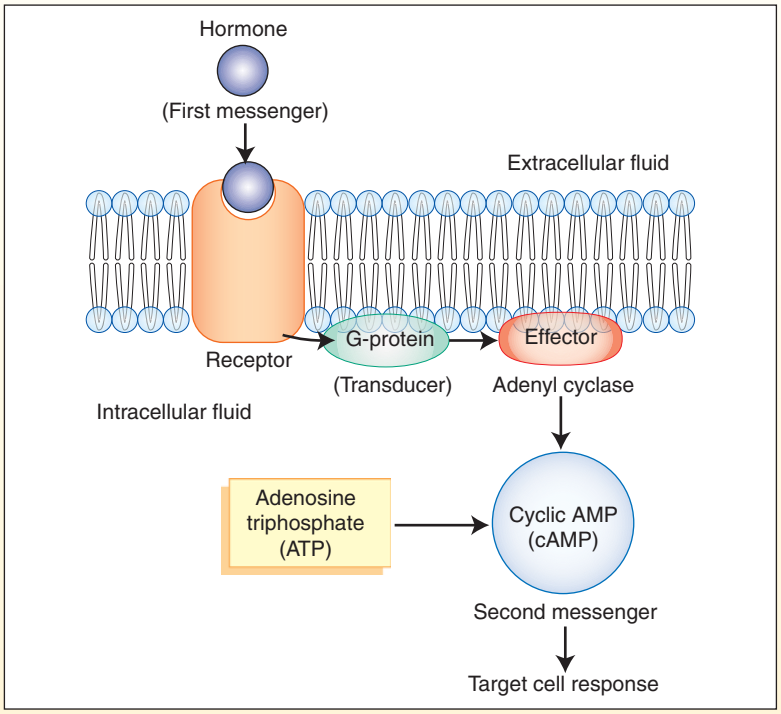
The affinity of receptors for binding hormones is also affected by a number of conditions. For example, the pH of the body fluids plays an important role in the affinity of insulin receptors. In ketoacidosis, a lower pH reduces insulin binding.

UNDERSTANDING → Hormone Receptors

Hormones bring about their effects on cell activity by binding to specific cell receptors. There are two general types of receptors: (1) cell surface receptors that exert their actions through cytoplasmic second messenger systems, and (2) intracellular nuclear receptors that modulate gene expression by binding to DNA or promoters of target genes.

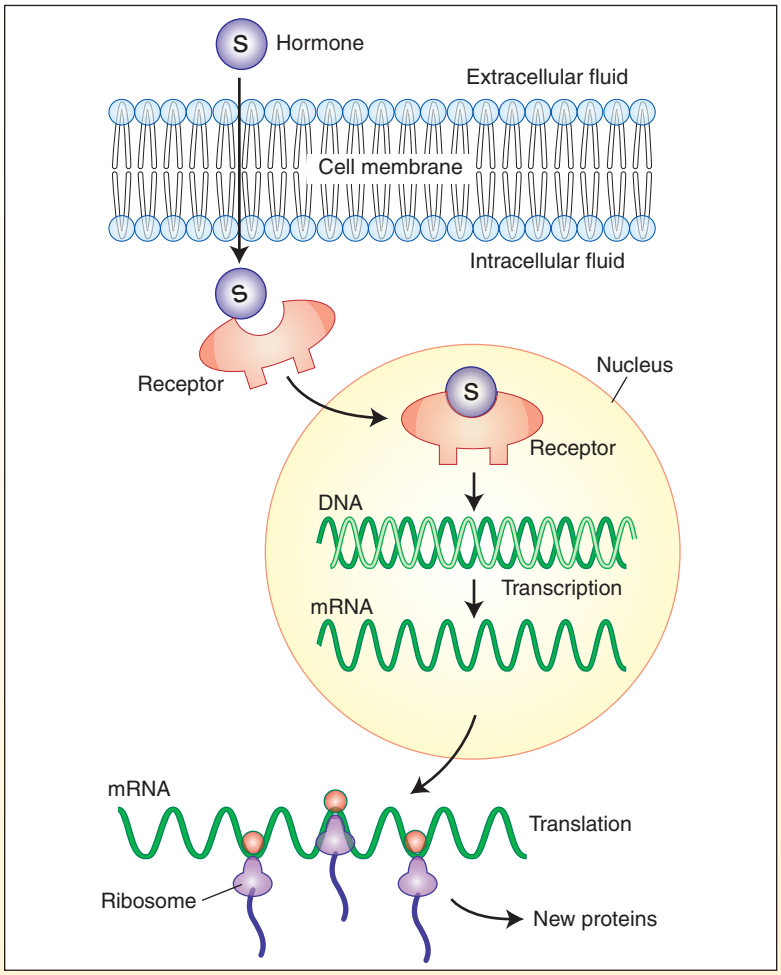
1

Cell Surface Receptors. Water-soluble peptide hormones, such as parathyroid hormone and glucagon, which cannot penetrate the lipid layer of the cell plasma membrane, exert their effects through intracellular second messengers. They bind to a portion of a membrane receptor that protrudes through the surface of the cell. This produces a structural change in the receptor molecule itself, causing activation of a hormone-regulated signal system located on the inner aspect of the cell membrane. This system allows the cell to sense extra-cellular events and pass this information to the intracellular environment. There are several types of cell surface receptors, including G-protein–coupled receptors that mediate the actions of catecholamines, prostaglandins, thyroid-stimulating hormone, and others. Binding of the hormone to the receptor activates a G protein, which in turn acts on an effector such as adenyl cyclase to generate a second messenger such as cyclic adenosine monophosphate (cAMP). The second messenger, in turn, activates other enzymes that participate in cellular secretion, gene activation, or other target cell responses



2

Nuclear Receptors. Steroid hormones, vitamin D, thyroid hormones, and other lipid-soluble hormones diffuse across the cell membrane into the cytoplasm of the target cell. Once inside, they bind to an intracellular receptor that is activated by the interaction. The activated hormone–receptor complex then moves to the nucleus, where the hormone binds to a hormone response element (HRE) in the promoters on a target gene or to another transcription factor. Attachment to the HRE results in transcription of a specific messenger RNA (mRNA). The mRNA then moves into the cytoplasm, where the "transcribed message" is translated and used by cytoplasmic ribosomes to produce new cellular proteins or changes in the production of existing proteins. These proteins promote a specific cellular response or, in some cases, the synthesis of a structural protein that is exported from the cell.



Some hormone receptors are located on the surface of the cell and act through second messenger mechanisms, and others are located within the cell, where they modulate the synthesis of enzymes, transport proteins, or structural proteins. The receptors for thyroid hormones, which are found in the nucleus, are thought to be directly associated with controlling the activity of genes located on one or more of the chromosomes. Chart 31-1 lists examples of hormones that act through the two types of receptors.

Cell Surface Receptors. Because of their low solubility in the lipid layer of cell membranes, peptide hormones and catecholamines cannot readily cross the cell membrane. Instead, these hormones interact with surface receptors in a manner that incites the generation of an intracellular signal or message. The intracellular signal system is termed the *second messenger,* and the hormone is considered to be the first messenger. For example, the first messenger glucagon binds to surface receptors on liver cells to incite glycogen breakdown by way of the second messenger system.

The most widely distributed second messenger is cyclic adenosine monophosphate (cAMP), which is formed from adenosine triphosphate (ATP) by the enzyme adenylate cyclase, a membrane-bound enzyme that is located on the inner aspect of the cell membrane (see Chapter 1, Fig. 1-9). Adenylate cyclase is functionally coupled to various cell surface receptors by the regulatory actions of G proteins. A second messenger similar to cAMP is cyclic guanosine monophosphate (cGMP), derived from guanosine triphosphate (GTP). As a result of binding to specific cell receptors, many peptide hormones incite a series of enzymatic reactions that produce an almost immediate increase in cAMP and target cell response. Some hormones act to decrease cAMP levels and have another or an opposite effect on cell responses.

In some cells, the binding of a hormone or neurotransmitter to a surface receptor acts directly, rather than through a second messenger, to open an ion channel in the cell membrane. The influx of ions then serves as an intracellular signal to convey the hormonal message to the interior of the cell. In many instances, the activation

CHART 31-1 Hormone–Receptor Interactions

Second Messenger Interactions

Glucagon
Insulin
Epinephrine
Parathyroid hormone (PTH)
Thyroid-stimulating hormone (TSH)
Adrenocorticotropic hormone (ACTH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Antidiuretic hormone (ADH)
Secretin

Intracellular Interactions

Estrogens
Testosterone
Progesterone
Adrenal cortical hormones
Thyroid hormones
Vitamin D
Retinoids

of hormone receptors results in the opening of calcium channels. The increasing cytoplasmic concentration of calcium ions may result in the direct activation of calcium-dependent enzymes or in the formation of calcium–calmodulin complexes with their attendant effects.

Nuclear Receptors. A second type of receptor mechanism is involved in mediating the action of thyroid and steroid hormones, as well as vitamin D, retinoic acid, and other molecules. In contrast to peptide and catecholamine hormones, these hormones enter the cell and bind to receptors in the cell nucleus that are gene regulatory proteins. Many of these hormones and molecules bind to receptors in the cytoplasm and the hormone–receptor complexes then travel to the nucleus. Nuclear receptors can also be activated by second messenger signaling pathways, thereby linking cell surface receptors to nuclear receptor activation pathways.

Six subfamilies of nuclear receptors are currently recognized on the basis of structural similarity. One subfamily consists of receptors for thyroid hormone, retinoic acid, and vitamin D. A second subfamily consists of glucocorticoid, progesterone, androgen, and estrogen receptors. Other subfamilies contain "orphan receptors" for which natural ligands have not as yet been identified.

Activated nuclear receptors act by binding to deoxyribonucleic acid (DNA) response elements in the promoter sites where gene transcription is initiated. These DNA-binding elements, which are termed *hormone response elements* (HREs), then activate or suppress intracellular mechanisms such as gene activity, with the subsequent production or inhibition of mRNA and protein synthesis. The importance of the nuclear effects of thyroid and steroid hormones is illustrated by the fact that each regulates protein synthesis. Proteins whose synthesis is regulated up or down by these hormones may be enzymes, structural proteins, receptor proteins, transcriptional proteins that regulate the expression of other genes, or proteins that are exported from the cell.

Some nuclear receptors are regulated by intracellular metabolites rather than secreted signal molecules. The peroxisome proliferator-activated receptors (PPARs), for example, bind intracellular lipid metabolites and regulate the transcription of genes involved in lipid metabolism and fat cell metabolism. The thiazolidinediones, which are used in the treatment of type 2 diabetes mellitus, act at the level of nuclear PPAR-γ receptors to promote glucose uptake and utilization by adipose tissue cells (see Chapter 33).

Control of Hormone Levels

Hormone secretion varies widely over a 24-hour period. Some hormones, such as GH and adrenocorticotropic hormone (ACTH), have diurnal fluctuations that vary with the sleep–wake cycle. Others, such as the female sex hormones, are secreted in a complicated cyclic manner. The levels of hormones such as insulin and antidiuretic hormone (ADH) are regulated by feedback mechanisms that monitor substances such as glucose (insulin) and water (ADH) in the body. The levels of many of the hormones are regulated by feedback mechanisms that involve the hypothalamic-pituitary–target cell system.

Hypothalamic-Pituitary Regulation

The hypothalamus and pituitary gland, also known as the *hypophysis*, form a unit that exerts control over many functions of several endocrine glands as well as a wide range of other physiologic functions. These two structures are connected by blood flow in the hypophysial portal system, which begins in the hypothalamus and drains into the anterior pituitary gland, and by the nerve axons that connect the supraoptic and paraventricular nuclei of the hypothalamus with the posterior pituitary gland (Fig. 31-3). The pituitary is enclosed in the sella turcica, a saddlelike bony prominence on the upper surface of the body of the sphenoid bone. Embryologically, the anterior pituitary gland develops from glandular tissue and the posterior pituitary from neural tissue.

Hypothalamic Hormones. The synthesis and release of anterior pituitary hormones are largely regulated by the action of releasing or inhibiting hormones from the hypothalamus, which is the coordinating center of the brain for endocrine, behavioral, and autonomic nervous system function. It is at the level of the hypothalamus that emotion, pain, body temperature, and other neural input are communicated to the endocrine system. The posterior pituitary hormones, ADH and oxytocin, are synthesized in the cell bodies of neurons in the hypothalamus that have axons that travel to the posterior pituitary.

The hypothalamic hormones that regulate the secretion of anterior pituitary hormones include GH-releasing hormone (GHRH), somatostatin, dopamine, TRH, corticotropin-releasing hormone (CRH), and gonadotropin-

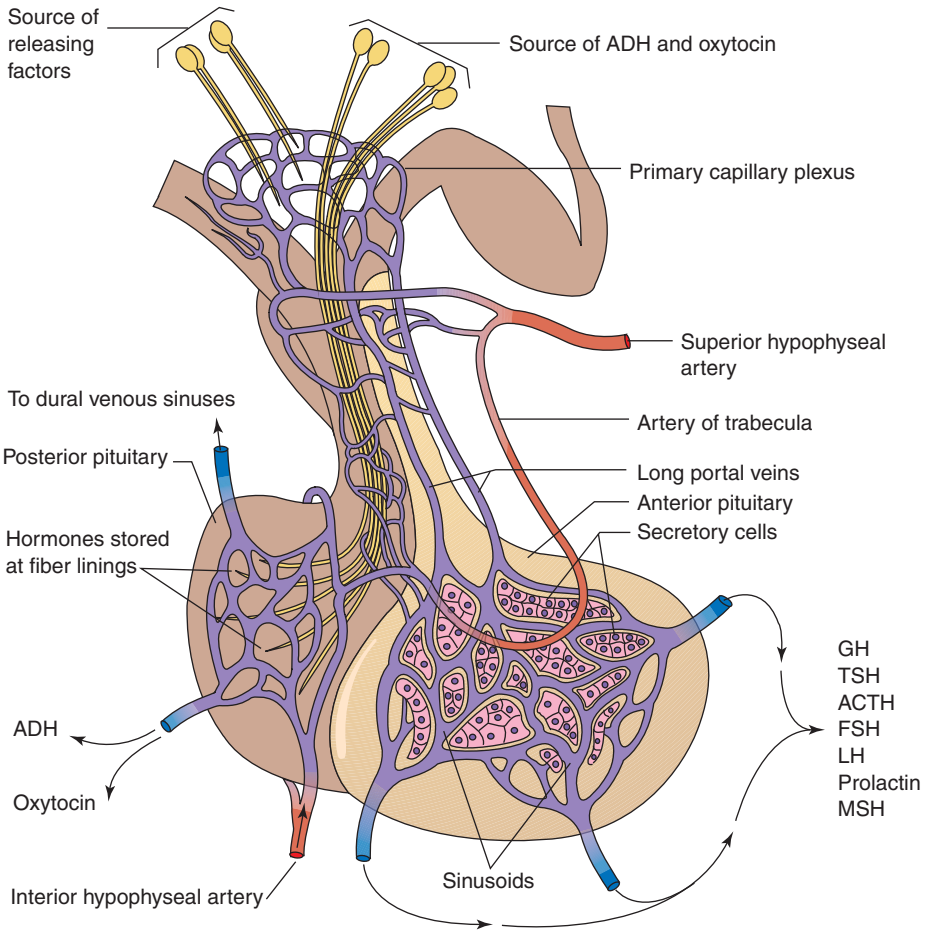


FIGURE 31-3. The hypothalamus and the anterior and posterior pituitary. The hypothalamic releasing or inhibiting hormones are transported to the anterior pituitary through the portal vessels. Antidiuretic hormone and oxytocin are produced by nerve cells in the supraoptic and paraventricular nuclei of the hypothalamus and then transported through the nerve axon to the posterior pituitary, where they are released into the circulation.

releasing hormone (GnRH). With the exception of GH and prolactin, most of the pituitary hormones are regulated by hypothalamic stimulatory hormones. GH secretion is stimulated by GHRH; thyroid-stimulating hormone (TSH) by TRH; ACTH by CRH; and luteinizing hormone (LH) and FSH by GnRH. Somatostatin functions as an inhibitory hormone for GH and TSH. Prolactin secretion is inhibited by dopamine; thus, persons receiving antipsychotic drugs that block dopamine often have increased prolactin levels.

The activity of the hypothalamus is regulated by both hormonally mediated signals (e.g., negative feedback signals) and by neuronal input from a number of sources. Neuronal signals are mediated by neurotransmitters such as acetylcholine, dopamine, norepinephrine, serotonin, γ-aminobutyric acid (GABA), and opioids. Cytokines that are involved in immune and inflammatory responses, such as the interleukins, also are involved in the regulation of hypothalamic function (see Chapter 15). This is particularly true of the hormones involved in the hypothalamic-pituitary-adrenal axis. Thus, the hypothalamus can be viewed as a bridge by which signals from multiple systems are relayed to the pituitary gland.

Pituitary Hormones. The pituitary gland has been called the *master gland* because its hormones control the functions of many target glands and cells. The anterior pituitary gland contains five cell types: (1) thyrotrophs, which produce thyrotropin, also called *TSH*; (2) corticotrophs, which produce corticotropin, also called *ACTH*; (3) gonadotrophs, which produce the gonadotropins, LH, and FSH; (4) somatotrophs, which produce GH; and (5) lactotrophs, which produce prolactin. Hormones produced by the anterior pituitary control body growth and metabolism (GH), function of the thyroid gland (TSH), glucocorticoid hormone levels (ACTH), function of the gonads (FSH and LH), and breast growth and milk production (prolactin). Melanocyte-stimulating hormone (MSH), which is involved in the control of pigmentation of the skin, is produced by the pars intermedia of the pituitary gland. The functions of many of these hormones are discussed in other parts of this book (e.g., thyroid hormone, GH, and the corticosteroids in Chapter 32; the sex hormones in Chapters 39 and 40; and ADH from the posterior pituitary in Chapter 8).

Feedback Regulation

The level of many of the hormones in the body is regulated by negative feedback mechanisms (Fig. 31-4). The function of this type of system is similar to that of the thermostat in a heating system. In the endocrine system, sensors detect a change in the hormone level and adjust hormone secretion so that blood levels are maintained

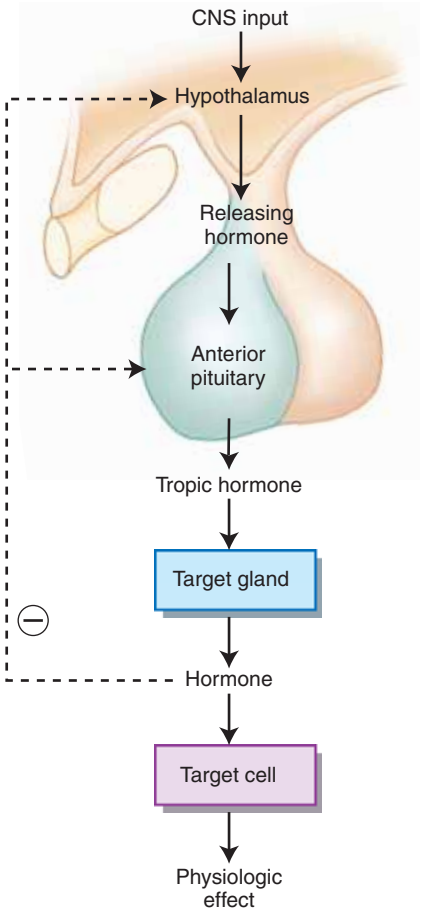


FIGURE 31-4. Hypothalamic-pituitary control of hormone levels. The dashed line represents feedback control.

within an appropriate range. When the sensors detect a decrease in blood levels, they initiate changes that cause an increase in hormone production; when blood levels rise above the set point of the system, the sensors cause hormone production and release to decrease. For example, an increase in thyroid hormone is detected by sensors in the hypothalamus or anterior pituitary gland, and this causes a reduction in the secretion of TSH, with a subsequent decrease in the output of thyroid hormone from the thyroid gland. The feedback loops for the hypothalamic-pituitary feedback mechanisms are illustrated in Figure 31-5.

Exogenous forms of hormones (given as drug preparations) can influence the normal feedback control of hormone production and release. One of the most common examples of this influence occurs with the administration of the corticosteroid hormones, which causes suppression of the hypothalamic-pituitary–target cell system that regulates the production of these hormones.

Although the blood levels of most hormones are regulated by negative feedback mechanisms, a small number are under positive feedback control, in which rising levels of a hormone cause another gland to release a hormone that is stimulating to the first. There must, however, be a mechanism for shutting off the release of the first hormone, or its production would continue unabated. An example of such a system is that of the female ovarian hormone

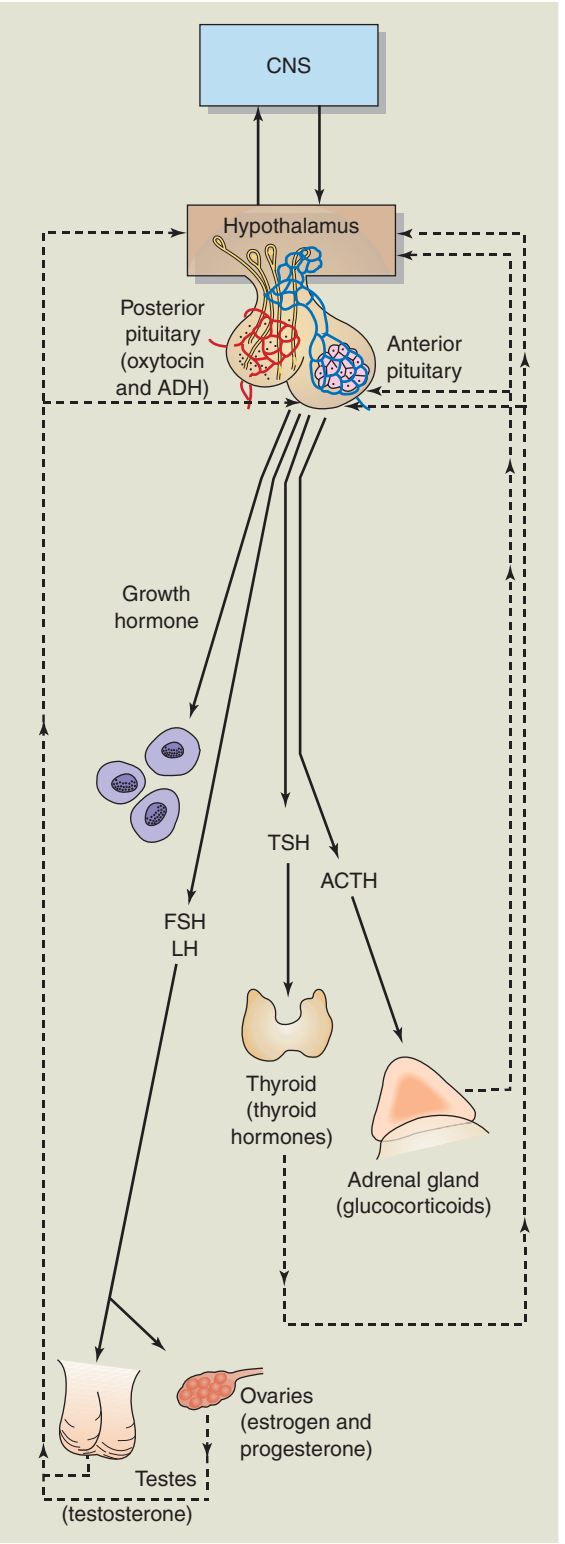


FIGURE 31-5. Control of hormone production by the hypothalamic-pituitary–target cell feedback mechanism. Hormone levels from the target glands regulate the release of hormones from the anterior pituitary through a negative feedback system. The *dashed line* represents feedback control.

estradiol. Increased estradiol production during the follicular stage of the menstrual cycle causes increased gonadotropin (FSH) production by the anterior pituitary gland. This stimulates further increases in estradiol levels until the demise of the follicle, which is the source of estradiol, results in a fall in gonadotropin levels.

In addition to positive and negative feedback mechanisms that monitor changes in hormone levels, some hormones are regulated by the level of the substance they regulate. For example, insulin levels normally are regulated in response to blood glucose levels, and those of aldosterone in response to blood levels of sodium and potassium. Other factors such as stress, environmental temperature, and nutritional status can alter feedback regulation of hormone levels.

Diagnostic Tests

Several techniques are available for assessing endocrine function and hormone levels. One technique measures the effect of a hormone on body function. Measurement of blood glucose, for example, is an indirect method of assessing insulin availability. The most common method is to measure hormone levels directly.

Blood Tests

Hormones circulating in the plasma were first detected by bioassays using the intact animal or a portion of tissue from the animal. However, most bioassays lack the precision, sensitivity, and specificity to measure low concentrations of hormones in plasma, and they are inconvenient to perform.

Blood hormone levels provide information about hormone levels at a specific time. For example, blood insulin levels can be measured along with blood glucose after administration of a challenge dose of glucose to measure the time course of change in blood insulin levels.

Real progress in measuring plasma hormone levels came more than 40 years ago with the use of competitive binding and the development of radioimmunoassay (RIA) methods. This method uses a radiolabeled form of the hormone and a hormone antibody that has been prepared by injecting an appropriate animal with a purified form of the hormone. The unlabeled hormone in the sample being tested competes with the radiolabeled hormone for attachment to the binding sites of the antibody. Measurement of the radiolabeled hormone–antibody complex then provides a means of arriving at a measure of the hormone level in the sample. Because hormone binding is competitive, the amount of radiolabeled hormone–antibody complex that is formed decreases as the amount of unlabeled hormone in the sample is increased. Newer techniques of RIA have been introduced, including the immunoradiometric assay (IRMA). IRMA uses two antibodies instead of one. These two antibodies are directed against two different parts of the molecule, and therefore IRMA assays are more specific. RIA has several disadvantages, including limited shelf life of the radiolabeled hormone and the cost for the disposal of radioactive waste.

Nonradiolabeled methods have been developed in which the antigen of the hormone being measured is linked to an enzyme-activated label (e.g., fluorescent label, chemiluminescent label) or latex particles that can be agglutinated with an antigen and measured. The enzyme-linked immunosorbent assays (ELISAs) use antibody-coated plates and an enzyme-labeled reporter antibody. Binding of the hormone to the enzyme-labeled reporter antibody produces a colored reaction that can be measured using a spectrophotometer.

Other blood tests that are routinely measured in endocrine disorders include various autoantibodies. For example, antithyroid peroxidase (anti-TPO) antibodies are measured during the initial diagnostic workup and subsequent follow-up of patients with Hashimoto thyroiditis. Other endocrine disorders that use autoantibody testing include type 1 diabetes, Graves disease, autoimmune hypoparathyroidism, and autoimmune Addison disease.

Urine Tests

Measurements of urinary hormone or hormone metabolite excretion often are done on a 24-hour urine sample and provide a better measure of hormone levels during that period than hormones measured in an isolated blood sample. The advantages of a urine test include the relative ease of obtaining urine samples and the fact that blood sampling is not required. The disadvantage is that reliably timed urine collections often are difficult to obtain. For example, a person may be unable to urinate at specific timed intervals, and urine samples may be accidentally discarded or inaccurately preserved. Because many urine tests involve the measurement of a hormone metabolite rather than the hormone itself, drugs or disease states that alter hormone metabolism may interfere with the test result. Some urinary hormone metabolite measurements include hormones from more than one source and are of little value in measuring hormone secretion from a specific source. For example, urinary 17-ketosteroids are a measure of both adrenal and gonadal androgens.

Stimulation and Suppression Tests

Stimulation tests are used when hypofunction of an endocrine organ is suspected. A tropic or stimulating hormone can be administered to test the capacity of an endocrine organ to increase hormone production. The capacity of the target gland to respond is measured by an increase in the appropriate hormone. For example, the function of the hypothalamic-pituitary-thyroid system can be evaluated through stimulation tests using TRH and measuring TSH response. Failure to increase TSH levels after a TRH stimulation test suggests an inadequate capacity to produce TSH by the pituitary (i.e., the pituitary is dysfunctional in some way).

Suppression tests are used when hyperfunction of an endocrine organ is suspected. When an organ or tissue is functioning autonomously (i.e., it is not responding to

the normal negative feedback control mechanisms and continues to secrete excessive amounts of hormone), a suppression test may be useful to confirm the situation. For example, when a GH-secreting tumor is suspected, the GH response to a glucose load is measured as part of the diagnostic workup (see Chapter 32). Normally, a glucose load would suppress GH levels. However, in adults with GH-secreting tumors (a condition known as *acromegaly*), GH levels are not suppressed (and paradoxically increase in 50% of cases).

Genetic Tests

The diagnosis of genetic diseases using DNA analysis is rapidly becoming a routine part of endocrine practice. Completion of the human genome sequence has revealed the presence of about 30,000 to 40,000 genes. The considerable interest in the field of genomics (i.e., examination of the DNA) and transcriptomics (i.e., examination of the mRNA) has been complemented by advances in proteomics (i.e., examination of the proteome, which is all of the proteins expressed by a cell or tissue type). It is proposed that compared with the size of the genome, the proteome is far larger, with several hundred thousand to several million different protein forms possible. Analysis of the proteins produced by normal and abnormal endocrine cells, tissues, and organs will lead to a better understanding of the pathophysiologic processes of endocrine conditions. This may also lead to selective targeting for new drug development.

The cloning of many endocrine system genes has had an enormous impact on everyday clinical practice. For example, identification of a gene for a given disorder (e.g., the *RET* proto-oncogene in certain multiple endocrine neoplasia syndromes) means that faster diagnosis and more appropriate management for the affected individual can occur, but also that screening of family members for kindred harboring a known mutation can be undertaken.

Imaging

Imaging studies are important in the diagnosis and follow-up of endocrine disorders. Imaging modalities related to endocrinology can be divided into isotopic and nonisotopic types. Isotopic imaging includes radioactive scanning of the thyroid (e.g., using radioiodine) and parathyroids (e.g., using sestamibi). Nonisotopic imaging includes magnetic resonance imaging (MRI), which is the preferred choice for pituitary and hypothalamic imaging, and computed tomography (CT) scanning, which is preferred for adrenal lesions and abdominal endocrine lesions. Ultrasonographic scanning provides excellent and reproducible anatomic images for the thyroid, parathyroids, and neighboring structures. Thyroid ultrasonography is recommended for managing thyroid nodules and can aid in visualization of the nodule for biopsy (fine needle aspiration), which is necessary to help distinguish benign from malignant etiology. Selective venography is usually accompanied by venous sampling to determine hormonal output from a gland or organ (e.g., adrenal, pituitary, and kidney). Positron emission tomography (PET) scanning is being used more widely for evaluation of endocrine tumors. Dual electron x-ray absorptiometry (DEXA) is used routinely for the diagnosis and monitoring of osteoporosis and metabolic bone diseases.

In summary, the endocrine system acts as a communication system that uses chemical messengers, or hormones, for the transmission of information from cell to cell and from organ to organ. Hormones act by binding to receptors that are specific for the different types of hormones. Many of the endocrine glands are under the regulatory control of other parts of the endocrine system. The hypothalamus and the pituitary gland form a complex integrative network that joins the nervous system and the endocrine system; this central network controls the output from many of the other glands in the body.

Endocrine function can be assessed directly by measuring blood hormone levels or indirectly by assessing the effects that a hormone has on the body (e.g., assessment of insulin function through blood glucose). Imaging techniques are increasingly used to visualize endocrine structures, and genetic techniques are used to determine the presence of genes that contribute to the development of endocrine disorders.

REVIEW EXERCISES

1. Vitamin D is often considered a hormone rather than a vitamin.

A. Explain.

2. Thyroid hormones are transported in the serum bound to transport proteins such as thyroid-binding globulin and albumin.

A. Explain why free thyroxine (T_4) levels are usually used to assess thyroid function rather than total T_4 levels.

3. People who are being treated with exogenous forms of corticosteroid hormones often experience diminished levels of ACTH and exogenously produced cortisol.

A. Explain, using information regarding the hypothalamic-pituitary feedback control of cortisol production by the adrenal cortex.

BIBLIOGRAPHY

Alberts B., Aranda A., Pascual A. (2001). Nuclear hormone receptors and gene expression. *Physiological Reviews* 81(3), 1239–1304.

Alberts B., Johnson A., Lewis V., et al. (2008). *Molecular biology of the cell* (5th ed., pp. 889–903). New York: Garland Science.

Gardner D.G. (Ed.). (2007). *Greenspan's basic and clinical endocrinology* (8th ed.). New York: Lange Medical Books/McGraw-Hill.

Genuth S.M. (2004). The endocrine system. In Berne R.M., Levy M.N., Koeppen B.M., et al. *Physiology* (5th ed., pp. 719–742). St. Louis: Elsevier Mosby.

Griffin J.E., Sergio R.O. (2005). *Textbook of endocrine physiology* (5th ed.). New York: Oxford University Press.

Guyton A.C., Hall J.E. (2006). *Medical physiology* (11th ed., pp. 905–919). Philadelphia: Elsevier Saunders.

Holt R.I.G., Hanley N.A. (2007). *Essential endocrinology and diabetes* (5th ed.). Malden, MA: Blackwell.

Jameson J.L. (Ed.). (2006). *Harrison's endocrinology.* New York: McGraw-Hill.

Molina P.E. (2006). *Endocrine physiology* (2nd ed.). New York: Lange Medical Books/McGraw-Hill.

Sam S., Frohman L.A. (2008). Normal physiology of hypothalamic pituitary regulation. *Endocrinology and Metabolism Clinics of North America* 37, 1–22.

General Aspects of Altered Endocrine Function
Hypofunction
Hyperfunction
Primary, Secondary, and Tertiary Disorders
Pituitary and Growth Disorders
Control of Anterior Pituitary Function
Assessment of Hypothalamic-Pituitary Function
Pituitary Adenomas and Hyperpituitarism
Hypopituitarism
Growth and Growth Hormone Disorders
Growth Hormone
Short Stature in Children
Growth Hormone Deficiency in Adults
Tall Stature and Growth Hormone Excess in Children
Growth Hormone Excess in Adults
Precocious Puberty
Thyroid Disorders
Control of Thyroid Function
Actions of Thyroid Hormone
Tests of Thyroid Function
Disorders of Thyroid Function
Hypothyroidism
Hyperthyroidism
Disorders of Adrenal Cortical Function
Control of Adrenal Cortical Function
Adrenal Cortical Hormones
Pharmacologic Suppression of Adrenal Function
Tests of Adrenal Function
Disorders of the Adrenal Cortex
Congenital Adrenal Hyperplasia
Adrenal Cortical Insufficiency
Glucocorticoid Hormone Excess
Incidental Adrenal Mass

Chapter 32

Disorders of Endocrine Control of Growth and Metabolism

Disorders of the endocrine system can affect many aspects of body functioning, including growth and development, energy metabolism, muscle and adipose tissue distribution, sexual development, fluid and electrolyte balance, and inflammation and immune responses. This chapter focuses on disorders of the anterior pituitary gland, growth and growth hormone, thyroid function, and adrenocortical function. Disorders of the parathyroid hormone are discussed in Chapter 8, insulin in Chapter 33, and the male and female gonadal hormones in Chapters 39 and 40.

General Aspects of Altered Endocrine Function

Several processes can disturb the normal function of the endocrine system, including impaired or uncontrolled synthesis or release of hormones, altered interactions between hormones and their target tissues, or abnormal responses of the target tissues to their hormones. Diseases involving the endocrine system most commonly present with signs of hypofunction or hyperfunction.[1] The disorder can occur as a primary disorder of an endocrine organ or as a secondary or tertiary disorder involving hormones produced by the pituitary gland or hypothalamus.

Hypofunction

Hypofunction of an endocrine gland can occur for a variety of reasons. Congenital defects can result in the absence or impaired development of the gland or the absence of an enzyme needed for hormone synthesis. The gland may be destroyed by a disruption in blood flow, infection, inflammation, autoimmune responses, or

neoplastic growth. There may be a decline in function with aging, or the gland may atrophy as the result of drug therapy or for unknown reasons. Some endocrine-deficient states are associated with receptor defects: hormone receptors may be absent, the receptor binding of hormones may be defective, or the cellular responsiveness to the hormone may be impaired. It is suspected that in some cases a gland may produce a biologically inactive hormone or that an active hormone may be destroyed by circulating antibodies before it can exert its action.

Hyperfunction

Hyperfunction usually is associated with excessive hormone production. This can result from excessive stimulation and hyperplasia of the endocrine gland or from a hormone-producing tumor. Hyperfunction symptoms may also be *paraneoplastic*, meaning they are caused by hormones secreted by tumors of nonendocrine tissue (see Chapter 7). In addition to excessive endogenous hormone production, syndromes of hormone excess may result from deliberate or inadvertent administration of exogenous hormones. For example, administration of glucocorticoid drugs to suppress the inflammatory response may lead to Cushing syndrome, or androgen excess with suppression of pituitary gonadotropins may occur in athletes who take androgens to improve their performance.

Primary, Secondary, and Tertiary Disorders

Endocrine disorders in general can be divided into primary, secondary, and tertiary disorders. *Primary* disorders originate in the target gland responsible for producing the hormone. In *secondary disorders* of endocrine function, the target gland is essentially normal, but its function is altered by defective levels of stimulating hormones or releasing hormones from the pituitary system. For example, total thyroidectomy produces a primary deficiency of thyroid hormones. Removal or destruction of the pituitary gland eliminates thyroid-stimulating hormone (TSH) stimulation of the thyroid and brings about a secondary deficiency. A *tertiary disorder* results from hypothalamic dysfunction (as may occur with craniopharyngiomas or cerebral irradiation); thus, both the pituitary and target gland are understimulated.

In summary, endocrine disorders are the result of hypofunction or hyperfunction of an endocrine gland. They can occur as a primary defect in hormone production by a target gland or as a secondary or tertiary disorder resulting from a defect in the hypothalamic-pituitary system that controls a target gland's function.

Pituitary and Growth Disorders

The pituitary gland, also known as the *hypophysis,* is a pea-sized gland located at the base of the brain, where it lies in a saddle-shaped depression in the sphenoid bone called the *sella turcica*. A short funnel-shaped stalk, the *infundibulum,* connects the pituitary gland with the hypothalamus. The pituitary gland has two components: a posterior lobe (neurohypophysis) or neural component, which stores and releases the oxytocin and the antidiuretic hormone (discussed in Chapter 8), and an anterior lobe (adenohypophysis) or glandular component (see Chapter 31, Fig. 31-3).

Control of Anterior Pituitary Function

The anterior lobe of the pituitary gland produces adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), the gonadotropic hormones (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), and prolactin.[2,3] The release of these hormones is in turn under the control of hormones produced in the hypothalamus (see Chapter 31). Four of the pituitary hormones control the biosynthesis and secretion of hormones from other target endocrine glands. ACTH controls the release of cortisol from the adrenal gland, TSH controls the secretion of thyroid hormone from the thyroid gland, and LH and FSH control sex hormone production and fertility.

Diseases of the pituitary are uncommon but may present with a variety of manifestations including pituitary hormone hypersecretion, hyposecretion, and/or the localized mass effect that causes compression of the optic chiasm or basal portion of the brain. In adults, the most common cause of hypothalamic-pituitary dysfunction is a pituitary adenoma. In children, pituitary adenomas are uncommon; the most common cause of pituitary dysfunction is hypothalamic tumors, of which craniopharyngiomas (neoplasms arising from cells of an embryonic hypophysial structure called the *Rathke pouch)* are the most common. These tumors usually manifest with signs of pituitary hyposecretion (e.g., short stature due to low GH levels and delayed puberty due to gonadotropin deficiency) prior to development of headache, visual loss, and other neurologic symptoms due to the mass effect of the expanding tumor.

Assessment of Hypothalamic-Pituitary Function

The precise assessment of hypothalamic-pituitary function has been made possible by radioimmunoassay of the anterior pituitary hormones and their specific target gland hormones. Magnetic resonance imaging (MRI) is used for imaging the hypothalamus and pituitary. It has largely replaced the use of computed tomography (CT) because it allows better visualization of normal structures and has better resolution in defining tumors.[2] When further information regarding pituitary function

is required, combined hypothalamic-pituitary function tests are undertaken (although these are performed less often today).[2] These tests consist mainly of hormone stimulation tests (e.g., rapid ACTH stimulation test) or suppression tests (e.g., GH suppression test).

Pituitary Adenomas and Hyperpituitarism

The most common cause of hyperpituitarism is an adenoma arising from the anterior pituitary.[2–5] Other, less common causes of hyperpituitarism are hyperplasia and carcinoma of the anterior pituitary, secretion of hormones by extrapituitary tumors, and certain hypothalamic lesions. Clinically diagnosed pituitary adenomas are responsible for about 10% of intracranial neoplasms. They are discovered incidentally in as many as 25% of routine autopsies. Pituitary lesions are also being increasingly detected as incidental findings on head MRI and CT scans performed for other reasons.[6]

The usual pituitary adenoma is a well-circumscribed lesion that can range in size from small lesions that do not enlarge the gland (microadenomas, <1 cm) to large, expansive tumors (macroadenomas, >1 cm) that erode the sella turcica and impinge on surrounding cranial structures.[2,5] The adenomas can be divided into nonfunctional tumors and functional tumors that secrete pituitary hormones.

The signs and symptoms of pituitary adenomas include endocrine abnormalities related specifically to functional adenomas and local mass effects of the expanding tumor. Lactotrophic adenomas are the most frequent type of hyperfunctioning pituitary adenoma, accounting for about 30% of all diagnosed cases.[2,4,5] Lactotrophic adenomas are usually small, benign tumors composed of prolactin-secreting cells. Hyperprolactinemia inhibits the pulsatile secretion of LH, which is essential for normal ovulation in women. Thus, the manifestations of hyperprolactinemia are most easily recognized in women of reproductive age and include amenorrhea (lack of menstruation), galactorrhea (spontaneous milk secretion unrelated to pregnancy), and infertility. In males, the symptoms of hyperprolactinemia are vague and may include impotence and loss of libido.

Because of the close proximity of the sella turcica to the optic nerves and chiasm, expanding pituitary lesions often compress the decussating fibers of the optic chiasm, giving rise to visual field abnormalities.[2,5] Cranial nerve deficits, which are much less common, can result in blurred or double vision or very rarely paresthesia on one side of the face. As in the case of any expanding intracranial mass, pituitary adenomas may produce signs and symptoms of increased intracranial pressure, including headache, nausea, and vomiting. In some cases, pituitary adenomas may extend beyond the sella turcica into the base of the brain, producing seizures and obstructive hydrocephalus. On occasion, acute hemorrhage into an adenoma may occur, producing rapid enlargement of the pituitary. The condition, termed *pituitary apoplexy*, is accompanied by a combination of acute nerve palsies, severe headache, and systemic symptoms related to ACTH deficiency.

Hypopituitarism

Hypopituitarism is characterized by a decreased secretion of pituitary hormones that causes hypofunction of secondary organs, which depend on trophic stimuli from the pituitary.[1] It may selectively involve one subset of pituitary cells (e.g., somatotropes) or all of the pituitary cells (*panhypopituitarism*). Typically, 70% to 90% of the anterior pituitary must be destroyed before hypopituitarism becomes clinically evident. The cause may be congenital or result from a variety of acquired abnormalities that cause destruction of the anterior pituitary or a secondary phenomenon resulting from deficiency of hypothalamic hormones normally acting on the pituitary. Space-occupying lesions cause hypopituitarism by destroying the pituitary gland or hypothalamic nuclei or by disrupting the hypothalamic-hypophysial portal system.

Anterior pituitary hormone loss is usually gradual, especially with progressive loss of pituitary reserve due to tumors or previous pituitary radiation therapy (which may take 10 to 20 years to produce hypopituitarism). The loss of pituitary function tends to follow a classic course beginning with the loss of GH, LH, and FSH secretion followed by deficiencies in TSH, then ACTH, and finally prolactin. Impairment of GH secretion causes decreased growth in children but may be clinically unapparent in adults. Hypogonadism, manifested by amenorrhea in women and decreased libido and erectile function in men, may precede the clinical appearance of other manifestations. The manifestations of hypothyroidism caused by TSH deficiency (e.g., cold intolerance, dry skin, mental dullness) are similar to those observed in primary thyroid failure but less severe. ACTH deficiency is the most serious endocrine deficiency. It causes secondary adrenal insufficiency, leading to weakness, nausea, anorexia, fever, and postural hypotension.

Treatment of hypopituitarism includes treating any identified underlying cause. Hormone deficiencies require replacement therapy with appropriate hormones. Cortisol replacement is started when ACTH deficiency is present, thyroid replacement when TSH deficiency is detected, and sex hormone replacement when LH and FSH are deficient. GH replacement is indicated for pediatric GH deficiency and is being increasingly used to treat GH deficiency in adults.[2,7,8]

Growth and Growth Hormone Disorders

Several hormones are essential for normal body growth and maturation, including growth hormone, insulin, thyroid hormone, and androgens.[9] In addition to its actions on carbohydrate and fat metabolism, insulin plays an essential role in growth processes. Children with diabetes, particularly those with poor control, often fail to grow normally even though GH levels are normal. When levels of thyroid hormone are lower than normal, bone growth

and epiphyseal closure are delayed. Androgens such as testosterone and dihydrotestosterone exert anabolic growth effects through their actions on protein synthesis. Glucocorticoids at excessive levels inhibit growth, apparently because of their antagonistic effect on GH secretion.

Growth Hormone

Growth hormone, also called *somatotropin,* is a 191–amino-acid polypeptide hormone synthesized and secreted by special cells in the anterior pituitary called *somatotropes*.[2] For many years, it was thought that GH was produced primarily during periods of growth. However, this has proved to be incorrect because the rate of GH production in adults is almost as great as in children. GH is necessary for growth and contributes to the regulation of metabolic functions (Fig. 32-1). All aspects of cartilage growth are stimulated by GH; one of the most striking effects of GH is on linear bone growth, resulting from its action on the epiphyseal growth plates of long bones. The width of bone bone increases because of enhanced periosteal growth; visceral and endocrine organs, skeletal and cardiac muscle, skin, and connective tissue all undergo increased growth in response to GH. In many instances, the increased growth of visceral and endocrine organs is accompanied by enhanced functional capacity. For example, increased growth of cardiac muscle is accompanied by an increase in cardiac output.

In addition to its effects on growth, GH facilitates the rate of protein synthesis by all of the cells of the body, enhances fatty acid mobilization and increases the use of fatty acids for fuel, and maintains or increases blood glucose levels by decreasing the use of glucose for fuel. GH has an initial effect of increasing insulin levels. However, the predominant effect of prolonged GH excess is to increase glucose levels despite an insulin increase. This is because GH induces a resistance to insulin in the peripheral tissues, inhibiting the uptake of glucose by muscle and adipose tissues.[2]

Many of the effects of GH are mediated by *insulin-like growth factors* (IGFs), which are produced mainly by the liver.[9] GH cannot directly produce bone growth; instead, it acts indirectly by causing the liver to produce IGFs. These peptides act on cartilage and bone to promote their growth. At least four IGFs have been identified; of these, IGF-1 (previously known as somatomedin C) appears to be the more important in terms of growth, and it is the one that usually is measured in laboratory tests. The IGFs have been sequenced and found to have structures that are similar to those of proinsulin. This undoubtedly explains the insulin-like activity of the IGFs and the weak action of insulin on growth. IGF levels are

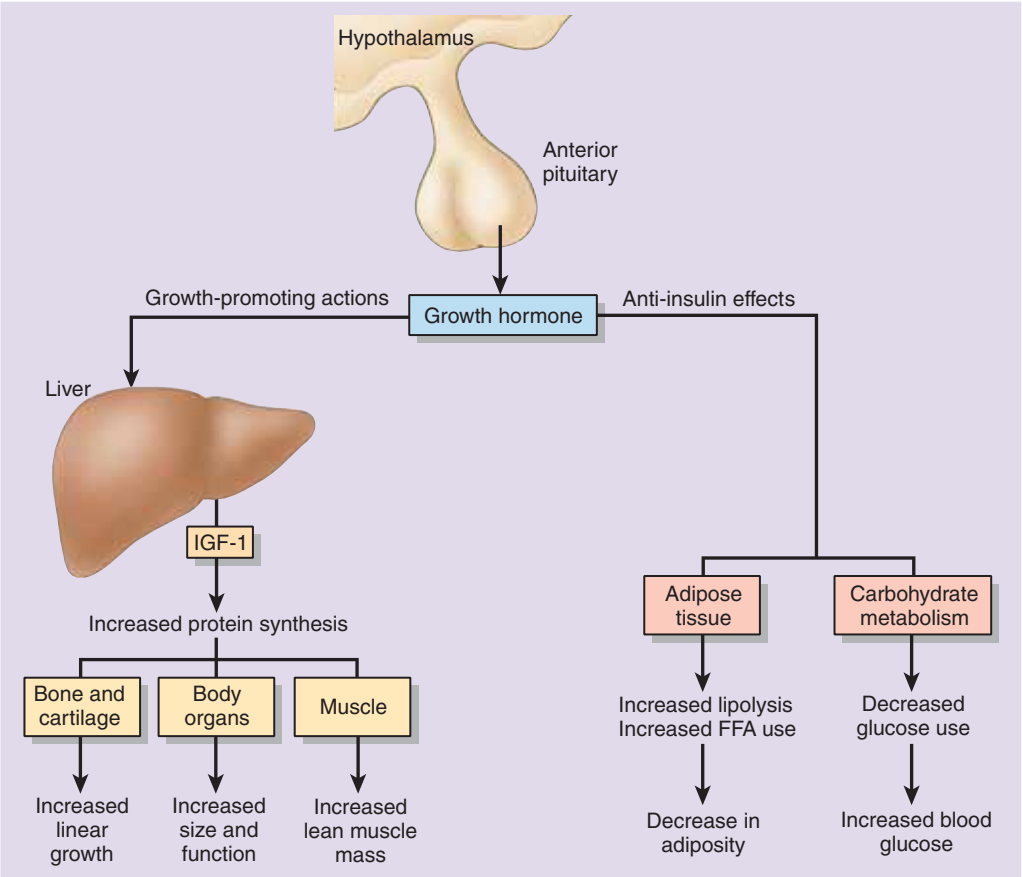


FIGURE 32-1. Growth-promoting and anti-insulin effects of growth hormone. FFA, free fatty acids; IGF-1, insulin-like growth factor-1.

Growth Hormone

- Growth hormone (GH), which is produced by somatotropes in the anterior pituitary, is necessary for linear bone growth in children. It also increases the rate at which cells transport amino acids across their cell membranes, and it increases the rate at which they utilize fatty acids and decreases the rate at which they use carbohydrates.
- The effects of GH on linear growth requires insulin-like growth factors (IGFs), which are produced mainly by the liver.
- GH (or IGF) deficiency in children interferes with linear bone growth, resulting in short stature or dwarfism.
- In children, GH excess results in increased linear growth or gigantism; in adults it results in overgrowth of the cartilaginous parts of the skeleton, enlargement of the heart and other organs, and metabolic disturbances in fat and carbohydrate metabolism.

themselves influenced by a family of at least six binding factors called *IGF-binding proteins* (IGFBPs).

GH is carried unbound in the plasma and has a half-life of approximately 20 to 50 minutes. The secretion of GH is regulated by two hypothalamic hormones: GH-releasing hormone (GHRH), which increases GH release, and somatostatin, which inhibits GH release. A third hormone, the recently identified *ghrelin*, also may be important. The hypothalamic influences of GHRH and somatostatin are tightly regulated by neural and metabolic influences. The secretion of GH fluctuates over a 24-hour period, with peak levels occurring 1 to 4 hours after onset of sleep. The nocturnal sleep bursts, which account for 70% of daily GH secretion, are greater in children than in adults.

GH secretion is stimulated by hypoglycemia, fasting, starvation, increased blood levels of amino acids (particularly arginine), and stress conditions such as trauma, excitement, emotional stress, and heavy exercise. GH is inhibited by increased glucose levels, free fatty acid release, cortisol, and obesity. Impairment of secretion, leading to growth retardation, is not uncommon in children with severe emotional deprivation.

Short Stature in Children

Short stature is a condition in which the attained height is well below the third percentile or linear growth is below normal for age and gender. Short stature, or growth retardation, has a variety of causes, including chromosomal abnormalities such as Turner syndrome (see Chapter 6), GH deficiency, hypothyroidism, and panhypopituitarism (i.e., deficiency of *all* pituitary-derived hormones).[9] Other conditions known to cause short stature include protein-calorie malnutrition, chronic diseases such as chronic kidney disease and poorly controlled diabetes mellitus, malabsorption syndromes such as celiac disease, and certain therapies such as excessive glucocorticoid administration. Emotional disturbances can lead to functional endocrine disorders, causing psychosocial dwarfism. The causes of short stature are summarized in Chart 32-1.

Accurate measurement of height is an extremely important part of the physical examination of children. Completion of the developmental history and growth charts is essential.[10,11] Growth curves and growth velocity studies also are needed. The Centers for Disease Control and Prevention (CDC) growth charts are available at http://www.cdc.gov/growthcharts. Diagnosis of short stature is not made on a single measurement, but is based

CHART 32-1 Causes of Short Stature

Variants of Normal
Genetic or "familial" short stature
Constitutional growth delay

Low Birth Weight (e.g., intrauterine growth retardation)

Endocrine Disorders
Growth hormone (GH) deficiency
  Primary GH deficiency
    Idiopathic GH deficiency
    Pituitary agenesis
  Secondary GH deficiency (panhypopituitarism)
Biologically inactive GH production
Deficient IGF-1 production in response to normal or elevated GH (Laron-type dwarfism)
Hypothyroidism
Diabetes mellitus in poor control
Glucocorticoid excess
  Endogenous (Cushing syndrome)
  Exogenous (glucocorticoid drug treatment)
Abnormal mineral metabolism
  (e.g., pseudohypoparathyroidism)

Chronic Illness and Malnutrition
Chronic organic or systemic disease (e.g., asthma, especially when treated with glucocorticoids; heart or renal disease)
Nutritional deprivation
Malabsorption syndrome (e.g., celiac sprue)

Functional Endocrine Disorders
(Psychosocial Dwarfism)

Chromosomal Disorders (e.g., Turner syndrome)

Skeletal Abnormalities (e.g., achondroplasia)

on sequential height measurements and on velocity of growth and parental height.[9]

The diagnostic procedures for short stature include tests to exclude nonendocrine causes. If the cause is hormonal, extensive hormonal testing procedures are initiated. Usually, GH and IGF-1 levels are determined (IGFBP-3 levels also are useful). Tests can be performed using insulin (to induce hypoglycemia), GHRH, levodopa, and arginine, all of which stimulate GH secretion so that GH reserve can be evaluated.[9] Because administration of pharmacologic agents can result in false-negative responses, two or more tests usually are performed. If a prompt rise in GH is realized, the child is considered normal. Physiologic tests of GH reserve (e.g., GH response to exercise) also can be performed. Levels of IGF-1 usually reflect those of GH and may be used to indicate GH deficiency. Radiologic films are used to assess bone age, which most often is delayed. MRI of the hypothalamic-pituitary area is recommended if a lesion is clinically suspected. After the cause of short stature has been determined, treatment can be initiated.

Idiopathic Short Stature. Idiopathic short stature, also referred to as normal-variant short stature, is short stature of undefined cause.[11–13] It has been defined as a condition in which the height of an individual is more than 2 standard deviations below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities.[10] This definition includes children with familial short stature and constitutional delay in growth and puberty. Children with familial short stature tend to be well proportioned and to have a height close to the midparental height of their parents. The midparental height for boys can be calculated by adding 13 cm (5 in) to the height of the mother, adding the father's height, and dividing the total by two. For girls, 13 cm (5 in) is subtracted from the father's height, the result is added to the mother's height, and the total is divided by two.[9] Ninety-five percent of normal children are within 8 cm (i.e., ±2 standard deviations) of the midparental height.

Constitutional delay in growth and puberty describes children (particularly boys) who have moderately short stature, thin build, delayed skeletal and sexual maturation, and absence of other causes of decreased growth. *Catch-up growth* is a term used to describe an abnormally high growth rate that occurs as a child approaches normal height for age. It also occurs after the initiation of therapy for GH deficiency and hypothyroidism and the correction of chronic diseases.[9]

Psychosocial Dwarfism. Psychosocial dwarfism involves a functional hypopituitarism and is seen in some emotionally deprived children. These children usually present with poor growth, potbelly, and poor eating and drinking habits. Typically, there is a history of disturbed family relationships in which the child has been severely neglected or disciplined. Often, the neglect is confined to one child in the family. GH function usually returns to normal after the child is removed from the constraining environment. The prognosis depends on improvement in behavior and catch-up growth. Family therapy usually is indicated, and foster care may be necessary.

Growth Hormone and Insulin-Like Growth Factor Deficiencies in Children. There are several forms of GH deficiency that present in childhood. Children with idiopathic GH deficiency lack the hypothalamic GHRH but have adequate somatotropes, whereas children with pituitary tumors or agenesis of the pituitary lack somatotropes.

Congenital GH deficiency is associated with decreased birth length, followed by a decrease in growth rate that can be identified by careful measurement during the first year and that becomes obvious by 1 to 2 years of age. Children with classic GH deficiency have normal intelligence, short stature, obesity with immature facial features, and some delay in skeletal maturation (Fig. 32-2). Puberty often is delayed, and males with the disorder have microphallus (abnormally small penis), especially if the condition is accompanied by gonadotropin-releasing hormone (GnRH) deficiency. In the neonate, GH deficiency can lead to hypoglycemia and seizures; if ACTH deficiency also is present, the hypoglycemia often is more severe. Acquired GH deficiency develops in later childhood; it may be caused by a hypothalamic-pituitary tumor, particularly if it is accompanied by other pituitary hormone deficiencies.

FIGURE 32-2. Child with growth hormone deficiency. A 5.5-year-old boy (*left*) with growth hormone deficiency was significantly shorter than his fraternal twin sister (*right*), with the discrepancy beginning early in childhood. Notice his chubby, immature appearance compared with his sister. (From Shulman D., Bercu B. [Eds.]. [2000]. *Atlas of clinical endocrinology, neuroendocrinology, and pituitary diseases.* Korenman S. [Series Ed.]. Philadelphia: Current Medicine.)

When short stature is caused by a GH deficiency, GH replacement therapy is the treatment of choice. GH is species specific, and only human GH is effective in humans. GH previously was obtained from human cadaver pituitaries, but now is produced by recombinant deoxyribonucleic acid (DNA) technology and is available in adequate supply. GH is administered by daily subcutaneous injection during the period of active growth and can be continued into adulthood.[9] Children with short stature due to Turner syndrome and chronic renal insufficiency also are treated with GH. GH therapy may also be considered for children with idiopathic short stature.[10]

In a rare condition called *Laron-type* dwarfism there is an extreme resistance to GH due to abnormalities in the growth hormone receptor.[9,14] Affected persons tend to be obese and have high levels of GH and low levels of IGF-1. The condition is seen predominantly in people of Mediterranean descent, especially Sephardic Jews. The same pathology is responsible for dwarfism of the African pygmies. IGF-1 is now produced by recombinant DNA technology. Since GH produces its effects by promoting IGF-1 secretion, IGF-1 is an effective replacement therapy for Laron dwarfism, mimicking most of the effects ascribed to GH.[9]

Growth Hormone Deficiency in Adults

There are two categories of GH deficiency in adults: GH deficiency that was present in childhood and GH deficiency that developed during adulthood, mainly as the result of hypopituitarism resulting from a pituitary tumor or its treatment.[15] GH levels also can decline with aging (described as the *somatopause*), and there has been interest in the effects of declining GH levels in the elderly.[16] GH replacement obviously is important in the growing child; however, the role in adults (especially for the somatopause) is being assessed.

The clinical features of adult GH deficiency include changes in body composition, such as a decrease in lean body mass and increase in fat mass, hyperlipidemia, decreased bone mineral density, and reduced exercise capacity, and diminished sense of well-being. GH deficiency is associated with a cluster of cardiovascular risk factors including central adiposity (associated with increased visceral fat), insulin resistance, and dyslipidemia.[15] These features also are associated with the *metabolic syndrome* (see Chapter 33). In addition to these so-called traditional cardiovascular risk factors, nontraditional cardiovascular risk factors (e.g., C-reactive protein [CRP], which is a marker of the inflammatory pathway) are also elevated.[17]

Several recombinant human GH preparations have been approved for treatment of adults with diagnosed GH deficiency. The most common side effects of GH treatment in adults with hypopituitarism are peripheral edema, arthralgias and myalgias, carpal tunnel syndrome, paresthesias, and decreased glucose tolerance.[15] Side effects appear to be more common in people who are older, have greater weight, and are overtreated as determined by high serum IGF-1 levels during therapy.

Tall Stature and Growth Hormone Excess in Children

Just as there are children who are short for their age and gender, there also are children who are tall for their age and gender.[9,18] Normal variants of tall stature include genetic tall stature and constitutional tall stature. Children with exceptionally tall parents tend to be taller than children with shorter parents. The term *constitutional tall stature* is used to describe a child who is taller than his or her peers and is growing at a velocity that is within the normal range for bone age. Other causes of tall stature are genetic or chromosomal disorders such as Marfan syndrome or XYY syndrome (see Chapter 6). Endocrine causes of tall stature include sexual precocity because of early onset of estrogen and androgen secretion and excessive GH.

Exceptionally tall children (i.e., genetic tall stature and constitutional tall stature) can be treated with sex hormones—estrogens in girls and testosterone in boys—to effect early epiphyseal closure. Such treatment is undertaken only after full consideration of the risks involved. To be effective, such treatment must be instituted 3 to 4 years before expected epiphyseal fusion.[9,18]

Growth hormone excess occurring before puberty and the fusion of the epiphyses of the long bones results in *gigantism* (Fig. 32-3). Excessive secretion of GH by somatotrope adenomas causes gigantism in the prepubertal child.[19] It occurs when the epiphyses are not fused and high levels of IGF-1 stimulate excessive skeletal growth. Fortunately, the condition is rare because of early recognition and treatment of the adenoma.

Growth Hormone Excess in Adults

When GH excess occurs in adulthood or after the epiphyses of the long bones have fused, it causes a condition called *acromegaly* (from the Greek words *acros*, meaning "end portion," and *megalos*, meaning "large"), which represents an exaggerated growth of the ends of the extremities (fingers, hands, and toes). The annual incidence of acromegaly is 3 to 4 cases per 1 million people, with a mean age at the time of diagnosis of 40 to 45 years.[2,20,21]

The most common cause of acromegaly are GH-secreting adenomas, most of which are benign.[21] The disorder usually has an insidious onset, and symptoms often are present for a considerable period before a diagnosis is made. When the production of excessive GH occurs after the epiphyses of the long bones have closed, as in the adult, the person cannot grow taller, but the soft tissues continue to grow. Enlargement of the small bones of the hands and feet and of the membranous bones of the face and skull results in a pronounced enlargement of the hands and feet, a broad and bulbus nose, a protruding jaw, and a slanting forehead (Fig. 32-4). The teeth become splayed, causing a disturbed bite and difficulty in chewing. The cartilaginous structures in the larynx and respiratory tract also become enlarged, resulting in a deepening of the voice and tendency to develop bronchitis. Vertebral changes often lead to kyphosis, or hunchback. Bone overgrowth often leads to arthralgias and

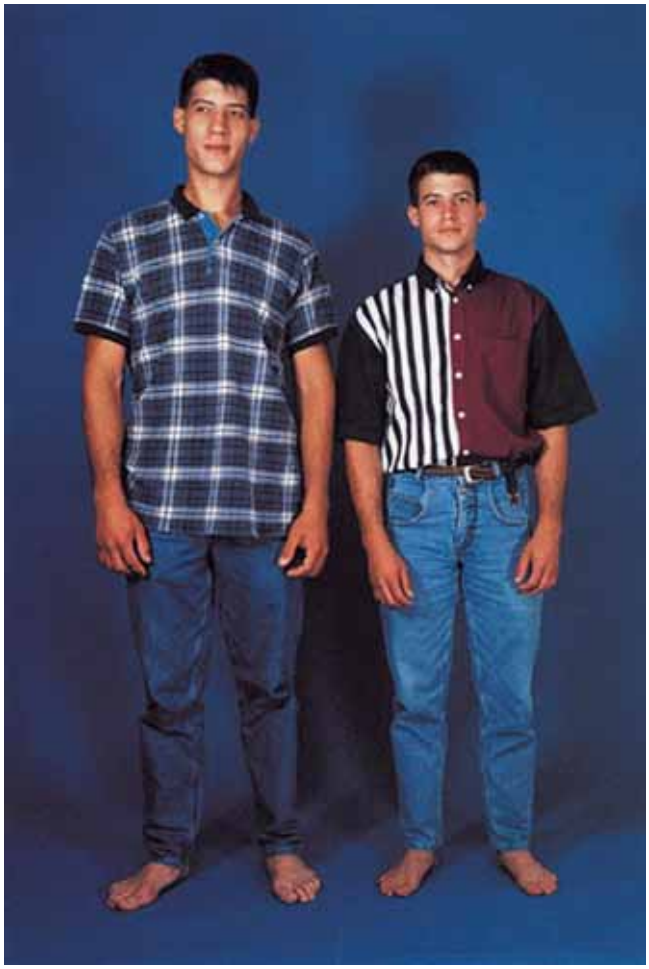


FIGURE 32-3. Primary gigantism. A 22-year-old man with gigantism due to excess growth hormone is shown to the left of his identical twin. (From Gagel R.F., McCutcheon I.E. [1999]. Images in clinical medicine. *New England Journal of Medicine* 340, 524. Copyright © 2003. Massachusetts Medical Society.)

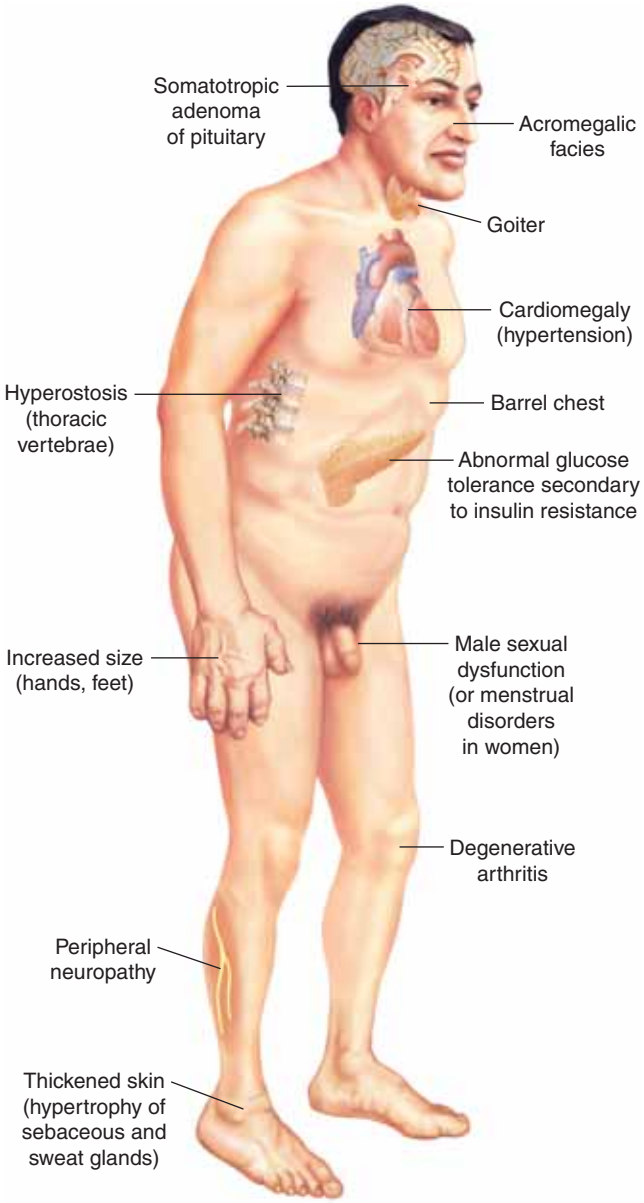


FIGURE 32-4. Clinical manifestations of acromegaly.

degenerative arthritis of the spine, hips, and knees. Virtually every organ of the body is increased in size. Enlargement of the heart and accelerated atherosclerosis may lead to an early death.

The metabolic effects of excess levels of GH include disorders of fat and carbohydrate metabolism. GH causes increased release of free fatty acids from adipose tissue, leading to increased concentration of free fatty acids in body fluids. In addition, GH exerts multiple effects on carbohydrate metabolism, including decreased glucose uptake by tissues such as skeletal muscle and adipose tissue, increased glucose production by the liver, and increased insulin secretion. Each of these changes results in GH-induced insulin resistance (see Chapter 33). Impaired glucose tolerance occurs in as many as 50% to 70% of persons with acromegaly; overt diabetes mellitus subsequently can result.

Other manifestations of acromegaly include excessive sweating with an unpleasant odor, oily skin, heat intolerance, moderate weight gain, muscle weakness and fatigue, menstrual irregularities, and decreased libido. Hypertension is relatively common. Sleep apnea syndrome is present in up to 90% of patients. The pathogenesis of the sleep apnea syndrome is obstructive in the majority of patients, due to increased pharyngeal soft tissue accumulation. Paresthesias may develop because of nerve entrapment and compression caused by excess soft tissue and accumulation of subcutaneous fluid (especially carpal tunnel syndrome). Headaches are frequent. Temporal hemianopia (loss of vision for one half of the visual field) may occur as a result of the optic chiasm being impinged by a suprasellar growth of the tumor.

The treatment goals for acromegaly focus on the correction of metabolic abnormalities and include normalization of the GH response to an oral glucose load; normalization of IGF-1 levels to age- and sex-matched control levels; removal or reduction of the tumor mass;

relieving the central mass effects; and improvement of adverse clinical features.[2] Pituitary tumors can be removed surgically using the transsphenoidal approach or, if that is not possible, a transfrontal craniotomy. Radiation therapy may be used, but remission (reduction in GH levels) may not occur for several years after therapy.

Somatostatin analogs (especially long-acting formulations of octreotide or lanreotide) produce feedback inhibition of GH and are effective in the medical management of acromegaly. Dopamine agonists also reduce GH levels and have been used with some success.[2] GH analogs (e.g., pegvisomant) antagonize the actions of GH by binding to GH receptors on the cell surfaces. These analogs produce symptom relief and normalize serum IGF-1 levels in most individuals with acromegaly.[2]

Precocious Puberty

Precocious puberty is defined as early activation of the hypothalamic-pituitary-gonadal axis, resulting in the development of secondary sexual characteristics and fertility.[22,23] Classically, sexual development was considered precocious and warranting investigation when it occurred before 8 years of age for girls and before 9 years of age for boys. However, these criteria were revised recently based on an office pediatric study of more than 17,000 American girls.[24] Precocious puberty is now defined as the appearance of secondary sexual development before the age of 7 years in white girls and 6 years in African American girls.[23] In boys of both races, the lower age limit remains 9 years; however, it is recognized that puberty can develop earlier in boys with obesity (an increasingly common problem).[23] Precocious sexual development may be idiopathic or may be caused by gonadal, adrenal, or hypothalamic disorders. Benign and malignant tumors of the central nervous system (CNS) can cause precocious puberty. These tumors are thought to remove the inhibitory influences normally exerted on the hypothalamus during childhood. CNS tumors are found more often in boys with precocious puberty than in girls. In girls, most cases are idiopathic.

Diagnosis of precocious puberty is based on physical findings of early thelarche (i.e., beginning of breast development), adrenarche (i.e., beginning of augmented adrenal androgen production), and menarche (i.e., beginning of menstrual function) in girls. The most common sign in boys is early genital enlargement. Radiologic findings may indicate advanced bone age. Persons with precocious puberty usually are tall for their age as children but short as adults because of the early closure of the epiphyses. MRI or CT should be used to exclude intracranial lesions.

Depending on the cause of precocious puberty, the treatment may involve surgery, medication, or no treatment. The administration of a long-acting GnRH agonist results in a decrease in pituitary responsiveness to GnRH, leading to decreased secretion of gonadotropic hormones and sex steroids (i.e., due to down-regulation of GnRH receptors). Parents often need education, support, and anticipatory guidance in dealing with their feelings and the child's physical needs and in relating to a child who appears older than his or her years.[23]

In summary, disorders of the pituitary are uncommon but may present with a variety of manifestations including pituitary hormone hypersecretion, hyposecretion, and/or localized mass effect causing compression of the optic chiasm or basal portion of the brain. The most common cause of hyperpituitarism is an adenoma arising from the anterior pituitary. The adenomas can be divided into functional tumors that secrete pituitary hormones and nonfunctional tumors that do not secrete hormones. Hypopituitarism, which is characterized by a decreased secretion of pituitary hormones, is a condition that affects many of the other endocrine systems.

A number of hormones are essential for normal body growth and maturation, including growth hormone, insulin, thyroid hormone, and androgens. GH exerts its growth effects through IGF-1. GH also exerts an effect on metabolism and is produced in the adult and in the child. Its metabolic effects include a decrease in peripheral use of carbohydrates and an increased mobilization and use of fatty acids.

In children, alterations in growth include short stature and tall stature. Short stature is a condition in which the attained height is well below the third percentile or the linear growth velocity is below normal for a child's age or gender. Short stature can occur as a variant of normal growth, idiopathic short stature, or as the result of endocrine disorders, chronic illness, malnutrition, emotional disturbances, or chromosomal disorders. Short stature resulting from GH deficiency can be treated with human GH preparations. In adults, GH deficiency represents a deficiency carried over from childhood or one that develops during adulthood as the result of a pituitary tumor or its treatment.

Tall stature refers to the condition in which children are tall for their age and gender. It can occur as a variant of normal growth (i.e., genetic tall stature or constitutional tall stature) or as the result of a chromosomal abnormality or GH excess. GH excess in adults results in acromegaly, which involves proliferation of bone, cartilage, and soft tissue along with the metabolic effects of excessive hormone levels.

Precocious puberty defines a condition of early activation of the hypothalamic-pituitary-gonadal axis (i.e., before 6 years of age in African American girls and 7 years of age in white girls, and before 9 years of age in boys of both races), resulting in the development of secondary sexual characteristics and fertility. It causes tall stature during childhood but results in short stature in adulthood because of the early closure of the epiphyses.

Thyroid Disorders

Control of Thyroid Function

The thyroid gland is a shield-shaped structure located immediately below the larynx in the anterior middle

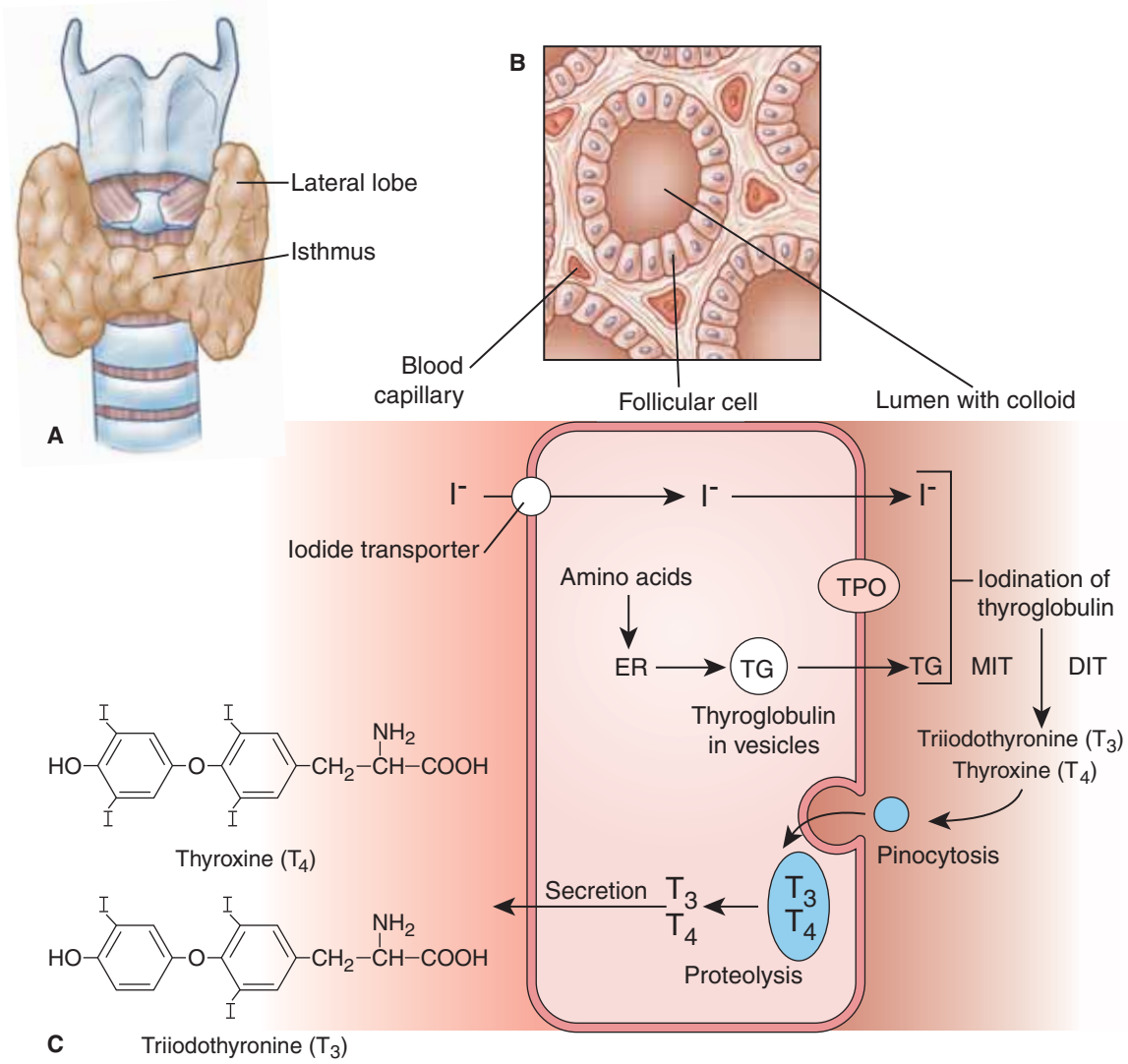


FIGURE 32-5. **(A)** The thyroid gland. **(B)** Microscopic structure of thyroid follicles. **(C)** Cellular mechanisms for transport of iodide (I^-), oxidation of I^- by thyroperoxidase (TPO), coupling of oxidized I^- with thyroglobulin (TG) to form thyroid hormones, and movement of T_3 and T_4 into the follicular cell by pinocytosis and release into the blood. ER, endoplasmic reticulum; MIT, monorodotyrosine; DIT, diiodotyrosine.

portion of the neck[25,26] (Fig. 32-5A). It is composed of a large number of tiny, saclike structures called *follicles* (see Fig. 32-5B). These are the functional units of the thyroid. Each follicle is formed by a single layer of epithelial (follicular) cells and is filled with a secretory substance called *colloid*, which consists largely of a glycoprotein–tyrosine complex called *thyroglobulin*. The thyroglobulin that fills the thyroid follicles is a large glycoprotein molecule that contains 140 tyrosine amino acids. In the process of thyroid synthesis, iodine is attached to these tyrosine molecules. Both thyroglobulin and iodide are secreted into the colloid of the follicle by the follicular cells.

The thyroid is remarkably efficient in its use of iodide. A daily absorption of 150 to 200 μg of dietary iodide is sufficient to form normal quantities of thyroid hormone. In the process of removing it from the blood and storing it for future use, iodide is pumped into the follicular cells against a concentration gradient. Iodide (I^-) is transported across the basement membrane of the thyroid cells by an intrinsic membrane protein called the *Na^+/I symporter* (NIS).[25] At the apical border, a second I^- transport protein called *pendrin* moves iodine into the colloid, where it is involved in hormone production. The NIS derives its energy from sodium (Na^+)/potassium (K^+)-adenosine triphosphatase (ATPase), which drives the process. As a result, the concentration of iodide in the normal thyroid gland is approximately 40 times that in the blood. The NIS is stimulated by both TSH and the TSH receptor–stimulating antibody found in Graves disease (to be discussed). Pendrin, encoded by the Pendred syndrome gene (*PDS*), is a transporter of chloride and iodide. Mutations in the *PDS* gene have been found in patients with goiter and congenital deafness (Pendred syndrome).

Once inside the follicle, most of the iodide is oxidized by the enzyme thyroid peroxidase (TPO) in a reaction that facilitates combination with a tyrosine molecule to

Thyroid Hormone

- Thyroid hormone increases the metabolism and protein synthesis in nearly all of the tissues of the body.
- It also is necessary for brain development and growth in infants and small children. Infants born with decreased or absent thyroid function have impaired mental and physical development.
- When hypothyroidism occurs in older children or adults, it produces a decrease in metabolic rate, an accumulation of a hydrophilic mucopolysaccharide substance (myxedema) in the connective tissues throughout the body, and an elevation in serum cholesterol.
- Hyperthyroidism has an effect opposite that of hypothyroidism. It produces an increase in metabolic rate and oxygen consumption, increased use of metabolic fuels, and increased sympathetic nervous system responsiveness.

form monoiodotyrosine (MIT) and then diiodotyrosine (DIT). Two diiodotyrosine residues are coupled to form thyroxine (T_4), or a monoiodotyrosine and a diiodotyrosine are coupled to form triiodothyronine (T_3). Only T_4 (90%) and T_3 (10%) are released into the circulation (see Fig. 32-5C). There is evidence that T_3 is the active form of the hormone and that T_4 is converted to T_3 before it can act physiologically.

Thyroid hormones are bound to thyroxine-binding globulin (TBG) and other plasma proteins for transport in the blood. Only the free hormone enters cells and regulates the pituitary feedback mechanism. Protein-bound thyroid hormone forms a large reservoir that is slowly drawn on as free thyroid hormone is needed. There are three major thyroid-binding proteins: TBG, transthyretin (formerly known as thyroxine-binding prealbumin [TBPA]), and albumin. More than 99% of T_4 and T_3 is carried in the bound form.[25,26] TBG carries approximately 70% of T_4 and T_3, transthyretin binds approximately 10% of circulating T_4 and lesser amounts of T_3, and albumin binds approximately 15% of circulating T_4 and T_3.

A number of disease conditions and pharmacologic agents can decrease the amount of binding protein in the plasma or influence the binding of hormone. Congenital TBG deficiency is an X-linked trait that occurs in 1 of every 5000 live births. Glucocorticoid medications and systemic disease conditions such as protein malnutrition, nephrotic syndrome, and cirrhosis decrease TBG concentrations. Medications such as phenytoin, salicylates, and diazepam can affect the binding of thyroid hormone to normal concentrations of binding proteins.

The secretion of thyroid hormone is regulated by the hypothalamic-pituitary-thyroid feedback system (Fig. 32-6). In this system, thyrotropin-releasing hormone

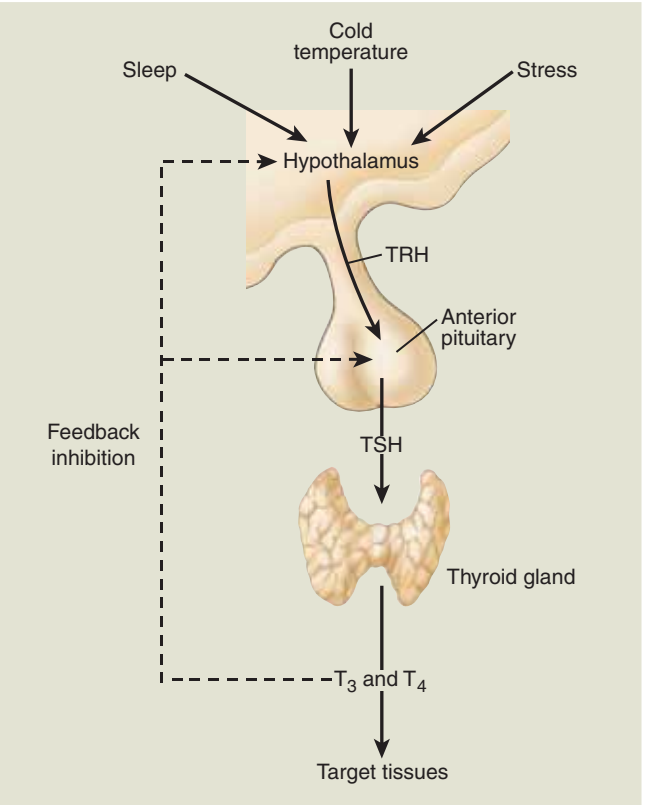


FIGURE 32-6. The hypothalamic-pituitary-thyroid feedback system, which regulates the body levels of thyroid hormone. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

(TRH), which is produced by the hypothalamus, controls the release of TSH from the anterior pituitary gland. TSH increases the overall activity of the thyroid gland by increasing thyroglobulin breakdown and the release of thyroid hormone from follicles into the bloodstream, activating the iodide pump (by increasing NIS activity), increasing the oxidation of iodide and the coupling of iodide to tyrosine, and increasing the number and the size of the follicle cells. The effect of TSH on the release of thyroid hormones occurs within approximately 30 minutes, but the other effects require days or weeks.

Increased levels of thyroid hormone act in the feedback inhibition of TRH or TSH. High levels of iodide (e.g., from iodide-containing cough syrup or kelp tablets) also cause a temporary decrease in thyroid activity that lasts for several weeks, probably through a direct inhibition of TSH on the thyroid. Cold exposure is one of the strongest stimuli for increased thyroid hormone production and probably is mediated through TRH from the hypothalamus. Various emotional reactions also can affect the output of TRH and TSH and therefore indirectly affect secretion of thyroid hormones.

Actions of Thyroid Hormone

Most of the major organs in the body are affected by altered levels of thyroid hormone. Thyroid hormone

increases metabolism and protein synthesis; it is necessary for growth and development in children, including mental development and attainment of sexual maturity; and it affects the function of many other organ systems in the body. These actions are mainly mediated by T_3. In the cell, T_3 binds to a nuclear receptor, resulting in transcription of specific thyroid hormone response genes.[25,26]

Metabolic Rate. Thyroid hormone increases the metabolism of all body tissues except the retinas, spleen, testes, and lungs. The basal metabolic rate can increase by 60% to 100% above normal when large amounts of T_4 are present. As a result of this higher metabolism, the rate of glucose, fat, and protein use increases. Lipids are mobilized from adipose tissue, and the catabolism of cholesterol by the liver is increased. Blood levels of cholesterol are decreased in hyperthyroidism and increased in hypothyroidism. Muscle proteins are broken down and used as fuel, probably accounting for some of the muscle fatigue that occurs with hyperthyroidism. The absorption of glucose from the gastrointestinal tract is increased. Because vitamins are essential parts of metabolic enzymes and coenzymes, an increase in metabolic rate tends to "speed up" the use of vitamins and cause vitamin deficiency.

Cardiovascular Function. Cardiovascular and respiratory functions are strongly affected by thyroid function. With an increase in metabolism, there is a rise in oxygen consumption and production of metabolic end products, with an accompanying increase in vasodilation. Blood flow to the skin, in particular, is augmented as a means of dissipating the body heat that results from the higher metabolic rate. Blood volume, cardiac output, and ventilation all are increased as a means of maintaining blood flow and oxygen delivery to body tissues. Heart rate and cardiac contractility are enhanced as a means of maintaining the needed cardiac output. On the other hand, blood pressure is likely to change little because the increase in vasodilation tends to offset the increase in cardiac output.

Gastrointestinal Function. Thyroid hormone enhances gastrointestinal function, causing an increase in motility and production of gastrointestinal secretions that often results in diarrhea. An increase in appetite and food intake accompanies the higher metabolic rate that occurs with increased thyroid hormone levels. At the same time, weight loss occurs because of the increased use of calories.

Neuromuscular Effects. Thyroid hormone has marked effects on neural control of muscle function and tone. Slight elevations in hormone levels cause skeletal muscles to react more vigorously, and a drop in hormone levels causes muscles to react more sluggishly. In the hyperthyroid state, a fine muscle tremor is present. The cause of this tremor is unknown, but it may represent an increased sensitivity of the neural synapses in the spinal cord that control muscle tone. In the infant, thyroid hormone is necessary for normal brain development. The hormone enhances cerebration; in the hyperthyroid state, it causes extreme nervousness, anxiety, and difficulty in sleeping.

Evidence suggests a strong interaction between thyroid hormone and the sympathetic nervous system. Many of the signs and symptoms of hyperthyroidism suggest overactivity of the sympathetic division of the autonomic nervous system, such as tachycardia, palpitations, and sweating. Tremor, restlessness, anxiety, and diarrhea also may reflect autonomic nervous system imbalances. Drugs that block sympathetic activity have proved to be valuable adjuncts in the treatment of hyperthyroidism because of their ability to relieve some of these undesirable symptoms.

Tests of Thyroid Function

Various tests aid in the diagnosis of thyroid disorders.[25,27] Measures of T_3, T_4, and TSH have been made available through immunoassay methods. The free T_4 test measures the unbound portion of T_4 that is free to enter cells to produce its effects. TSH levels are used to differentiate between primary and secondary thyroid disorders. T_3, T_4, and free T_4 levels are low in primary hypothyroidism, and the TSH level is elevated. The assessment of thyroid autoantibodies (e.g., anti-TPO antibodies in Hashimoto thyroiditis) is important in the diagnostic workup and consequent follow-up of patients with thyroid disorders.

The radioiodine (^{123}I) uptake test measures the ability of the thyroid gland to remove and concentrate iodine from the blood. Thyroid scans (^{123}I, ^{99m}Tc-pertechnetate) can be used to detect thyroid nodules and determine the functional activity of the thyroid gland. Ultrasonography can be used to differentiate cystic from solid thyroid lesions, and CT and MRI scans are used to demonstrate tracheal compression or impingement on other neighboring structures. Fine needle aspiration biopsy of a thyroid nodule has proved to be the best method for differentiation of benign from malignant thyroid disease.

Disorders of Thyroid Function

An alteration in thyroid function can represent a hypofunctional or a hyperfunctional state. The manifestations of these two altered states are summarized in Table 32-1. Disorders of the thyroid may be due to a congenital defect in thyroid development, or they may develop later in life, with a gradual or sudden onset.

Goiter is an increase in the size of the thyroid gland. It can occur in hypothyroid, euthyroid, and hyperthyroid states. Goiters may be diffuse, involving the entire gland without evidence of nodularity, or they may contain nodules. Diffuse goiters usually become nodular. Goiters may be toxic, producing signs of extreme hyperthyroidism or thyrotoxicosis, or they may be nontoxic. Diffuse nontoxic and multinodular goiters are the result of compensatory hypertrophy and hyperplasia of follicular epithelium from some derangement that impairs thyroid hormone output.

The degree of thyroid enlargement usually is proportional to the extent and duration of thyroid deficiency.

TABLE 32-1 Manifestations of Hypothyroid and Hyperthyroid States

Level of Organization	Hypothyroidism	Hyperthyroidism
Basal metabolic rate	Decreased	Increased
Sensitivity to catecholamines	Decreased	Increased
General features	Myxedematous features	Exophthalmos (in Graves disease)
	Deep voice	Lid lag
	Impaired growth (child)	Accelerated growth (child)
Blood cholesterol levels	Increased	Decreased
General behavior	Mental retardation (infant)	Restlessness, irritability, anxiety
	Mental and physical sluggishness	Hyperkinesis
	Somnolence	Wakefulness
Cardiovascular function	Decreased cardiac output	Increased cardiac output
	Bradycardia	Tachycardia and palpitations
Gastrointestinal function	Constipation	Diarrhea
	Decreased appetite	Increased appetite
Respiratory function	Hypoventilation	Dyspnea
Muscle tone and reflexes	Decreased	Increased, with tremor and twitching
Temperature tolerance	Cold intolerance	Heat intolerance
Skin and hair	Decreased sweating	Increased sweating
	Coarse and dry skin and hair	Thin and silky skin and hair
Weight	Gain	Loss

Multinodular goiters produce the largest thyroid enlargements. When sufficiently enlarged, they may compress the esophagus and trachea, causing difficulty in swallowing, a choking sensation, and inspiratory stridor. Such lesions also may compress the superior vena cava, producing distention of the veins of the neck and upper extremities, edema of the eyelids and conjunctiva, and syncope with coughing.

Hypothyroidism

Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism develops prenatally and is present at birth. Acquired hypothyroidism develops later in life because of primary disease of the thyroid gland or secondary to disorders of hypothalamic or pituitary origin.

Congenital Hypothyroidism. Congenital hypothyroidism is a common cause of preventable mental retardation. It affects approximately 1 of 5000 infants. Hypothyroidism in the infant may result from a congenital lack of the thyroid gland or from abnormal biosynthesis of thyroid hormone or deficient TSH secretion.[25] With congenital lack of the thyroid gland, the infant usually appears normal and functions normally at birth because of hormones supplied in utero by the mother. Prolongation of physiologic jaundice, caused by delayed maturation of the hepatic system for conjugating bilirubin, may be the first sign (Fig. 32-7). There may be respiratory difficulties and a hoarse cry, due in part to the enlarged tongue; feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking during nursing; an enlarged abdomen; and an umbilical hernia. The manifestations of untreated congenital hypothyroidism are referred to as *cretinism*. However, the term does not apply to the normally developing infant in whom replacement thyroid hormone therapy was instituted shortly after birth.

Thyroid hormone is essential for normal growth and brain development, almost half of which occurs during the first 6 months of life. If untreated, congenital hypothyroidism causes mental retardation and impairs physical growth. Long-term studies show that closely

FIGURE 32-7. A 6-week-old female infant who presented with symptoms of jaundice, which was proven to be due to hypothyroidism. She was placed on supplemental thyroid hormonal therapy and appeared to be a normal healthy child at 1 year of age. (From Centers for Disease Control and Prevention. Public Images Library. ID# 5604. [Online] Available: http://phil.cdc/phil/details.asp.)

monitored T_4 supplementation begun in the first 6 weeks of life results in normal intelligence. Fortunately, developed countries throughout the world now routinely screen newborns for hypothyroidism, providing the means for early diagnosis and treatment. The screening test involves taking a drop of blood from the infant's heel and sending it to a central laboratory, where it is analyzed for T_4 or TSH.[25] Screening is done 24 to 48 hours after birth, usually in the hospital nursery.

Transient congenital hypothyroidism has been recognized more frequently since the introduction of neonatal screening. It is characterized by high TSH levels and low or normal thyroid hormone levels. The fetal and infant thyroids are sensitive to iodine excess. Iodine crosses the placenta and mammary glands and is readily absorbed by infant skin.[25] Transient hypothyroidism may be caused by maternal or infant exposure to substances such as povidone-iodine used as a disinfectant (i.e., vaginal douche or skin disinfectant in the nursery). Antithyroid drugs such as propylthiouracil and methimazole can cross the placenta and in large doses will impair fetal thyroid function.

Congenital hypothyroidism is treated by hormone replacement. Evidence indicates that it is important to normalize T_4 levels as rapidly as possible because a delay is accompanied by poorer psychomotor and mental development. Dosage levels are adjusted as the child grows. Infants with transient hypothyroidism usually can have the replacement therapy withdrawn at 6 to 12 months. When early and adequate treatment regimens are followed, the risk of mental retardation in infants detected by screening programs essentially is nonexistent.

Acquired Hypothyroidism. Hypothyroidism in older children and adults causes a general slowing down of metabolic processes and myxedema.[25] Myxedema implies the presence of a nonpitting mucous type of edema caused by an accumulation of a hydrophilic mucopolysaccharide substance in the connective tissues throughout the body. The hypothyroid state may be mild, with only a few signs and symptoms, or it may progress to a life-threatening condition called *myxedematous coma*. It can result from destruction or dysfunction of the thyroid gland (i.e., primary hypothyroidism), as a secondary disorder caused by impaired pituitary function, or as a tertiary disorder caused by a hypothalamic dysfunction.

Primary hypothyroidism is much more common than secondary (and tertiary) hypothyroidism. It may result from thyroidectomy (i.e., surgical removal) or ablation of the gland with radiation. Certain goitrogenic agents, such as lithium carbonate (used in the treatment of manic-depressive states), and the antithyroid drugs propylthiouracil and methimazole in continuous dosage can block hormone synthesis and produce hypothyroidism with goiter. Large amounts of iodine (i.e., ingestion of kelp tablets or iodide-containing cough syrups, or administration of iodide-containing radiographic contrast media or the cardiac drug amiodarone, which contains 75 mg of iodine per 200-mg tablet) also can block thyroid hormone production and cause goiter, particularly in persons with autoimmune thyroid disease. Iodine deficiency, which can cause goiter and hypothyroidism, is rare in the United States because of the widespread use of iodized salt and other iodide sources. However, iodine deficiency affects an estimated 100 million people worldwide.

The most common cause of hypothyroidism is *Hashimoto thyroiditis*, an autoimmune disorder in which the thyroid gland may be totally destroyed by an immunologic process.[28,29] It is the major cause of goiter and hypothyroidism in children and adults. Hashimoto thyroiditis is predominantly a disease of women, with a female-to-male ratio of 5:1. The course of the disease varies. At the onset, only a goiter may be present. In time, hypothyroidism usually becomes evident. Although the disorder usually causes hypothyroidism, a hyperthyroid state may develop midcourse in the disease. The transient hyperthyroid state is caused by leakage of preformed thyroid hormone from damaged cells of the gland. Subacute thyroiditis, which can occur in up to 10% of pregnancies postpartum (postpartum thyroiditis), also can result in hypothyroidism.

Hypothyroidism may affect almost all body functions (Table 32-1).[25,29,30] The manifestations of the disorder are related largely to two factors: the hypometabolic state resulting from thyroid hormone deficiency, and myxedematous involvement of body tissues. The hypometabolic state associated with hypothyroidism is characterized by a gradual onset of weakness and fatigue, a tendency to gain weight despite a loss of appetite, and cold intolerance (Fig. 32-8). As the condition progresses, the skin becomes dry and rough and the hair becomes coarse and brittle. Reduced conversion of carotene to vitamin A and increased blood levels of carotene may give the skin a yellowish color. The face becomes puffy with edematous eyelids, and there is thinning of the outer third of the eyebrows. Fluid may collect in almost any serous cavity and in the middle ear, giving rise to conductive deafness. Gastrointestinal motility is decreased, producing constipation, flatulence, and abdominal distention. Delayed relaxation of deep tendon reflexes and bradycardia are sometimes noted. Central nervous system involvement is manifested in mental dullness, lethargy, and impaired memory.

Although the myxedematous fluid is usually most obvious in the face, it can collect in the interstitial spaces of almost any body structure and is responsible for many of the manifestations of the severe hypothyroid state. The tongue is often enlarged, and the voice becomes hoarse and husky. Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain. Pericardial or pleural effusion may develop. Mucopolysaccharide deposits in the heart cause generalized cardiac dilation, bradycardia, and other signs of altered cardiac function.

Diagnosis of hypothyroidism is based on history, physical examination, and laboratory tests. A low serum T_4 and elevated TSH levels are characteristic of primary hypothyroidism. The tests for antithyroid antibodies should be done when Hashimoto thyroiditis is suspected (anti-TPO antibody titer is the preferred test).

Hypothyroidism is treated by replacement therapy with synthetic preparations of T_3 or T_4. Most people are treated

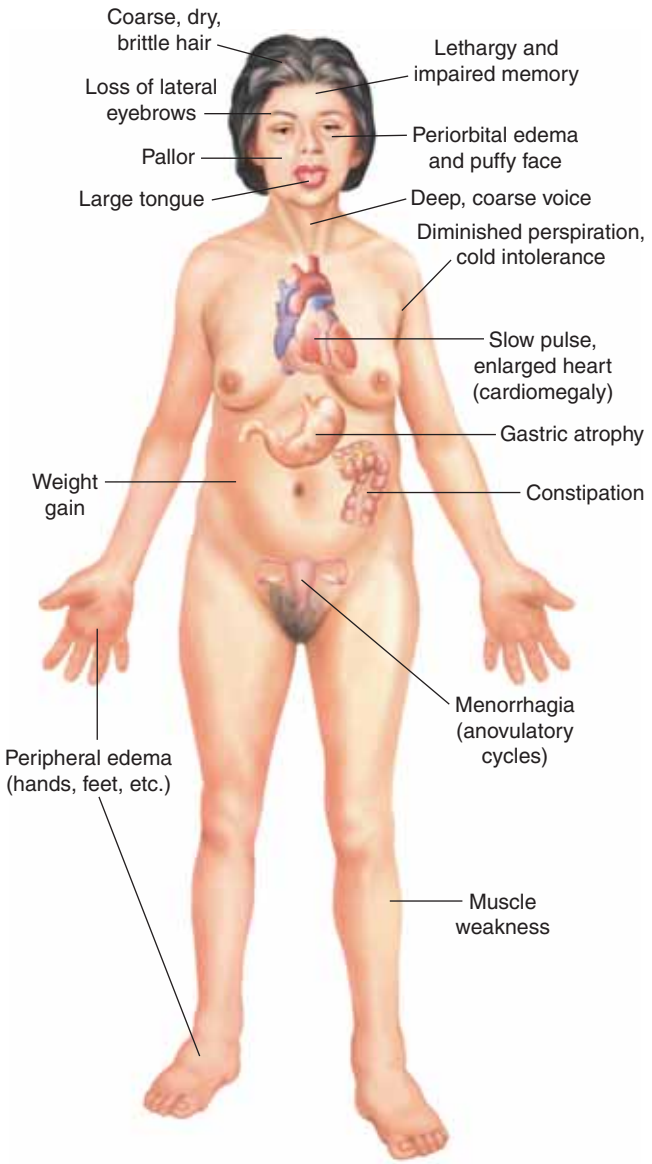


FIGURE 32-8. Clinical manifestations of hypothyroidism.

with T_4. Serum TSH levels are used to estimate the adequacy of T_4 replacement therapy. When the TSH level is normalized, the T_4 dosage is considered satisfactory (for primary hypothyroidism only). A "go low and go slow" approach should be considered in the treatment of elderly with hypothyroidism because of the risk of inducing acute coronary syndromes in susceptible individuals.

Myxedematous Coma. Myxedematous coma is a life-threatening, end-stage expression of hypothyroidism.[31] It is characterized by coma, hypothermia, cardiovascular collapse, hypoventilation, and severe metabolic disorders that include hyponatremia, hypoglycemia, and lactic acidosis. The pathophysiology of myxedema coma involves three major aspects: (1) carbon dioxide retention and hypoxemia, (2) fluid and electrolyte imbalance, and (3) hypothermia.[31] It occurs most often in elderly women who have chronic hypothyroidism from a spectrum of causes. The fact that it occurs more frequently in winter months suggests that cold exposure may be a precipitating factor. The severely hypothyroid person is unable to metabolize sedatives, analgesics, and anesthetic drugs, and buildup of these agents may precipitate coma.

Treatment includes aggressive management of precipitating factors; supportive therapy such as management of cardiorespiratory status, hyponatremia, and hypoglycemia; and thyroid replacement therapy. If hypothermia is present (a low-reading thermometer should be used), active rewarming of the body is contraindicated because it may induce vasodilation and vascular collapse. Prevention is preferable to treatment and entails special attention to high-risk populations, such as women with a history of Hashimoto thyroiditis. These persons should be informed about the signs and symptoms of severe hypothyroidism and the need for early medical treatment.

Hyperthyroidism

Hyperthyroidism is the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormone. In most instances, hyperthyroidism is due to hyperactivity of the thyroid gland.[25,32,33] The most common causes of hyperthyroidism are Graves disease, which is accompanied by ophthalmopathy (or dermopathy) and diffuse goiter. Other causes of hyperthyroidism are multinodular goiter, adenoma of the thyroid, and thyroiditis. Iodine-containing agents can induce hyperthyroidism as well as hypothyroidism. Thyroid crisis, or storm, is an acutely exaggerated manifestation of the thyrotoxic state.

Many of the manifestations of hyperthyroidism are related to the increase in oxygen consumption and use of metabolic fuels associated with the hypermetabolic state, as well as to the increase in sympathetic nervous system activity that occurs (Table 32-1).[25,32,33] The fact that many of the signs and symptoms of hyperthyroidism resemble those of excessive sympathetic nervous system activity suggests that thyroid hormone may heighten the sensitivity of the body to the catecholamines or that it may act as a pseudocatecholamine. With the hypermetabolic state, there are frequent complaints of nervousness, irritability, and fatigability (Fig. 32-9). Weight loss is common despite a large appetite. Other manifestations include tachycardia, palpitations, shortness of breath, excessive sweating, muscle cramps, and heat intolerance. The person appears restless and has a fine muscle tremor. Even in persons without exophthalmos (i.e., bulging of the eyeballs seen in ophthalmopathy), there is an abnormal retraction of the eyelids and infrequent blinking such that they appear to be staring. The hair and skin usually are thin and have a silky appearance. About 15% of elderly individuals with new-onset atrial fibrillation have thyrotoxicosis.[32]

The treatment of hyperthyroidism is directed toward reducing the level of thyroid hormone. This can be accomplished with eradication of the thyroid gland with radioactive iodine, through surgical removal of part or all of the gland, or with the use of drugs that decrease thyroid function and thereby the effect of thyroid hormone on the

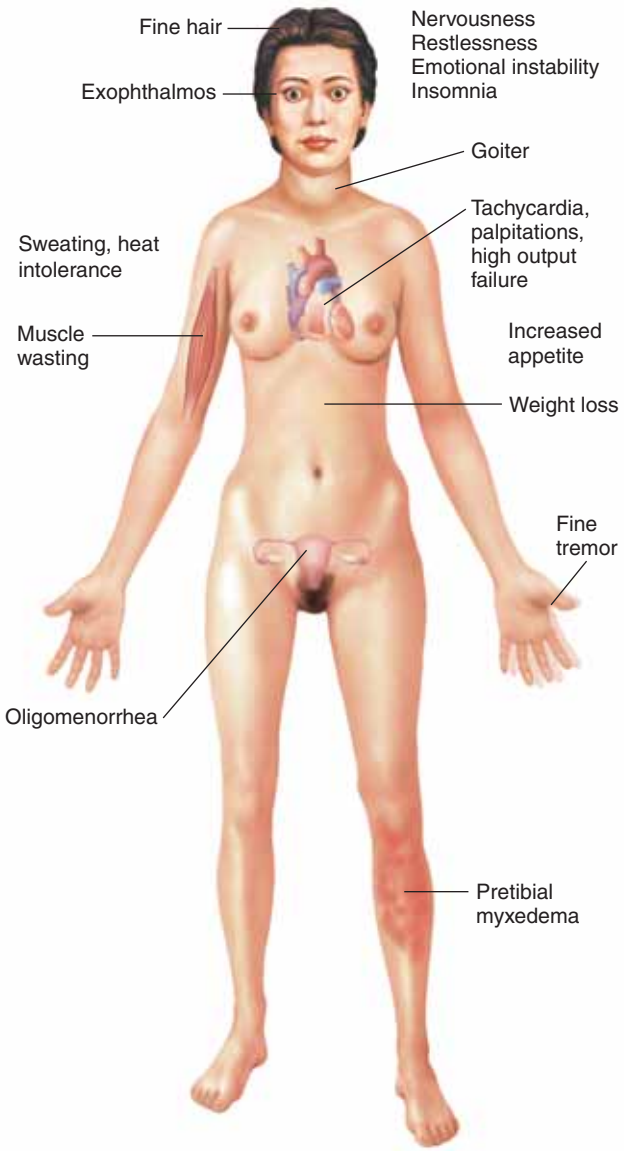


FIGURE 32-9. Clinical manifestations of hyperthyroidism.

peripheral tissues. Eradication of the thyroid with radioactive iodine is used more frequently than surgery. The β-adrenergic blocking drugs (e.g., propranolol, metoprolol, atenolol, nadolol) are administered to block the effects of the hyperthyroid state on sympathetic nervous system function. They are given in conjunction with antithyroid drugs (e.g., propylthiouracil and methimazole) that act by inhibiting the thyroid gland from using iodine in thyroid hormone synthesis and by blocking the conversion of T_4 to T_3 in the tissues (propylthiouracil only).

Graves Disease. Graves disease is a state of hyperthyroidism, goiter, ophthalmopathy, or, less commonly, dermopathy.[25,34,35] The onset usually is between the ages of 20 and 40 years, and women are five times more likely to develop the disease than men. Graves disease is an autoimmune disorder characterized by abnormal stimulation of the thyroid gland by thyroid-stimulating antibodies (TSH-receptor antibodies) that act through the normal TSH receptors. It may be associated with other autoimmune disorders such as myasthenia gravis and pernicious anemia. The disease is associated with human leukocyte antigen (HLA)-DR3 and HLA-B8, and a familial tendency is evident.

The ophthalmopathy, which occurs in up to one third of persons with Graves disease, is thought to result from a cytokine-mediated activation of fibroblasts in orbital tissue behind the eyeball.[25,36,37] Humoral autoimmunity also is important; an ophthalmic immunoglobulin may exacerbate lymphocytic infiltration of the extraocular muscles. The ophthalmopathy of Graves disease can cause severe eye problems, including abnormal positioning of the extraocular muscles resulting in diplopia; involvement of the optic nerve, with some visual loss; and corneal ulceration because the lids do not close over the protruding eyeball (due to the exophthalmos). The ophthalmopathy usually tends to stabilize after treatment of the hyperthyroidism. Since the ophthalmopathy can worsen acutely after radioiodine treatment, some physicians prescribe glucocorticoids for several weeks surrounding the radioiodine treatment if the person had signs of ophthalmopathy. Others do not use radioiodine therapy under these circumstances, but prefer antithyroid therapy with drugs (which may decrease the immune activation in the condition). Unfortunately, not all of the ocular changes are reversible with treatment. Ophthalmopathy also can be aggravated by smoking, which should be strongly discouraged.

Thyroid Storm. Thyroid storm, or crisis, is an extreme and life-threatening form of thyrotoxicosis, rarely seen today because of improved diagnosis and treatment methods.[25,38] When it does occur, it is seen most often in undiagnosed cases or in persons with hyperthyroidism who have not been adequately treated. It often is precipitated by stress such as an infection (usually respiratory), diabetic ketoacidosis, physical or emotional trauma, or manipulation of a hyperactive thyroid gland during thyroidectomy. Thyroid storm is manifested by a very high fever, extreme cardiovascular effects (i.e., tachycardia, congestive failure, and angina), and severe CNS effects (i.e., agitation, restlessness, and delirium). The mortality rate is high.

Thyroid storm requires rapid diagnosis and implementation of treatment. Peripheral cooling is initiated with cold packs and a cooling mattress. For cooling to be effective, the shivering response must be prevented. General supportive measures to replace fluids, glucose, and electrolytes are essential during the hypermetabolic state. A β-adrenergic blocking drug, such as propranolol, is used to block the undesirable effects of T_4 on cardiovascular function. Glucocorticoids are used to correct the relative adrenal insufficiency resulting from the stress imposed by the hyperthyroid state and to inhibit the peripheral conversion of T_4 to T_3. Propylthiouracil or methimazole may be given to block thyroid synthesis. Aspirin increases the level of free thyroid hormones by displacing the hormones from their protein carriers and should not be used during thyroid storm.

In summary, thyroid hormones play a role in the metabolic process of almost all body cells and are necessary for normal physical and mental growth in the infant and young child. Alterations in thyroid function can manifest as a hypothyroid or a hyperthyroid state. Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism leads to mental retardation and impaired physical growth unless treatment is initiated during the first months of life. Acquired hypothyroidism leads to a decrease in metabolic rate and an accumulation of a mucopolysaccharide substance in the intercellular spaces; this substance attracts water and causes a mucous type of edema called *myxedema*. Hyperthyroidism causes an increase in metabolic rate and alterations in body function similar to those produced by enhanced sympathetic nervous system activity. Graves disease is characterized by the triad of hyperthyroidism, goiter, and ophthalmopathy or dermopathy.

Disorders of Adrenal Cortical Function

Control of Adrenal Cortical Function

The adrenal glands are small, bilateral structures that weigh approximately 5 g each and lie retroperitoneally at the apex of each kidney (Fig. 32-10A). The medulla or inner portion of the gland (which constitutes approximately 10% of each adrenal) secretes epinephrine and norepinephrine and is part of the sympathetic nervous system. The cortex forms the bulk of the adrenal gland (approximately 90%) and is responsible for secreting three types of hormones: the glucocorticoids, the mineralocorticoids, and the adrenal androgens.[26,39] Because the sympathetic nervous system also secretes epinephrine and norepinephrine, adrenal medullary function is not essential for life, but adrenal cortical function is. The total loss of adrenal cortical function is fatal in 4 to 14 days if untreated. This section of the chapter describes the synthesis and function of the adrenal cortical hormones and the effects of adrenal cortical insufficiency and excess.

Adrenal Cortical Hormones

More than 30 hormones are produced by the adrenal cortex. Of these hormones, aldosterone is the principal mineralocorticoid, cortisol (hydrocortisone) is the major glucocorticoid, and androgens are the chief sex hormones. All of the adrenal cortical hormones have a similar structure in that all are steroids and are synthesized from acetate and cholesterol. Each of the steps involved in the synthesis of the various hormones requires a specific enzyme (see Fig. 32-10B). The secretion of the glucocorticoids and the adrenal androgens is controlled by ACTH secreted by the anterior pituitary gland.

Cortisol, aldosterone, and the adrenal androgens are secreted in an unbound state and bind to plasma proteins

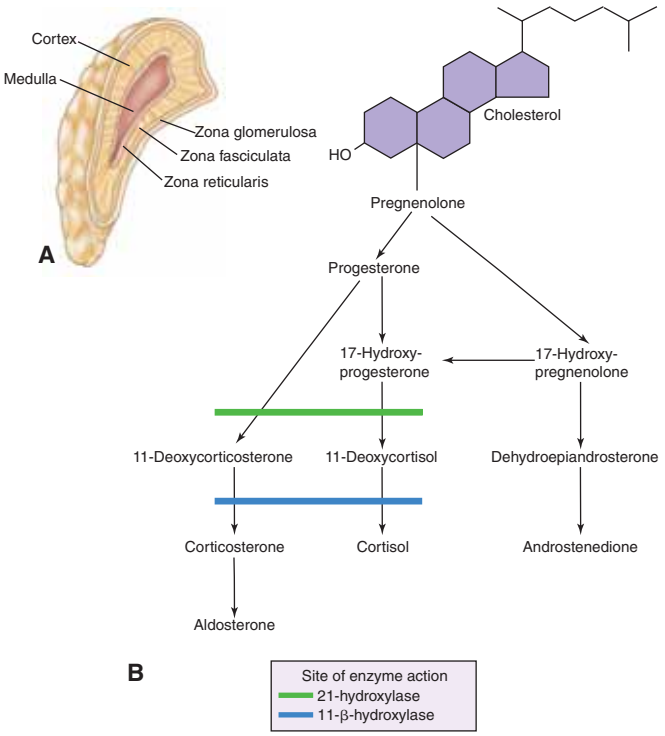


FIGURE 32-10. **(A)** The adrenal gland, showing the medulla and the three layers of the cortex. The outer layer of the cortex (zona glomerulosa) is primarily responsible for mineralocorticoid production, and the middle layer (zona fasciculata) and the inner layer (zona reticularis) produce the glucocorticoids and the adrenal androgens. **(B)** Predominant biosynthetic pathways of the adrenal cortex. Critical enzymes in the biosynthetic process include 11-β-hydroxylase and 21-hydroxylase. A deficiency in one of these enzymes blocks the synthesis of hormones dependent on that enzyme and routes the precursors into alternative pathways.

for transport in the circulatory system. Cortisol binds largely to corticosteroid-binding globulin and to a lesser extent to albumin. Aldosterone and androgens circulate mostly bound to albumin. It has been suggested that the pool of protein-bound hormones may extend the duration of their action by delaying metabolic clearance.

The main site for metabolism of the adrenal cortical hormones is the liver, where they undergo a number of metabolic conversions before being conjugated and made water soluble. They are then eliminated in either the urine or the bile.

Adrenal Androgens. The adrenal androgens are synthesized primarily by the zona reticularis and the zona fasciculata of the adrenal cortex (see Fig. 32-10A). These sex hormones probably exert little effect on normal sexual function. There is evidence, however, that the adrenal androgens (the most important of which is dehydroepiandrosterone [DHEA] and its sulfate conjugate [DHEAS]) contribute to the pubertal growth of body hair, particularly pubic and axillary hair in women. They also may play a role in the steroid hormone economy of the pregnant woman and the fetal–placental unit. DHEAS

Adrenal Cortical Hormones

- The adrenal cortex produces three types of steroid hormones: the mineralocorticoids (principally aldosterone), which function in sodium, potassium, and water balance; the glucocorticoids (principally cortisol), which aid in regulating the metabolic functions of the body and in controlling the inflammatory response, and are essential for survival in stress situations; and the adrenal sex hormones (principally androgens), which serve mainly as a source of androgens for women.
- The manifestations of primary adrenal cortical insufficiency are related mainly to mineralocorticoid deficiency (impaired ability to regulate salt and water elimination) and glucocorticoid deficiency (impaired ability to regulate blood glucose and control the effects of the immune and inflammatory responses).
- Adrenal cortical excess results in derangements in glucose metabolism, disorders of sodium and potassium regulation (increased sodium retention and potassium loss), impaired ability to respond to stress because of inhibition of inflammatory and immune responses, and signs of increased androgen levels such as hirsutism.

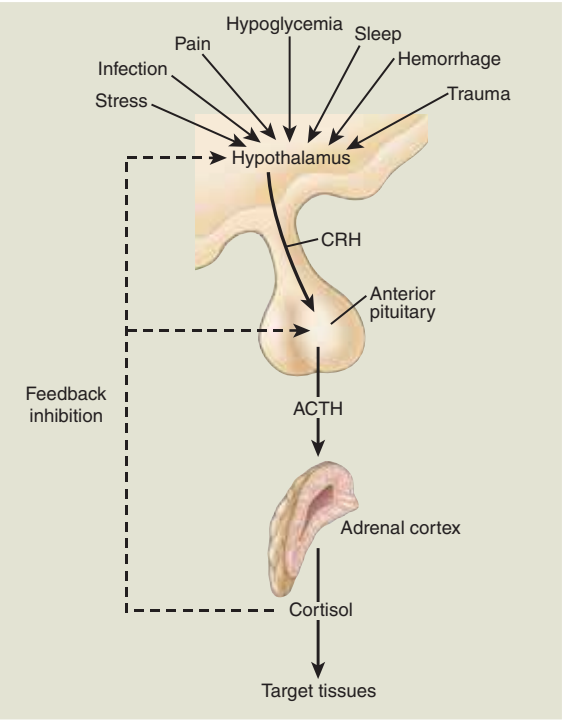


FIGURE 32-11. The hypothalamic-pituitary-adrenal (HPA) feedback system that regulates glucocorticoid (cortisol) levels. Cortisol release is regulated by adrenocorticotropic hormone (ACTH). Stress exerts its effects on cortisol release through the HPA system and corticotropin-releasing hormone (CRH), which controls the release of ACTH from the anterior pituitary gland. Increased cortisol levels incite a negative feedback inhibition of ACTH release.

is increasingly being used in the treatment of both Addison disease (to be discussed) and adults who have decreased levels of DHEAS. Because the testes produce these hormones, there is no rationale for using it in men. The levels of DHEAS decline to approximately one-sixth the levels of a 20-year-old by 60 years of age (the *adrenopause*). The value of routine replacement of DHEAS in the adrenopause is largely unproven, but replacement may improve general well-being and sexuality and have other important effects in women.

Mineralocorticoids. The mineralocorticoids play an essential role in regulating potassium and sodium levels and water balance. They are produced in the zona glomerulosa, the outer layer of cells of the adrenal cortex. Aldosterone secretion is regulated by the renin-angiotensin mechanism and by blood levels of potassium. Increased levels of aldosterone promote sodium retention by the distal tubules of the kidney while increasing urinary losses of potassium. The influence of aldosterone on fluid and electrolyte balance is discussed in Chapter 8.

Glucocorticoids. The glucocorticoid hormones, mainly cortisol, are synthesized in the zona fasciculata and the zona reticularis of the adrenal cortex. The blood levels of these hormones are regulated by negative feedback mechanisms of the hypothalamic-pituitary-adrenal (HPA) system (Fig. 32-11). Just as other pituitary hormones are controlled by releasing hormones from the hypothalamus, corticotropin-releasing hormone (CRH) is important in controlling the release of ACTH. Cortisol levels increase as ACTH levels rise and decrease as ACTH levels fall. There is considerable diurnal variation in ACTH levels, which reach their peak in the early morning (around 6 to 8 AM) and decline as the day progresses.[26] This appears to be due to rhythmic activity in the CNS, which causes bursts of CRH secretion and, in turn, ACTH secretion. This diurnal pattern is reversed in people who work during the night and sleep during the day. The rhythm also may be changed by physical and psychological stresses, endogenous depression, and liver disease or other conditions that affect cortisol metabolism. One of the earliest signs of Cushing syndrome, a disorder of glucocorticoid excess, is the loss of diurnal variation in CRH and ACTH secretion.[40,41]

The glucocorticoids perform a necessary function in response to stress and are essential for survival. When produced as part of the stress response, these hormones aid in regulating the metabolic functions of the body and in controlling the inflammatory response. The actions of cortisol are summarized in Table 32-2. Many of the

TABLE 32-2 Actions of Cortisol

Major Influence	Effect on Body
Glucose metabolism	Stimulates gluconeogenesis
	Decreases glucose use by the tissues
Protein metabolism	Increases breakdown of proteins
	Increases plasma protein levels
Fat metabolism	Increases mobilization of fatty acids
	Increases use of fatty acids
Anti-inflammatory action (pharmacologic levels)	Stabilizes lysosomal membranes of the inflammatory cells, preventing the release of inflammatory mediators
	Decreases capillary permeability to prevent inflammatory edema
	Depresses phagocytosis by white blood cells to reduce the release of inflammatory mediators
	Suppresses the immune response
	Causes atrophy of lymphoid tissue
	Decreases eosinophils
	Decreases antibody formation
	Decreases the development of cell-mediated immunity
	Reduces fever
	Inhibits fibroblast activity
Psychic effect	May contribute to emotional instability
Permissive effect	Facilitates the response of the tissues to humoral and neural influences, such as that of the catecholamines, during trauma and extreme stress

anti-inflammatory actions attributed to cortisol result from the administration of pharmacologic levels of the hormone.

By far the best-known metabolic effect of cortisol and other glucocorticoids is their ability to stimulate gluconeogenesis (glucose production) by the liver. In the process, body proteins are broken down and their amino acids are mobilized and transported to the liver, where they are used in the production of glucose. In much the same manner that cortisol promotes amino acid mobilization from muscle, it promotes mobilization of fatty acids from adipose tissue. This increased mobilization of fats by cortisol converts cell metabolism from the use of glucose for energy to the use of fatty acids. As glucose production by the liver rises and peripheral glucose use falls, a moderate resistance to insulin develops. In persons with diabetes and those who are diabetes prone, this has the effect of raising the blood glucose level.

Cortisol also influences multiple aspects of immunologic function and inflammatory responsiveness. Large quantities of cortisol are required for an effective anti-inflammatory action. This is achieved by the administration of pharmacologic rather than physiologic doses of cortisol. The increased cortisol blocks inflammation at an early stage by decreasing capillary permeability and stabilizing the lysosomal membranes so that inflammatory mediators are not released. Cortisol suppresses the immune response by reducing humoral and cell-mediated immunity. During the healing phase, cortisol suppresses fibroblast activity and thereby lessens scar formation. Cortisol also inhibits prostaglandin synthesis, which may account in large part for its anti-inflammatory actions.

The glucocorticoid hormones also appear to be involved directly or indirectly in emotional behavior. Receptors for these hormones have been identified in brain tissue, which suggests that they play a role in the regulation of behavior. Persons treated with adrenal cortical hormones have been known to display behavior ranging from mildly aberrant to psychotic.

Pharmacologic Suppression of Adrenal Function

A highly significant aspect of long-term therapy with pharmacologic preparations of the glucocorticoids is adrenal insufficiency upon withdrawal of the drugs. The deficiency results from suppression of the HPA system. Chronic suppression causes atrophy of the adrenal gland, and the abrupt withdrawal of drugs can cause acute adrenal insufficiency. Recovery to a state of normal adrenal function may be prolonged, requiring up to 12 months or more.

Tests of Adrenal Function

Several diagnostic tests can be used to evaluate adrenal cortical function and the HPA system.[17] Blood levels of cortisol, aldosterone, and ACTH can be measured using immunoassay methods. A 24-hour urine specimen measuring the excretion of various metabolic end products of the adrenal hormones provides information about alterations in the biosynthesis of the adrenal cortical hormones. The 24-hour urinary free cortisol, late-night (between 11 PM and midnight) serum or salivary cortisol levels, and the overnight 1-mg dexamethasone suppression test (see later) are excellent screening tests for Cushing syndrome.[39,40] Suppression and stimulation tests afford a means of assessing the state of the HPA feedback system. For example, a test dose of ACTH can be given to assess the response of the adrenal cortex to stimulation. Similarly, administration of dexamethasone, a

synthetic glucocorticoid drug, provides a means of measuring negative feedback suppression of ACTH. The insulin-induced hypoglycemic test, which is the gold standard for assessing the function of the HPA axis, induces a central nervous system stress response, increases CRH release, and in this way increases ACTH and cortisol secretion. It therefore measures the integrity of the axis and its ability to respond to stress.

Disorders of the Adrenal Cortex

Disorders of the adrenal cortex include disorders of adrenocortical hormone insufficiency or excess. They can be congenital or acquired and can occur as the result of primary disorders of the adrenal cortex or secondary to altered ACTH secretion.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), or the adrenogenital syndrome, describes a congenital disorder caused by an autosomal recessive trait in which a deficiency exists in any of the enzymes necessary for the synthesis of cortisol[3,42] (see Fig. 32-10). A common characteristic of all types of CAH is a defect in the synthesis of cortisol that results in increased levels of ACTH and adrenal hyperplasia. The increased levels of ACTH overstimulate the pathways for production of adrenal androgens. Mineralocorticoids may be produced in excessive or insufficient amounts, depending on the precise enzyme deficiency. Infants of both sexes are affected. Boys seldom are diagnosed at birth unless they have enlarged genitalia or lose salt and manifest adrenal crisis. In female infants, an increase in androgens is responsible for creating the virilization syndrome of ambiguous genitalia with an enlarged clitoris, fused labia, and urogenital sinus (Fig. 32-12). In male and female children, other secondary sex characteristics are normal, and fertility is unaffected if appropriate therapy is instituted.

FIGURE 32-12. A female infant with congenital adrenal hyperplasia demonstrating virilization of the genitalia with hypertrophy of the clitoris and partial fusion of labioscrotal folds. (From Merino M., Quezado M., Rubin E., et al. [2008]. The endocrine system. In Rubin E., Strayer D. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 960]. Philadelphia: Lippincott Williams & Wilkins.)

The two most common enzyme deficiencies are 21-hydroxylase (accounting for >90% of cases) and 11-β-hydroxylase deficiency. The clinical manifestations of both deficiencies are largely determined by the functional properties of the steroid intermediates and the completeness of the block in the cortisol pathway.

A spectrum of 21-hydroxylase deficiency states exists, ranging from simple virilizing CAH to a complete salt-losing enzyme deficiency.[42,43] Simple virilizing CAH impairs the synthesis of cortisol, and steroid synthesis is shunted to androgen production. Persons with these deficiencies usually produce sufficient aldosterone or aldosterone intermediates to prevent signs and symptoms of mineralocorticoid deficiency. The salt-losing form is accompanied by deficient production of aldosterone and its intermediates. This results in fluid and electrolyte disorders after the fifth day of life (including hyponatremia, hyperkalemia, vomiting, dehydration, and shock).

The 11-β-hydroxylase deficiency is rare and manifests a spectrum of severity. Affected persons have excessive androgen production and impaired conversion of 11-deoxycorticosterone to corticosterone. The overproduction of 11-deoxycorticosterone, which has mineralocorticoid activity, is responsible for the hypertension that accompanies this deficiency. Diagnosis of CAH depends on the precise biochemical evaluation of metabolites in the cortisol pathway and on clinical signs and symptoms. Genetic testing is also invaluable; however, correlation between the phenotype and genotype is not always straightforward.[42]

Medical treatment of CAH includes oral or parenteral glucocorticoid replacement. Fludrocortisone acetate, a mineralocorticoid, also may be given to children who are salt losers. Depending on the degree of virilization, reconstructive surgery during the first 2 years of life is indicated to reduce the size of the clitoris, separate the labia, and exteriorize the vagina. Advances in surgical techniques have led to earlier use of single-stage surgery—between 2 and 6 months of life in girls with 21-hydroxylase deficiency, a time when the tissues are maximally pliable and psychological trauma to the child is minimized.[21] Surgery has provided excellent results and does not usually impair sexual function.

Adrenal Cortical Insufficiency

There are two forms of adrenal insufficiency: primary and secondary[44–46] (Table 32-3). Primary adrenal insufficiency, or Addison disease, is caused by destruction of the adrenal gland. Secondary adrenal insufficiency results from a disorder of the HPA system.

Primary Adrenal Cortical Insufficiency. In 1855, Thomas Addison, an English physician, provided the first detailed clinical description of primary adrenal insufficiency, now called *Addison disease*.[46] The use of this term is reserved for primary adrenal insufficiency in which adrenal cortical hormones are deficient and ACTH levels are elevated because of lack of feedback inhibition.

Addison disease is a relatively rare disorder in which all the layers of the adrenal cortex are destroyed. Autoimmune destruction is the most common cause of

TABLE 32-3 Clinical Findings of Adrenal Insufficiency

Finding	Primary	Secondary/Tertiary
Anorexia and weight loss	Yes (100%)	Yes (100%)
Fatigue and weakness	Yes (100%)	Yes (100%)
Gastrointestinal symptoms, nausea, diarrhea	Yes (50%)	Yes (50%)
Myalgia, arthralgia, abdominal pain	Yes (10%)	Yes (10%)
Orthostatic hypotension	Yes	Yes
Hyponatremia	Yes (85%–90%)	Yes (60%)
Hyperkalemia	Yes (60%–65%)	No
Hyperpigmentation	Yes (>90%)	No
Secondary deficiencies of testosterone, growth hormone, thyroxine, antidiuretic hormone	No	Yes
Associated autoimmune conditions	Yes	No

Addison disease in the United States. Before 1950, tuberculosis was the major cause of Addison disease in the United States and Canada, and it continues to be a major cause of the disease in countries where the infection is more prevalent. Rare causes include metastatic carcinoma, fungal infection (particularly histoplasmosis), cytomegalovirus infection, amyloid disease, and hemochromatosis. Bilateral adrenal hemorrhage may occur in persons taking anticoagulants, during open heart surgery, and during birth or major trauma. Adrenal insufficiency can be caused by acquired immunodeficiency syndrome (AIDS), in which the adrenal gland is destroyed by a variety of opportunistic infectious agents. Drugs (e.g., ketoconazole) that inhibit synthesis or cause excessive breakdown of glucocorticoids can also result in adrenal insufficiency.

Addison disease, like type 1 diabetes mellitus, is a chronic metabolic disorder that requires lifetime hormone replacement therapy. The adrenal cortex has a large reserve capacity, and the manifestations of adrenal insufficiency usually do not become apparent until approximately 90% of the gland has been destroyed.[4] These manifestations are related primarily to mineralocorticoid deficiency, glucocorticoid deficiency, and hyperpigmentation resulting from elevated ACTH levels. Although lack of the adrenal androgens (i.e., DHEAS) exerts few effects in men because the testes produce these hormones, women have sparse axillary and pubic hair.

Mineralocorticoid deficiency causes increased urinary losses of sodium, chloride, and water, along with decreased excretion of potassium (Fig. 32-13). The result is hyponatremia, loss of extracellular fluid, decreased cardiac output, and hyperkalemia. There may be an abnormal appetite for salt. Orthostatic hypotension is common. Dehydration, weakness, and fatigue are common early symptoms. If loss of sodium and water is extreme, cardiovascular collapse and shock ensue. Because of a lack of glucocorticoids, the person with Addison disease has poor tolerance to stress. This deficiency causes hypoglycemia, lethargy, weakness, fever, and gastrointestinal symptoms such as anorexia, nausea, vomiting, and weight loss.

Hyperpigmentation results from elevated levels of ACTH. The skin looks bronzed or suntanned in exposed

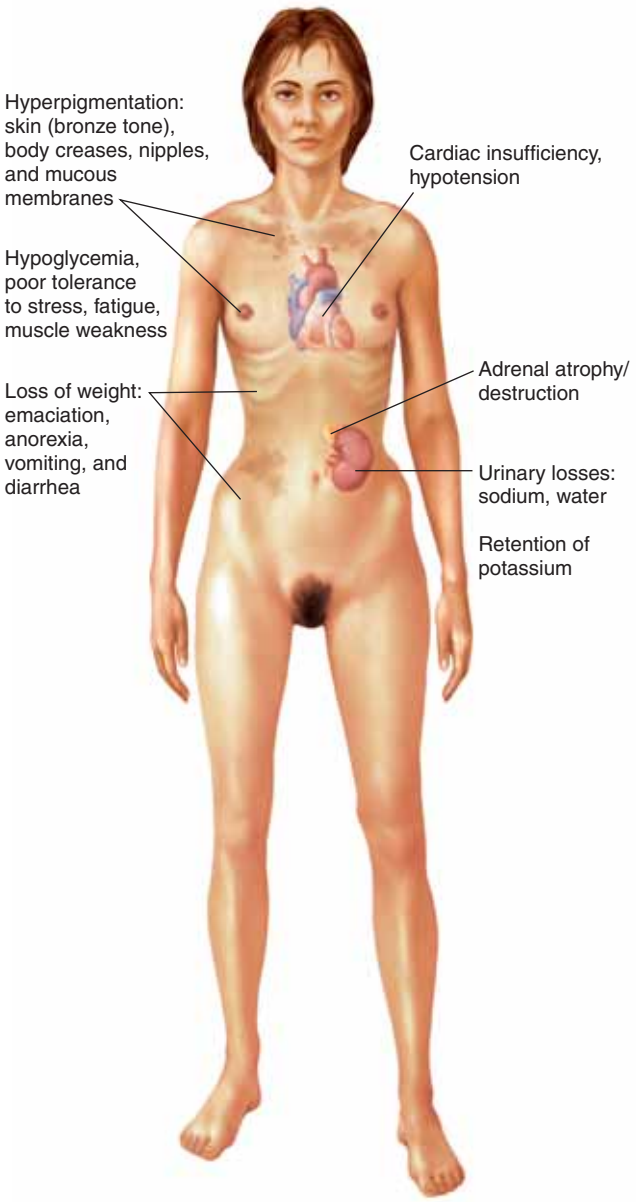


FIGURE 32-13. Clinical manifestations of primary (Addison disease) and secondary adrenal insufficiency.

and unexposed areas, and the normal creases and pressure points tend to become especially dark. The gums and oral mucous membranes may become bluish-black. The amino acid sequence of ACTH is strikingly similar to that of melanocyte-stimulating hormone; hyperpigmentation occurs in greater than 90% of persons with Addison disease and is helpful in distinguishing the primary and secondary forms of adrenal insufficiency.

The daily regulation of the chronic phase of Addison disease usually is accomplished with oral replacement therapy, with higher doses being given during periods of stress. The pharmacologic agent that is used should have both glucocorticoid and mineralocorticoid activity. Mineralocorticoids are needed only in primary adrenal insufficiency. Hydrocortisone usually is the drug of choice. In mild cases, hydrocortisone alone may be adequate. Fludrocortisone (a mineralocorticoid) is used for persons who do not obtain a sufficient salt-retaining effect from hydrocortisone. DHEAS replacement also may be helpful in the female patient.[44] Because persons with the disorder are likely to have episodes of hyponatremia and hypoglycemia, they need to have a regular schedule for meals and exercise. Persons with Addison disease also have limited ability to respond to infections, trauma, and other stresses. Such situations require immediate medical attention and treatment. All persons with Addison disease should be advised to wear a medical alert bracelet or medal.

Secondary Adrenal Cortical Insufficiency. Secondary adrenal insufficiency can occur as the result of hypopituitarism or because the pituitary gland has been surgically removed. Tertiary adrenal insufficiency results from a hypothalamic defect. However, a far more common cause than either of these is the rapid withdrawal of glucocorticoids that have been administered therapeutically. These drugs suppress the HPA system, with resulting adrenal cortical atrophy and loss of cortisol production. This suppression continues long after drug therapy has been discontinued and can be critical during periods of stress or when surgery is performed.

Acute Adrenal Crisis. Acute adrenal crisis is a life-threatening situation.[44,45] If Addison disease is the underlying problem, exposure to even a minor illness or stress can precipitate nausea, vomiting, muscular weakness, hypotension, dehydration, and vascular collapse. The onset of adrenal crisis may be sudden, or it may progress over a period of several days. The symptoms may occur suddenly in children with salt-losing forms of CAH. Massive bilateral adrenal hemorrhage causes an acute fulminating form of adrenal insufficiency. Hemorrhage can be caused by meningococcal septicemia (i.e., Waterhouse-Friderichsen syndrome), adrenal trauma, anticoagulant therapy, adrenal vein thrombosis, or adrenal metastases.

Acute adrenal insufficiency is treated with extracellular fluid restoration and glucocorticosteroid replacement therapy. Extracellular fluid volume should be restored with several liters of 0.9% saline and 5% dextrose. Oral hydrocortisone replacement therapy can be resumed once the saline infusion has been discontinued and the person is taking food and fluids by mouth. Mineralocorticoid therapy is not required when large amounts of hydrocortisone are being given, but as the dose is reduced it usually is necessary to add fludrocortisone. Glucocorticoid and mineralocorticoid replacement therapy is monitored using heart rate and blood pressure measurements, serum electrolyte values, and titration of plasma renin activity into the upper-normal range. Since bacterial infection frequently precipitates acute adrenal crisis, broad-spectrum antibiotic therapy may be needed.

Glucocorticoid Hormone Excess

The term *Cushing syndrome* refers to the manifestations of hypercortisolism from any cause.[39,40,47] Three important forms of Cushing syndrome result from excess glucocorticoid production by the body. One is a pituitary form, which results from excessive production of ACTH by a tumor of the pituitary gland. This form of the disease was the one originally described by Cushing; therefore, it is called *Cushing disease*. The second form is the adrenal form, caused by a benign or malignant adrenal tumor. The third form is ectopic Cushing syndrome, caused by a nonpituitary ACTH-secreting tumor. Certain extrapituitary malignant tumors such as small cell carcinoma of the lung may secrete ACTH or, rarely, CRH and produce Cushing syndrome. Cushing syndrome also can result from long-term therapy with one of the potent pharmacologic preparations of glucocorticoids; this form is called *iatrogenic Cushing syndrome*.

The major manifestations of Cushing syndrome represent an exaggeration of the many actions of cortisol. Altered fat metabolism causes a peculiar deposition of fat characterized by a protruding abdomen; subclavicular fat pads or "buffalo hump" on the back; and a round, plethoric "moon face" (Fig. 32-14). There is muscle weakness, and the extremities are thin because of protein breakdown and muscle wasting. In advanced cases, the skin over the forearms and legs becomes thin, having the appearance of parchment. Purple striae, or stretch marks, from stretching of the catabolically weakened skin and subcutaneous tissues are distributed over the breast, thighs, and abdomen. Osteoporosis may develop because of destruction of bone proteins and alterations in calcium metabolism, resulting in back pain, compression fractures of the vertebrae, and rib fractures. As calcium is mobilized from bone, renal calculi may develop.

Derangements in glucose metabolism are found in approximately 75% of patients, with clinically overt diabetes mellitus occurring in approximately 20%. The glucocorticoids possess mineralocorticoid properties; this causes hypokalemia as a result of excessive potassium excretion and hypertension resulting from sodium retention. Inflammatory and immune responses are inhibited, resulting in increased susceptibility to infection. Cortisol increases gastric acid secretion, which may provoke gastric ulceration and bleeding. An accompanying increase in androgen levels causes hirsutism, mild acne, and menstrual irregularities in women. Excess levels of the

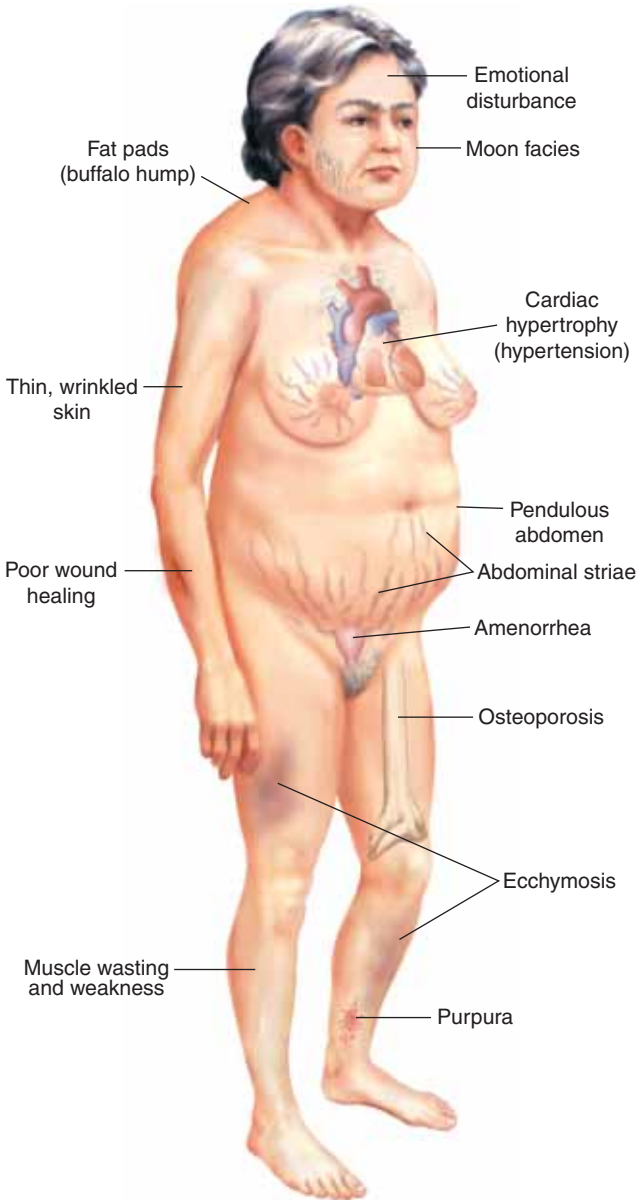


FIGURE 32-14. Clinical features of Cushing syndrome.

glucocorticoids may give rise to extreme emotional lability, ranging from mild euphoria and absence of normal fatigue to grossly psychotic behavior.

Diagnosis of Cushing syndrome depends on the finding of cortisol hypersecretion.[39,40,47,48] The determination of 24-hour excretion of cortisol in urine provides a reliable and practical index of cortisol secretions. One of the prominent features of Cushing syndrome is loss of the diurnal pattern of cortisol secretion. This is why late-night (between 11 PM and midnight) serum or salivary cortisol levels can be inappropriately elevated, aiding in the diagnosis of Cushing syndrome. The overnight dexamethasone suppression test is also used as a screening tool for Cushing syndrome.

Other tests include measurement of the plasma levels of ACTH.[39,40,47,48] ACTH levels should be normal or elevated in ACTH-dependent Cushing syndrome (Cushing disease and ectopic ACTH), and low in non–ACTH-dependent Cushing syndrome (adrenal tumors). Various suppression or stimulation tests of the HPA system are performed to delineate the cause further. MRI or CT scans afford a means for locating adrenal or pituitary tumors.

Untreated, Cushing syndrome produces serious morbidity and even death. The choice of surgery, irradiation, or pharmacologic treatment is determined largely by the cause of the hypercortisolism. The goal of treatment for Cushing syndrome is to remove or correct the source of hypercortisolism without causing permanent pituitary or adrenal damage.[40,48] Transsphenoidal removal of a pituitary adenoma or a hemihypophysectomy is the preferred method of treatment for Cushing disease. This allows removal of only the tumor rather than the entire pituitary gland. After successful removal, the person must receive cortisol replacement therapy for 6 to 12 months or until adrenal function returns. Pituitary radiation therapy may also be used, but the full effects of treatment may not be realized for 3 to 12 months. Unilateral or bilateral adrenalectomy may be done in the case of adrenal adenoma. When possible, ectopic ACTH-producing tumors are removed. Pharmacologic agents that block steroid synthesis (i.e., mitotane, ketoconazole, and metyrapone) may be used to treat persons with ectopic tumors or adrenal carcinomas that cannot be resected.[39,40] Many of these patients also require *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) pneumonia prophylaxis because of the profound immunosuppression caused by the excessive glucocorticoid levels.

Incidental Adrenal Mass

An incidentaloma is a mass lesion found unexpectedly in an adrenal gland by an imaging procedure (done for other reasons), most commonly CT (but also MRI and ultrasonography).[49] They have been increasingly recognized since the early 1980s.[50] The prevalence of adrenal incidentalomas at autopsy is approximately 10 to 100 per 1000. In CT series, 0.4% to 0.6% are the usual figures published. Incidentalomas also can occur in other organs (e.g., pituitary, thyroid). The two most important questions are (1) is the mass malignant, and (2) is the mass hormonally active (i.e., is it functioning)?

Primary adrenal carcinoma is quite rare, but other cancers, particularly lung cancers, commonly metastasize to the adrenal gland (other cancers include breast, stomach, pancreas, colon, kidney, melanomas, and lymphomas). The size and imaging characteristics of the mass may help determine whether the tumor is benign or malignant. The risk of cancer is high in adrenal masses larger than 6 cm. Many experts recommend surgical removal of masses larger than 4 cm, particularly in younger patients.[49,50] Appropriate screening to exclude a hormonally active lesion includes tests to rule out pheochromocytoma, Cushing syndrome, and Conn syndrome (mineralocorticoid excess).

In summary, the adrenal cortex produces three types of hormones: mineralocorticoids, glucocorticoids, and adrenal androgens. The mineralocorticoids, along with the renin-angiotensin mechanism, aid in controlling body levels of sodium and potassium. The glucocorticoids have anti-inflammatory actions and aid in regulating glucose, protein, and fat metabolism during periods of stress. These hormones are under the control of the HPA system. The adrenal androgens exert little effect on daily control of body function, but they probably contribute to the development of body hair in women.

Disorders of the adrenal cortex include those that produce adrenocortical hormone insufficiency or excess. Congenital adrenal hyperplasia describes a genetic defect in the cortisol pathway resulting from a deficiency of one of the enzymes needed for its synthesis. Depending on the enzyme involved, the disorder causes virilization of female infants and, in some instances, fluid and electrolyte disturbances because of impaired mineralocorticoid synthesis. Chronic adrenal insufficiency can be caused by destruction of the adrenal gland (Addison disease) or by dysfunction of the HPA system. Adrenal insufficiency requires replacement therapy with adrenal cortical hormones. Acute adrenal insufficiency is a life-threatening situation. Cushing syndrome refers to the manifestations of excessive glucocorticoid levels. This syndrome may be a result of pharmacologic doses of glucocorticoids, a pituitary or adrenal tumor, or an ectopic tumor that produces ACTH. The clinical manifestations of Cushing syndrome reflect the very high level of glucocorticoid that is present.

An incidentaloma is a mass lesion found unexpectedly in an adrenal gland (and other glands) by an imaging procedure done for other reasons. Incidentalomas are being recognized with increasing frequency, emphasizing the need for correct diagnosis and treatment.

REVIEW EXERCISES

1. A 59-year-old man was referred to a neurologist for evaluation of headaches. Subsequent MRI studies revealed a large suprasellar mass (2.5 × 2.4 cm), consistent with a pituitary tumor. His history is positive for hypertension and, on direct inquiry, he believes that his hands are slightly larger than previously, with increased sweating. Family history is negative, as are weight change, polyuria and polydipsia, visual disturbance, and erectile dysfunction. Subsequent laboratory findings reveal a baseline serum GH of 8.7 ng/mL (normal is 0 to 5 ng/mL), which is unsuppressed after oral glucose tolerance testing; glucose intolerance; and increased IGF-1 on two occasions (1044 and 1145 μg/L [upper limit of normal is 480 μg/L]). Other indices of pituitary function are within the normal range.

A. What diagnosis would this man's clinical features, MRI, and laboratory findings suggest?
B. What is the reason for asking the patient about weight change, polyuria and polydipsia, visual disturbance, and erectile dysfunction?
C. How would you explain his impaired glucose tolerance?
D. What are the possible local effects of a large pituitary tumor?

2. A 76-year-old woman presents with weight gain, subjective memory loss, dry skin, and cold intolerance. On examination she is found to have a multinodular goiter. Laboratory findings reveal a low serum T_4 and elevated TSH.

A. What diagnosis would this woman's history, physical, and laboratory tests suggest?
B. Explain the possible relationship between the diagnosis and her weight gain, dry skin, cold intolerance, and subjective memory loss.
C. What type of treatment would be indicated?

3. A 45-year-old woman presents with a history of progressive weakness, fatigue, weight loss, nausea, and increased skin pigmentation (especially of creases, pressure areas, and nipples). Her blood pressure is 120/78 mm Hg when supine and 105/52 mm Hg when standing. Laboratory findings reveal a serum sodium of 120 mEq/L (normal is 135 to 145 mEq/L), potassium level of 5.9 mEq/L (normal is 3.5 to 5 mEq/L), and low plasma cortisol and high ACTH levels.

A. What diagnosis would this woman's clinical features and laboratory findings suggest?
B. Would her diagnosis be classified as a primary or secondary endocrine disorder?
C. What is the significance of her darkened skin?
D. What type of treatment would be indicated?

REFERENCES

1. Webb P., Baxter J.D. (2007). Introduction to endocrinology. In Gardner D.G., Shoback D. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 23–34). New York: Lange Medical Books/McGraw-Hill.
2. Aron D.C., Findling J.W., Tyrrell J.B. (2007). Hypothalamus and pituitary gland. In Gardner D.G., Shoback D. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 101–156). New York: Lange Medical Books/McGraw-Hill.
3. Merino M., Quezado M., Rubin E., et al. (2008). The endocrine system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 933–955, 958–973). Philadelphia: Lippincott Williams & Wilkins.
4. Maitra A. (2010). The endocrine system. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1097–1129, 1148–1163). Philadelphia: Saunders Elsevier.

5. Pickett C.A. (2003). Diagnosis and management of pituitary tumors: Recent advances. *Primary Care* 30, 765–789.
6. Serhal D., Weil R.J., Hambrahian A.H. (2008). Evaluation and management of pituitary incidentalomas. *Cleveland Clinic Journal of Medicine* 75(11), 793–801.
7. Toogood A.A., Stewart P.M. (2008). Hypopituitarism: Clinical features, diagnosis, and management. *Endocrinology and Metabolism Clinics of North America* 37, 235–261.
8. Molitch M.E., Clemmons D.R., Malzowski S., et al. (2006). Evaluation and treatment of adult growth hormone deficiency: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 91, 1621–1634.
9. Styne D. (2007). Growth. In Gardner D.G., Shoback D. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 171–208). New York: Lange Medical Books/McGraw-Hill.
10. Cohen P., Rogol A.D., Deal C.L., et al. (2008). Consensus statement of the diagnosis and treatment of children with idiopathic short stature: A summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society of Paediatric Endocrinology Workshop. *Journal of Clinical Endocrinology and Metabol*ism 93(11), 4210–4217.
11. Nwosu B., Lee M.M. (2008). Evaluation of short and tall stature in children. *American Family Physician* 78(5), 597–604.
12. Lee M.M. (2006). Idiopathic short stature. *New England Journal of Medicine* 354(24), 2575–2582.
13. Guitosi-Kug R.A., Cuttler L. (2005). Idiopathic short stature. *Endocrine and Metabolism Clinics of North America* 34, 565–580.
14. Laron Z. (2004). Laron syndrome (primary GH resistance): The personal experience 1958–2003. *Journal of Clinical Endocrinology and Metabolism* 89, 1031–1044.
15. Molitch M.E., Clemmons D.R., Malozowski G.R., et al. (2006). Clinical practice guideline evaluation and treatment of adult growth hormone deficiency: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 91(5), 1621–1634.
16. Nass R., Park J., Thorner M.O. (2007). Growth hormone supplementation in the elderly. *Endocrinology and Metabolism Clinics of North America* 36, 233–245.
17. Sesmilo G., Biller B.M., Levadot J., et al. (2000). Effects of GH administration on inflammatory and other cardiovascular risk markers in men with GH deficiency. *Annals of Internal Medicine* 133, 111–122.
18. Root A. (2001). The tall, rapidly growing infant, child, and adolescent. *Current Opinion in Endocrinology and Diabetes* 8, 6–16.
19. Cohen P., Shin M. (2007). *Hyperpituitarism, tall stature, and overgrowth syndromes* In Kliegman R.M., Behrman R.E., Jenson J.B., Stanton B.F. *Nelson Textbook of Pediatrics* (18th ed., pp. 2303–2307). Philadelphia: Saunders Elsevier.
20. Melmed S. (2006). Acromegaly. *New England Journal of Medicine* 355, 2558–2573.
21. Ben-Shlomo A., Melmed S. (2008). Acromegaly. *Endocrinology and Metabolism Clinics of North America* 37, 101–122.
22. Lebrethon M.C., Bourguignon J.P. (2001). Central and peripheral isosexual precocious puberty. *Current Opinion in Endocrinology and Diabetes* 8, 17–22.
23. Styne D. (2007). Puberty. In Gardner D.G., Shoback D. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 611–640). New York: Lange Medical Books/McGraw-Hill.
24. Kaplowitz P.B., Oberfield S.E. (1999). Reexamination of the age limit for defining when puberty is precocious in girls in the United States: Implications for evaluation and treatment. *Pediatrics* 104, 936–941.
25. Cooper D.S., Greenspan F.S., Ladenson P.W. (2007). The thyroid gland. In Gardner D.G., Shoback D. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 209–280). New York: Lange Medical Books/McGraw-Hill.
26. Guyton A.C., Hall J.E. (2006). *Medical physiology* (11th ed., pp. 931–960). Philadelphia: Elsevier Saunders.
27. Dayan C.M. (2001). Interpretation of thyroid function tests. *Lancet* 357, 619–624.
28. Pearce E.N., Farwell A.P., Braverman L.E. (2003). Thyroiditis. *New England Journal of Medicine* 348, 2646–2655.
29. Devdhar M., Ousman Y.H., Burman K.D. (2007). Hypothyroidism. *Endocrinology and Metabolism Clinics of North America* 36, 595–615.
30. Fatourechl V. (2009). Subclinical hypothyroidism: An update for primary care physicians. *Mayo Clinic Proceedings* 84(1), 65–71.
31. Wartofsky L. (2006). Myxedema coma. *Endocrinology and Metabolism Clinics of North America* 35, 687–698.
32. Cooper D.S. (2003). Hyperthyroidism. *Lancet* 362, 459–468.
33. Nayak B., Hodak S.P. (2007). Hyperthyroidism. *Endocrinology and Metabolism Clinics of North America* 36, 617–656.
34. McKenna T.J. (2001). Graves' disease. *Lancet* 357, 1793–1796.
35. Brent G.A. (2008). Graves' disease. *New England Journal of Medicine* 358 (24), 2594–2605.
36. Bartalena L., Tanda M.L. (2009). Graves' ophthalmopathy. *New England Journal of Medicine* 360(10), 994–1001.
37. Bahn R. (2003). Pathophysiology of Graves' ophthalmopathy: The cycle of disease. *Journal of Clinical Endocrinology and Metabolism* 88, 1939–1946.
38. Nayak B., Burman K. (2006). Thyrotoxicosis and thyroid storm. Hyperthyroidism. *Endocrinology and Metabolism Clinics of North America* 35, 663–686.
39. Aron D.C., Findling J.W., Tyrrell J.B., et al. (2007). Glucocorticoids and adrenal androgens. In Gardner D.G., Shoback D. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 346–395). New York: Lange Medical Books/McGraw-Hill.
40. Newell-Price J., Bertagna X., Grossman A.B., et al. (2006). Cushing's syndrome. *Lancet* 367, 1605–1617.
41. Pivonello R., Cristina M., DeMartino C.M., DeLeo M., et al. (2008). Cushing's syndrome. *Endocrinology and Metabolism Clinics of North America* 37, 135–149.
42. Speiser P.W., White P.C. (2003). Congenital adrenal hyperplasia. *New England Journal of Medicine* 349, 776–788.
43. Boos C.J., Rumsby G., Matfin G. (2002). Multiple tumors associated with late onset congenital hyperplasia due to aberrant splicing of adrenal 21-hydroxylase gene. *Endocrine Practice* 8, 470–473.
44. Arlt W., Allolio B. (2003). Adrenal insufficiency. *Lancet* 361, 1881–1893.
45. Bouillon R. (2006). Acute adrenal insufficiency. *Endocrinology and Metabolism Clinics of North America* 35, 767–775.
46. Bornstein S.R. (2009). Predisposing factors for adrenal insufficiency. *New England Journal of Medicine* 360(22), 2328–2339.
47. Raff H., Findling J.W. (2003). A physiological approach to the diagnosis of Cushing's syndrome. *Annals of Internal Medicine* 138, 980–991.
48. Nieman L.K., Ilias I. (2005). Evaluation and treatment of Cushing's syndrome. *American Journal of Medicine* 118, 1340–1346.
49. Gopan T., Remer E., Hamrahian A.H. (2006). Evaluating and managing adrenal incidentalomas. *Cleveland Clinic Journal of Medicine* 73, 561–568.
50. Grumbach M.M., Biller B.M.K., Braunstein G.D., et al. (2003). Management of the clinically inapparent adrenal mass ("incidentaloma"). *Annals of Internal Medicine* 138, 424–429.

Hormonal Control of Nutrient Metabolism and Storage
Nutrient Metabolism and Storage
Glucose Metabolism and Storage
Fat Metabolism and Storage
Protein Metabolism and Storage
Glucose-Regulating Hormones
Insulin
Glucagon
Amylin, Somatostatin, and Gut-Derived Hormones
Counterregulatory Hormones
Diabetes Mellitus
Classification and Etiology
Categories of Risk for Diabetes
Type 1 Diabetes Mellitus
Type 2 Diabetes Mellitus and the Metabolic Syndrome
Other Specific Types of Diabetes
Gestational Diabetes
Clinical Manifestations of Diabetes
Diagnostic Tests
Blood Tests
Urine Tests
Diabetes Management
Dietary Management
Exercise
Oral and Injectable Antidiabetic Agents
Insulin
Pancreas or Islet Cell Transplantation
Management of Diabetes in Children
Acute Complications
Diabetic Ketoacidosis
Hyperosmolar Hyperglycemic State
Hypoglycemia
The Somogyi Effect and Dawn Phenomenon
Chronic Complications
Theories of Pathogenesis
Neuropathies
Nephropathies
Retinopathies
Macrovascular Complications
Diabetic Foot Ulcers
Infections

Chapter 33

Diabetes Mellitus and the Metabolic Syndrome

Diabetes mellitus is an abnormality in blood glucose regulation and nutrient storage related to an absolute deficiency of insulin or resistance to the actions of insulin. In the United States alone, diabetes mellitus affects 23.6 million people or approximately 7.8% of the population.[1] Type 1 diabetes, which is caused by an absolute deficiency of insulin, accounts for 1 million of these people with the remainder having type 2 diabetes. In addition, another 57 million people have been categorized as having "prediabetes." Two million of these people are adolescents (1 in 6 overweight adolescents) aged 12 to 19 years. Globally, the prevalence of prediabetes and type 2 diabetes is increasing at an alarming rate.

Hormonal Control of Nutrient Metabolism and Storage

Nutrient intake and storage in the form of adipose tissue, along with the action of insulin and other hormones, play an important role in the development of insulin resistance, the metabolic syndrome, and type 2 diabetes. This section provides a brief overview of nutrient (glucose, fat, protein) metabolism and storage and the hormones, including insulin, that are involved in the process. Overweight and obesity, as well as adipose tissue and its function in energy storage and as an endocrine organ, are discussed in Chapter 10.

Nutrient Metabolism and Storage

The body uses glucose, fatty acids, and other substrates as fuel to satisfy its energy needs. Although the respiratory and circulatory systems combine efforts to furnish the body with the oxygen needed for metabolic purposes, it is the liver, in concert with insulin and other hormones, that controls the storage and mobilization of the body's fuel supply.

Glucose Metabolism and Storage

Glucose, a six-carbon molecule, is an efficient fuel that, when metabolized in the presence of oxygen, breaks down to form carbon dioxide and water. Although many tissues and organ systems are able to use other forms of fuel, such as fatty acids and ketones, the brain and nervous system rely almost exclusively on glucose as a fuel source. Because the brain can neither synthesize nor store more than a few minutes' supply of glucose, normal cerebral function requires a continuous supply from the circulation. Severe and prolonged hypoglycemia can cause brain death, and even moderate hypoglycemia can result in substantial brain dysfunction.

Body tissues obtain glucose from the blood. In individuals without diabetes, fasting blood glucose levels are tightly regulated between 80 and 90 mg/dL (4.4 and 5.0 mmol/L). After a meal, blood glucose levels rise, and insulin is secreted in response to this rise in glucose. Approximately two thirds of the glucose that is ingested with a meal is removed from the blood and stored in the liver as glycogen. Between meals, the liver releases glucose as a means of maintaining the blood glucose within its normal range.

Glucose that is not needed for energy is removed from the blood and stored as glycogen or converted to fat. When tissues such as those in the liver and skeletal muscle become saturated with glycogen, the additional glucose is converted into fatty acids by the liver and then stored as triglycerides in the fat cells of adipose tissue. When blood glucose levels fall below normal, as they do between meals, glycogen is broken down by a process called *glycogenolysis,* and glucose is released. Although skeletal muscle has glycogen stores, it lacks the enzyme glucose-6-phosphatase that allows glucose to be broken down sufficiently to pass through the cell membrane and enter the bloodstream, limiting its usefulness to the muscle cell.

In addition to mobilizing its glycogen stores, the liver synthesizes glucose from amino acids, glycerol, and lactic acid in a process called *gluconeogenesis*. This glucose may be released directly into the circulation or stored as glycogen.

Fat Metabolism and Storage

Fat is the most efficient form of fuel storage, providing 9 kcal/g of stored energy, compared with the 4 kcal/g provided by carbohydrates and proteins. About 40% of the calories in the normal American diet are obtained from fats, which is about equal to the amount obtained from carbohydrates.[2] Therefore, the use of fats by the body for energy is as important as the use of carbohydrates. In addition, many of the carbohydrates consumed in the diet are converted to triglycerides for storage in adipose tissue.

A triglyceride contains three fatty acids linked by a glycerol molecule. The mobilization of fatty acids for use as an energy source is facilitated by the action of enzymes (lipases) that break triglycerides into their glycerol and fatty acid components. The glycerol molecule can enter the glycolytic pathway and be used along with glucose to produce energy, or it can be used to produce glucose. The fatty acids are transported to tissues where they are used for energy. Almost all body cells, with the exception of the brain, nervous tissue, and red blood cells, can use fatty acids interchangeably with glucose for energy. Although many cells use fatty acids as a fuel source, fatty acids cannot be converted to the glucose needed by the brain for energy.

A large share of the initial degradation of fatty acids occurs in the liver, especially when excessive amounts of fatty acids are being used for energy. The liver uses only a small amount of the fatty acids for its own energy needs; it converts the rest into ketones and releases them into the blood. In situations that favor fat breakdown, such as diabetes mellitus and fasting, large amounts of ketones are released into the bloodstream. Because ketones are organic acids, they cause ketoacidosis when they are present in excessive amounts.

Protein Metabolism and Storage

Proteins are essential for the formation of all body structures, including genes, enzymes, contractile structures in muscle, matrix of bone, and hemoglobin of red blood cells.[2] Amino acids are the building blocks of proteins. Unlike glucose and fatty acids, there is only a limited facility for the storage of excess amino acids in the body. Most of the stored amino acids are contained in body proteins. Amino acids in excess of those needed for protein synthesis are converted to fatty acids, ketones, or glucose and then stored or used as metabolic fuel. Because fatty acids cannot be converted to glucose, the body must break down proteins and use the amino acids as a major substrate for gluconeogenesis during periods when metabolic needs exceed food intake.

Glucose-Regulating Hormones

The hormonal control of blood glucose resides largely within the endocrine pancreas. The pancreas is made up of two major tissue types: the acini and the islets of Langerhans (Fig. 33-1). The acini secrete digestive juices into

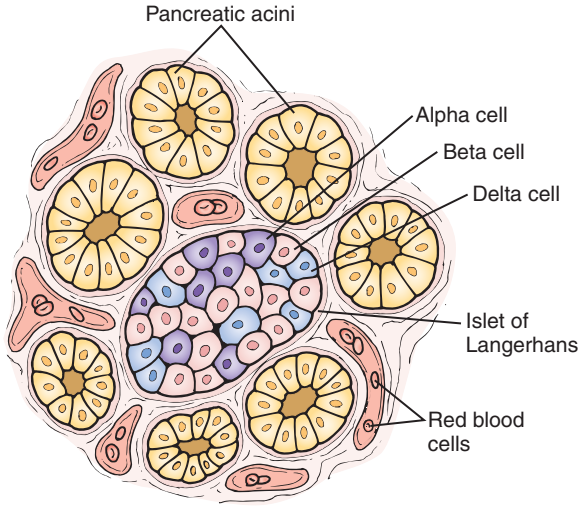


FIGURE 33-1. Islet of Langerhans in the pancreas.

the duodenum, whereas the islets of Langerhans, which account for only about 1% to 2% of the volume of the pancreas, secrete hormones into the blood. Each islet is composed of beta cells that secrete insulin and amylin, alpha cells that secrete glucagon, and delta cells that secrete somatostatin. In addition, at least one other cell type, the PP cell, is present in small numbers in the islets and secretes a hormone of uncertain function called *pancreatic polypeptide*.[2,3] Blood glucose regulation is also influenced by several gut-derived hormones that increase insulin release after nutrient intake and by counterregulatory hormones that help to maintain blood glucose levels during periods of limited glucose intake or excessive glucose use.

Insulin

Although several hormones are known to increase blood glucose levels, insulin is the only hormone known to have a direct effect in lowering blood glucose levels. The actions of insulin are threefold: (1) it promotes glucose uptake by target cells and provides for glucose storage as glycogen, (2) it prevents fat and glycogen breakdown, and (3) it inhibits gluconeogenesis and increases protein synthesis (Table 33-1).[2,3] Insulin acts to promote fat storage by increasing the transport of glucose into fat cells (Fig. 33-2). It also facilitates triglyceride synthesis from glucose in

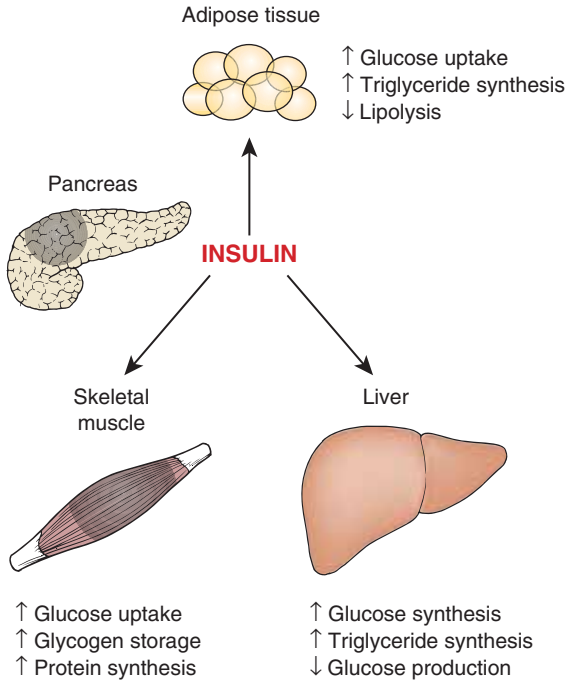


FIGURE 33-2. Effects of insulin on glucose transport and storage.

TABLE 33-1 Actions of Insulin and Glucagon on Glucose, Fat, and Protein Metabolism

	Insulin	Glucagon
Glucose		
Glucose transport	Increases glucose transport into skeletal muscle and adipose tissue	
Glycogen synthesis	Increases glycogen synthesis	Promotes glycogen breakdown
Gluconeogenesis	Decreases gluconeogenesis	Increases gluconeogenesis
Fats		
Fatty acid and triglyceride synthesis	Promotes fatty acid and triglyceride synthesis by the liver	
Fat storage in adipose tissue	Increases the transport of fatty acids into adipose cells	
	Increases conversion of fatty acids to triglycerides by increasing the availability of a-glycerol phosphate through increased transport of glucose in adipose cells	
	Maintains fat storage by inhibiting breakdown of stored triglycerides by adipose cell lipase	Activates adipose cell lipase, making increased amounts of fatty acids available to the body for use as energy
Proteins		
Amino acid transport	Increases active transport of amino acids into cells	Increases amino acid uptake by liver cells and their conversion to glucose by gluconeogenesis
Protein synthesis	Increases protein synthesis by increasing transcription of messenger RNA and accelerating protein synthesis by ribosomal RNA	
Protein breakdown	Decreases protein breakdown by enhancing the use of glucose and fatty acids as fuel	

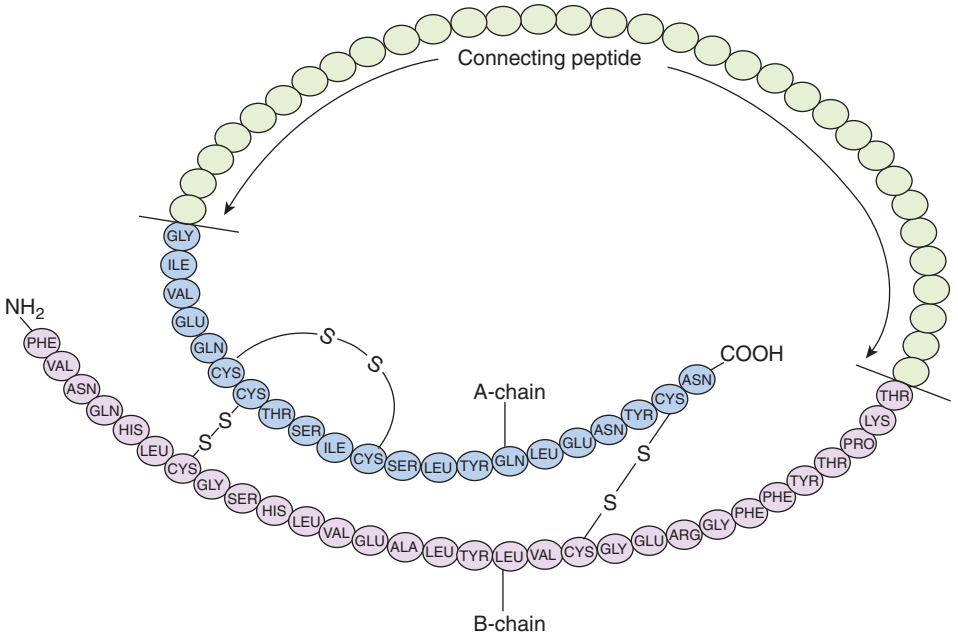


FIGURE 33-3. Structure of proinsulin. With removal of the connecting peptide (C peptide), proinsulin is converted to insulin.

fat cells and inhibits the intracellular breakdown of stored triglycerides. Insulin also inhibits protein breakdown and increases protein synthesis by increasing the active transport of amino acids into body cells, and it inhibits gluconeogenesis, or the building of glucose from new sources, mainly amino acids. When sufficient glucose and insulin are present, protein breakdown is minimal because the body is able to use glucose and fatty acids as a fuel source. In children and adolescents, insulin is needed for normal growth and development.

The active form of insulin is composed of two polypeptide chains—an A chain and a B chain (Fig. 33-3). Active insulin is formed in the beta cells from a larger molecule called *proinsulin*. In converting proinsulin to insulin, enzymes in the beta cell cleave proinsulin at specific sites to form two separate substances: active insulin and a biologically inactive C-peptide (connecting peptide) chain that joined the A and B chains before they were separated. Active insulin and the inactive C-peptide chain are packaged into secretory granules and released simultaneously from the beta cell. The C-peptide chains can be measured clinically, and this measurement can be used to study beta cell function (i.e., persons with type 2 diabetes with very little or no remaining beta cell function will have very low or nonexistent levels of C-peptide in their blood, and thus will likely need insulin replacement for treatment).

The release of insulin from the pancreatic beta cells is regulated by blood glucose levels, increasing as blood glucose levels rise and decreasing when blood glucose levels decline. Secretion of insulin occurs in a pulsatile fashion. After exposure to glucose, which is a nutrient secretagogue, a first-phase release of stored preformed insulin occurs, followed by a second-phase release of newly synthesized insulin (Fig. 33-4). Diabetes may result from dysregulation or deficiency in any of the steps involved in this process (e.g., impaired sensing of blood glucose levels and defects in insulin release or synthesis). Serum insulin levels begin to rise within minutes after a meal, reach a peak in approximately 3 to 5 minutes, and then return to baseline levels within 2 to 3 hours.

Insulin secreted by the beta cells enters the portal circulation and travels directly to the liver, where approximately 50% is used or degraded. Insulin, which is rapidly bound to peripheral tissues or destroyed by the liver or kidneys, has a half-life of approximately 15 minutes once it is released into the general circulation. To initiate its effects on target tissues, insulin binds to a membrane receptor. The insulin receptor consists of four subunits—two larger α subunits that extends outside the cell membrane and are involved in insulin binding, and two smaller β subunits that are predominantly located inside the cell membrane and contain a kinase enzyme that becomes activated during insulin binding (Fig. 33-5). Activation of the kinase enzyme

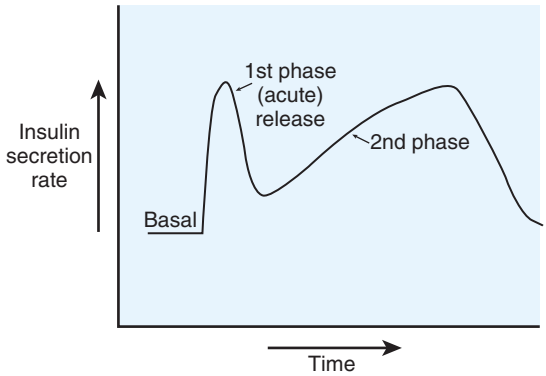


FIGURE 33-4. Biphasic insulin response to a constant glucose stimulus. The peak of the first phase in humans is 3 to 5 minutes; the second phase begins at 2 minutes and continues to increase slowly for at least 60 minutes or until the stimulus stops. (From Ward W.K., Beard J.C., Halter J.B., et al. [1984]. Pathology of insulin secretion in non-insulin-dependent diabetes mellitus. *Diabetes Care* 7, 491–502. Used with permission.)

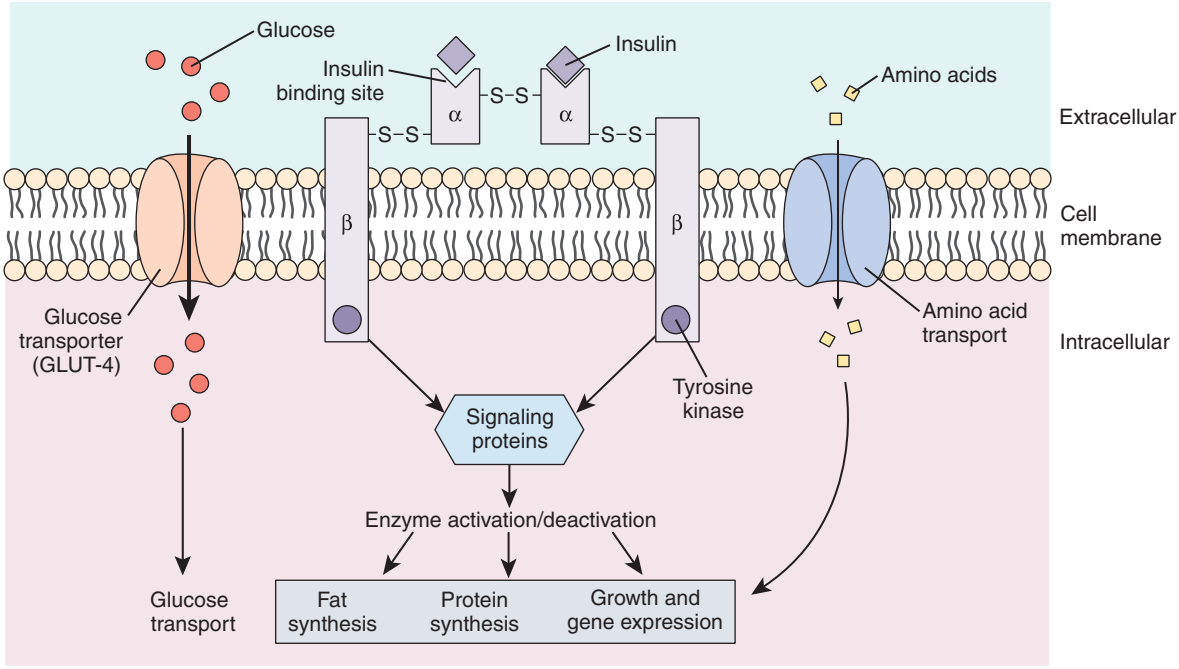


FIGURE 33-5. Insulin receptor. Insulin binds to the α subunits of the insulin receptor, which increases glucose and amino acid transport and causes autophosphorylation of the β subunit of the receptor, which induces tyrosine kinase activity. Tyrosine phosphorylation, in turn, activates a cascade of intracellular signaling proteins that mediate the effects of insulin on glucose, fat, and protein metabolism.

results in autophosphorylation of the β subunit itself. Phosphorylation of the β subunit in turn activates some enzymes and inactivates others, thereby directing the desired intracellular effect of insulin on glucose, fat, and protein metabolism.

Because cell membranes are impermeable to glucose, they require a special carrier, called a *glucose transporter*, to move glucose from the blood into the cell. These transporters move glucose across the cell membrane at a faster rate than would occur by diffusion alone. Considerable research has revealed a family of glucose transporters termed *GLUT-1*, *GLUT-2*, and so forth.[4] GLUT-4 is the insulin-dependent glucose transporter for skeletal muscle and adipose tissue (Fig. 33-6). It is sequestered inside the membrane of these cells and thus is unable to function as a glucose transporter until a signal from insulin causes it to move from its inactive site into the cell membrane, where it facilitates glucose entry. GLUT-2 is the major transporter of glucose into beta cells and liver cells. It has a low affinity for glucose and acts as a transporter only when plasma glucose levels are relatively high, such as after a meal. GLUT-1 is present in all tissues. It does not require the actions of insulin and is important in transport of glucose into cells of the nervous system.

Glucagon

Glucagon, a polypeptide molecule produced by the alpha cells of the islets of Langerhans, maintains blood glucose between meals and during periods of fasting.[2,3] Like insulin, glucagon travels through the portal vein to the liver, where it exerts its main action. Unlike insulin, glucagon produces an increase in blood glucose (Table 33-1). The most dramatic effect of glucagon is its ability to initiate glycogenolys: or the breakdown of glycogen as a means of raising blood glucose, usually within a matter of minutes. Glucagon also increases the transport of amino acids into the liver and stimulates their conversion into glucose through the process of gluconeogenesis. Because liver glycogen stores are limited, gluconeogenesis is important in maintaining blood glucose levels over time. Other actions of glucagon occur only when the

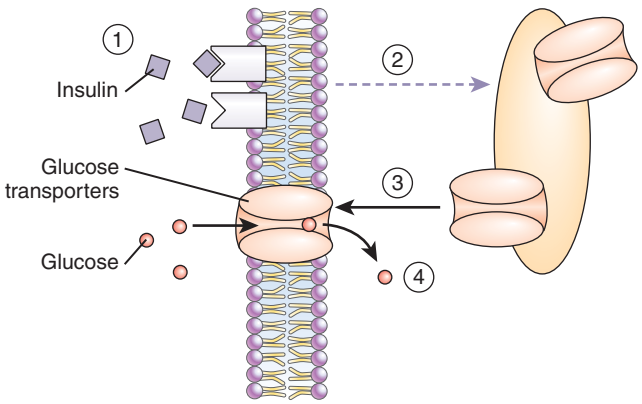


FIGURE 33-6. Insulin-dependent glucose transporter (GLUT-4). (*1*) Binding of insulin to insulin receptor on the surface of the cell membrane, (*2*) generation of intracellular signal, (*3*) insertion of GLUT-4 receptor from its inactive site into the cell membrane, and (*4*) transport of glucose across the cell membrane.

hormone is present in high concentrations, usually well above those normally present in the blood. At high concentrations, glucagon activates adipose cell lipase, making fatty acids available for use as energy.[2]

As with insulin, glucagon secretion is regulated by blood glucose. A decrease in blood glucose concentration produces an immediate increase in glucagon secretion, and an increase produces a decrease in glucagon secretion. High concentrations of amino acids, as occur after a protein meal, also can stimulate glucagon secretion. In this way, glucagon increases the conversion of amino acids to glucose as a means of maintaining the body's glucose levels. Glucagon levels also increase during strenuous exercise as a means of preventing a decrease in blood glucose.

Amylin, Somatostatin, and Gut-Derived Hormones

Islet amyloid polypeptide, or *amylin,* was originally identified as a major constituent of pancreatic amyloid deposits in persons with type 2 diabetes and subsequently shown to be a polypeptide that is cosecreted with insulin from the beta cells in the pancreas.[3,5] Plasma levels of amylin increase in response to nutritional stimuli to produce inhibition of gastric emptying and glucagon secretion. As with insulin, the active form of amylin is derived from a larger proamylin precursor. Although the active form of amylin is soluble and acts as a hormone, there has been renewed interest in the less soluble and insoluble forms, which may cause degeneration of the beta cells and contribute to the pathogenesis of overt diabetes.[5]

Somatostatin is a polypeptide hormone containing only 14 amino acids that has an extremely short half-life.[2,3] Somatostatin secreted by the delta cells acts locally in the islets of Langerhans to inhibit the release of insulin and glucagon. It also decreases gastrointestinal activity after ingestion of food. Almost all factors related to ingestion of food stimulate somatostatin secretion. By decreasing gastrointestinal activity, somatostatin is thought to extend the time during which food is absorbed into the blood, and by inhibiting insulin and glucagon, it is thought to extend the use of absorbed nutrients by the tissues.[2]

Several *gut-derived hormones* have been identified as having what is termed an *incretin effect,* meaning that they increase insulin release after an oral nutrient load[2,3,6] (see Chapter 28). This suggests that gut-derived factors can stimulate insulin secretion after a predominantly carbohydrate meal. The two hormones that account for about 90% of the incretin effect are glucagon-like peptide-1, which is released from L cells in the distal small bowel, and glucose-dependent insulinotropic polypeptide, which is released by K cells in the upper gut (mainly the jejunum).

Counterregulatory Hormones

Other hormones that can affect blood glucose include the catecholamines, growth hormone, and the glucocorticoids. These hormones, along with glucagon, are sometimes called *counterregulatory hormones* because they counteract the storage functions of insulin in regulating blood glucose levels during periods of fasting, exercise, and other situations that either limit glucose intake or deplete glucose stores.

Epinephrine. Epinephrine, a catecholamine, helps to maintain blood glucose levels during periods of stress. Epinephrine has the potent effect of causing glycogenolysis in the liver, thus causing large quantities of glucose to be released into the blood. It also inhibits insulin release from the beta cells and thereby decreases the movement of glucose into muscle cells, while at the same time increasing the breakdown of muscle glycogen stores. Although the glucose that is released from muscle glycogen cannot be released into the blood, the mobilization of these stores for muscle use conserves blood glucose for use by other tissues such as the brain and the nervous system. Epinephrine also has a direct lipolytic effect on adipose cells, thereby increasing the mobilization of fatty acids for use as an energy source. The blood glucose–elevating effect of epinephrine is an important homeostatic mechanism during periods of hypoglycemia.

Growth Hormone. Growth hormone has many metabolic effects. It increases protein synthesis in all cells of the body, mobilizes fatty acids from adipose tissue, and antagonizes the effects of insulin. Growth hormone decreases cellular uptake and use of glucose, thereby increasing the level of blood glucose. The increased blood glucose level stimulates further insulin secretion by the beta cells. The secretion of growth hormone normally is inhibited by insulin and increased levels of blood glucose. During periods of fasting, when both blood glucose levels and insulin secretion fall, growth hormone levels increase. Exercise, such as running and cycling, and various stresses, including anesthesia, fever, and trauma, also increase growth hormone levels.

Chronic hypersecretion of growth hormone, as occurs in acromegaly (see Chapter 32), can lead to glucose intolerance and the development of diabetes mellitus. In people who already have diabetes, moderate elevations in growth hormone levels that occur during periods of stress and periods of growth in children can produce the entire spectrum of metabolic abnormalities associated with poor regulation, despite optimized insulin treatment.

Glucocorticoid Hormones. The glucocorticoid hormones, which are synthesized in the adrenal cortex along with other corticosteroid hormones, are critical to survival during periods of fasting and starvation. They stimulate gluconeogenesis by the liver, sometimes producing a 6- to 10-fold increase in hepatic glucose production. These hormones also moderately decrease tissue use of glucose.

There are several steroid hormones with glucocorticoid activity; the most important of these is cortisol, which accounts for approximately 95% of all glucocorticoid activity (see Chapter 32). Almost any type of stress, whether physical or emotional, causes an immediate increase in adrenocorticotropic hormone (ACTH) secretion by the anterior pituitary gland, followed within

minutes by greatly increased secretion of cortisol by the adrenal gland. Hypoglycemia is a potent stimulus for cortisol secretion. In predisposed persons, the prolonged elevation of glucocorticoid hormones can lead to hyperglycemia and the development of diabetes mellitus. In people with diabetes, even transient increases in cortisol can complicate control.

In summary, the body uses glucose, fatty acids, and other substrates as fuel to satisfy its energy needs. Body tissues, including the brain, which depends exclusively on glucose for its energy, obtain glucose from the blood. The liver stores excess glucose as glycogen and it uses gluconeogenesis to convert amino acids, lactate, and glycerol into glucose during fasting or when glucose intake does not keep pace with demand. Blood glucose levels reflect the difference between the amount of glucose released into the circulation by the liver and the amount of glucose removed from the blood by body tissues. Fats, which serve as an efficient source of fuel for the body, are stored in adipose tissue as triglycerides, which consist of three fatty acids linked to a glycerol molecule. In situations that favor fat breakdown, such as fasting or diabetes mellitus, the triglycerides in adipose tissue are broken down and the fatty acids are used as fuel or transported to the liver, where they are converted to ketones. Proteins, which are made up of amino acids, are essential for the formation of all body structures. Unlike glucose and fatty acids, there is only a limited facility for storage of excess amino acids in the body. Because fatty acids cannot be converted to glucose, the body must break down proteins and use the amino acids for gluconeogenesis.

Energy metabolism is controlled by a number of hormones, including insulin, glucagon, epinephrine, growth hormone, and the glucocorticoids. Of these hormones, only insulin has the effect of lowering the blood glucose level. Insulin's blood glucose–lowering action results from its ability to increase the transport of glucose into body cells and decrease hepatic production and release of glucose into the bloodstream. Insulin also has the effect of decreasing lipolysis and the use of fats as a fuel source. Other hormones—glucagon, epinephrine, growth hormone, and the glucocorticoids—maintain or increase blood glucose concentrations and are referred to as *counterregulatory hormones.* Glucagon and epinephrine promote glycogenolysis. Glucagon and the glucocorticoids increase gluconeogenesis. Growth hormone decreases the peripheral use of glucose. Epinephrine and glucagon also increase the use of fat for energy by increasing the release of fatty acids from adipose cells.

Diabetes Mellitus

The term *diabetes* is derived from a Greek word meaning "going through," and *mellitus* from the Latin word for "honey" or "sweet." Reports of the disorder can be traced back to the first century AD, when Aretaeus the Cappadocian described the disorder as a chronic affliction characterized by intense thirst and voluminous, honey-sweet urine: "the melting down of flesh into urine." It was the discovery of insulin by Banting and Best in 1922 that transformed the once-fatal disease into a manageable chronic health problem.[7]

Diabetes is a disorder of carbohydrate, protein, and fat metabolism resulting from a lack of insulin availability or a reduction in the biologic effects of insulin. It can represent an absolute insulin deficiency, impaired release of insulin by the pancreatic beta cells, inadequate or defective insulin receptors or postreceptor regulation, or the production of inactive insulin or insulin that is destroyed before it can carry out its action.

Classification and Etiology

Although diabetes mellitus clearly is a disorder of insulin availability, it is not a single disease. A revised classification system, which was developed in 1997 by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, divides diabetes into four clinical classes[8] (Table 33-2). Included in the classification system are the categories of type 1 diabetes (i.e., diabetes resulting from beta cell destruction and an absolute insulin deficiency); type 2 diabetes (i.e., diabetes due to insulin resistance and a relative insulin deficiency); gestational diabetes mellitus (i.e., diabetes that develops during pregnancy); and other specific types of diabetes, many of which occur secondary to other conditions (e.g., Cushing syndrome, acromegaly, and pancreatitis).

Categories of Risk for Diabetes

The revised classification system also includes a system for diagnosing diabetes according to stages of glucose intolerance.[8–11] The revised criteria include an intermediate group of persons whose glucose levels, although not meeting the criteria for diabetes, are too high to be considered normal. This group is defined as having *impaired fasting plasma glucose* (IFG) and/or *impaired glucose tolerance* (IGT). A fasting plasma glucose (FPG) less than 100 mg/dL (5.6 mmol/L) or a plasma glucose measured 2 hours after a 75-g oral glucose tolerance test (OGTT) less than 140 mg/dL (7.8 mmol/L) is considered normal (Table 33-3). IFG is defined by an elevated FPG of 100 to 125 mg/dL (5.6 to 6.9 mmol/L) and IGT as plasma glucose levels of 140 to 199 mg/dL (7.8 to 11.0 mmol/L) with a 2-hour OGGTT. Persons with IFG and/or IGT are often referred to as having *prediabetes*, meaning they are at relatively high risk for the future development of diabetes as well as cardiovascular disease.[10,11] Thus, calorie restriction and weight reduction (even 5% to 10%) are important in overweight people with prediabetes.

Person with a FPG greater than or equal to 126 mg/dL (7.0 mmol/L) or an OGTT of 200 mg/dL (11.1 mmol/L) are considered to have provisional diabetes.[10,11] The criteria in Table 33-3 are used to confirm the diagnosis of

TABLE 33-2 Etiologic Classification of Diabetes Mellitus

Type	Subtypes	Etiology of Glucose Intolerance
I. Type 1*	Beta cell destruction usually leading to absolute insulin deficiency	
	A. Immune mediated	Autoimmune destruction of beta cells
	B. Idiopathic	Unknown
II. Type 2*	May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance	
III. Other specific types	A. Genetic defects in beta cell function, e.g., glucokinase	Dysregulation insulin secretion due to a defect in glucokinase generation
	B. Genetic defects in insulin action, e.g., leprechaunism, Rabson-Mendenhall syndrome	Pediatric syndromes that have mutations in insulin receptors
	C. Diseases of exocrine pancreas, e.g., pancreatitis, neoplasms, cystic fibrosis	Loss or destruction of insulin-producing beta cells
	D. Endocrine disorders, e.g., acromegaly, Cushing syndrome	Diabetogenic effects of excess hormone levels
	E. Drug or chemical induced, e.g., Vacor, glucocorticosteroids, thiazide diuretics, interferon-alfa	Toxic destruction of beta cells Insulin resistance Impaired insulin secretion Production of islet cell antibodies
	F. Infections, e.g., congenital rubella, cytomegalovirus	Beta cell injury followed by autoimmune response
	G. Uncommon forms of immune-mediated diabetes, e.g., "stiff man syndrome"	Autoimmune disorder of central nervous system with immune-mediated beta cell destruction
	H. Other genetic syndromes sometimes associated with diabetes, e.g., Down syndrome, Klinefelter syndrome, Turner syndrome	Disorders of glucose tolerance related to defects associated with chromosomal abnormalities
IV. Gestational diabetes mellitus (GDM)	Any degree of glucose intolerance with onset or first recognition during pregnancy	Combination of insulin resistance and impaired insulin secretion

*Patients with any form of diabetes may require insulin treatment at some stage of the disease. Such use of insulin, does not, of itself, classify the patient.

Adapted from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (2004). Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 27, S5–S10. Reprinted with permission from the American Diabetes Association. Copyright © 2004 American Diabetes Association.

diabetes in persons with provisional diabetes. Glycosylated hemoglobin (i.e., HbA_{1c} [A1C]) is a widely used marker for chronic hyperglycemia, reflecting average blood glucose levels over a 2- to 3-month period of time (to be discussed). The A1C, which plays a critical role in the management of persons with diabetes, is now recommended for use in the diagnosis of diabetes, with a threshold of greater than 6.5%.[10,11] The test can also be used to identify persons at higher risk for developing diabetes (see Table 33-3). The A1C has several advantages over the FPG, including elimination of the need for fasting and fewer day-to-day variations during periods of stress and illness. These advantages have to be balanced by greater cost, limited availability of A1C testing in regions of developing countries of the world, and incomplete correlation between A1C and average glucose in certain individuals.[11] In addition, A1C can be misleading in persons with certain forms of anemia and hemoglobin disorders. For conditions with abnormal red cell turnover, such as pregnancy or anemia due to hemolysis or iron deficiency, the diagnosis of diabetes must use glucose criteria exclusively. Also, the A1C may not be significantly elevated in rapidly evolving diabetes, such as the development of type 1 diabetes in children.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus, which is characterized by destruction of the pancreatic beta cells and accounts for 5% to 10% of those with diabetes, is subdivided into type 1A immune-mediated diabetes and type 1B idiopathic (non–immune-related) diabetes.[10] In the United States and Europe, approximately 90% to 95% of people with type 1 diabetes mellitus have type 1A immune-mediated diabetes. The rate of beta cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some individuals, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others may have modest elevations in FPG that can rapidly change to severe hyperglycemia and ketoacidosis in the presence of stress and infection.

TABLE 33-3 Normal and Increased Fasting Plasma Glucose (FPG), Oral Glucose Tolerance Test (OGTT), and Hemoglobin A_{1c} (A1C) for Categories of Increased Risk for Diabetes and Criteria for Diagnosis of Diabetes

Test	Normoglycemia	Categories of Increased Risk for Diabetes*	Criteria for Diagnosis of Diabetes†
FPG‡	<100 mg/dL (5.6 mmol/L)	Impaired fasting glucose (IFG) 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L) or
2-h plasma glucose in 75-g OGTT	<140 mg/dL (7.8 mmol/L)	Impaired glucose tolerance (IGT) 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L) or
A1C§	3.9%–5.6%	5.7%–6.4%	≥6.5% or
Other			Classic symptoms of hyperglycemia or hyperglycemic crisis and a plasma glucose ≥200 mg/dL (11.1 mmol/L)

*For all three tests, risk is continuous below the lower limit of the range and becomes disproportionately greater at higher ends of the range.

†Diagnosis of diabetes can be based on criteria 1(FP), 2(OGTT), 3(A1C), or 4 (Other). In the absence of unequivocal hyperglycemia, criteria for 1–3 should be confirmed by repeat testing.

‡Fasting is defined as no caloric intake for at least 8 hours.

§A1C should be performed using a method that is certified by the National Glycohemoglobin Standardization Program and standardized or traceable to the Diabetes Control and Complications Trial reference assay.

Developed from American Diabetes Association. Diagnosis and classification of diabetes mellitus—2010. *Diabetes Care* 32(Suppl 1), S62–S69.

Still others, particularly adults, may retain sufficient beta cell function to prevent ketoacidosis for many years.

The destruction of beta cells and absolute lack of insulin in people with type 1 diabetes mellitus means that they are particularly prone to the development of ketoacidosis. One of the actions of insulin is the inhibition of *lipolysis* (i.e., fat breakdown) and release of free fatty acids (FFAs) from fat cells. In the absence of insulin, ketosis develops when these fatty acids are released from fat cells and converted to ketones in the liver. Because of the loss of insulin response, all people with type 1A diabetes require exogenous insulin replacement to reverse the catabolic state, control blood glucose levels, and prevent ketosis.

Type 1A Immune-Mediated Diabetes. Type 1A diabetes, commonly referred to simply as *type 1 diabetes*, is characterized by immune-mediated destruction of beta cells. This type of diabetes, formerly called *juvenile diabetes*, occurs more commonly in children and adolescents. In fact, three quarters of all cases of type 1 diabetes occur in individual younger than 18 years of age.[11]

Type 1A diabetes is an autoimmune disorder that is thought to result from a genetic predisposition (i.e., diabetogenic genes); an environmental triggering event, such as an infection; and a T-lymphocyte–mediated hypersensitivity reaction against some beta cell antigen. Much evidence has focused on the inherited major histocompatibility complex (MHC) genes on chromosome 6 that encode human leukocyte antigen (HLA)-DQ and HLA-DR, especially DR-3 and DR-4.[3] In addition to the MHC susceptibility genes for type 1 diabetes on chromosome 6, an insulin gene regulating beta cell replication and function has been identified on chromosome 11.

Type 1A diabetes–associated autoantibodies may exist for years before the onset of hyperglycemia. There are two main types of autoantibodies: insulin autoantibodies (IAAs) and islet cell autoantibodies, including antibodies directed at other islet autoantigens, including glutamic acid decarboxylase (GAD) and the protein tyrosine

Diabetes Mellitus

- Diabetes mellitus is a disorder of carbohydrate, fat, and protein metabolism brought about by impaired beta cell synthesis or release of insulin, or the inability of tissues to use insulin.
- Type 1 diabetes results from loss of beta cell function and an absolute insulin deficiency.
- Type 2 diabetes results from impaired ability of the tissues to use insulin (insulin resistance) accompanied by a relative lack of insulin or impaired release of insulin in relation to blood glucose levels (beta cell dysfunction).

phosphatase IA-2.[3,11] Testing for antibodies to GAD or IA-2 and for IAAs using sensitive radiobinding assays can be used to identify new or future cases of type 1 diabetes. The appearance of IAAs may precede that of antibodies to GAD or IA-2, and IAAs may be the only antibodies detected at diagnosis in young children. These people also may have other autoimmune disorders such as Graves disease, rheumatoid arthritis, and Addison disease.

The fact that type 1 diabetes is thought to result from an interaction between genetic and environmental factors has led to research into methods directed at prevention and early control of the disease. These methods include the identification of genetically susceptible persons and early intervention in newly diagnosed persons with type 1 diabetes. After the diagnosis of type 1 diabetes, there often is a short period of beta cell regeneration, during which symptoms of diabetes disappear and insulin injections are reduced or not needed. This is sometimes called the *honeymoon period*. Immune interventions (immunomodulation) designed to interrupt the destruction of beta cells before development of type 1 diabetes are being investigated in various trials. Unfortunately, none of the interventions studied to date has shown real clinical utility.

Idiopathic Type 1B Diabetes. The term *idiopathic type 1B diabetes* is used to describe those cases of beta cell destruction in which no evidence of autoimmunity is present. Only a small number of people with type 1 diabetes fall into this category; most are of African or Asian descent. Type 1B diabetes is strongly inherited. People with the disorder have episodic ketoacidosis due to varying degrees of insulin deficiency with periods of absolute insulin deficiency that may come and go.

Type 2 Diabetes Mellitus and the Metabolic Syndrome

Type 2 diabetes mellitus, previously described as *non–insulin-dependent diabetes*, describes a condition of hyperglycemia that accompanies a *relative* rather than an *absolute* insulin deficiency.[3,10,11] It currently accounts for about 90% to 95% of the cases of diabetes. Most people with type 2 diabetes are older and overweight. Recently, however, type 2 diabetes has become a more common occurrence in obese children and adolescents.[12,13] Although type 1 diabetes remains the main form of diabetes in children worldwide, it seems likely that type 2 diabetes will become the predominant form within 10 years in some ethnic groups.[13]

The metabolic abnormalities involved in type 2 diabetes include (1) insulin resistance, (2) increased glucose production by the liver, and (3) deranged secretion of insulin by the pancreatic beta cells[14–16] (Fig. 33-7). Insulin resistance predates the development of hyperglycemia and is usually accompanied by compensatory beta cell hyperfunction and hyperinsulinemia in the early stages of the evolution of type 2 diabetes.

Insulin resistance can be defined as the failure of target tissues to respond to insulin, leading to decreased uptake of glucose in skeletal muscle and impaired suppression of glucose production by the liver.[15,16] Hepatic insulin resistance is manifested by overproduction of glucose despite fasting hyperinsulinemia, with the rate of glucose production being the primary determinant of the elevated FPG in persons with type 2 diabetes.[16] Although muscle glucose uptake is slightly increased after a meal, the efficiency with which it is taken up (glucose clearance) is diminished, resulting in an increase in *postprandial* (following a meal) blood glucose levels.[16]

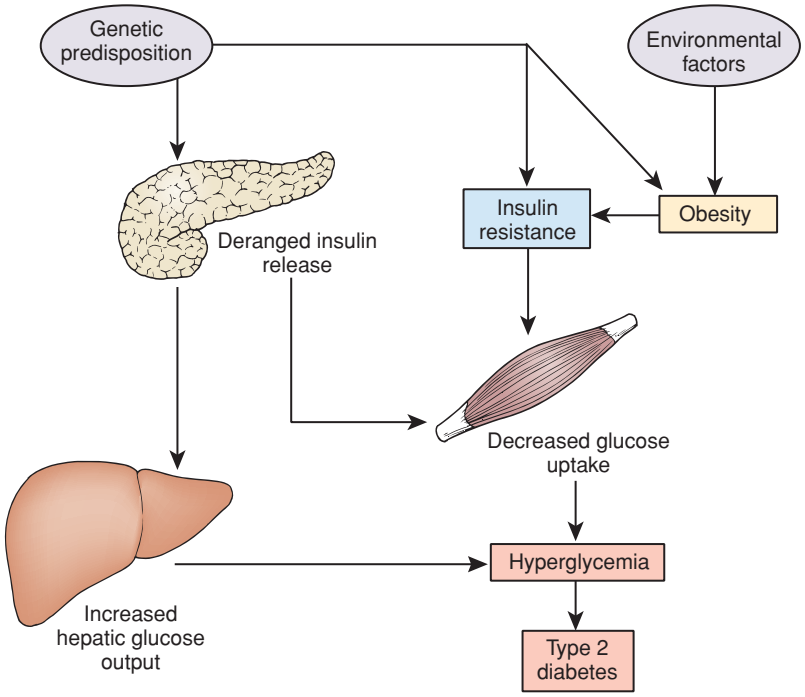


FIGURE 33-7. Pathogenesis of type 2 diabetes mellitus.

Specific causes of beta cell dysfunction include an initial decrease in the beta cell mass related to genetic or prenatal factors; increased apoptosis or decreased beta cell regeneration; beta cell exhaustion due to long-standing insulin resistance; glucotoxicity (i.e., glucose-induced beta cell desensitization); lipotoxicity (i.e., toxic effects of lipids on beta cells); and amyloid deposition or other conditions that have the potential to reduce beta cell mass.[15] According to one study, beta cell function was reduced by 50% at the time of diagnosis in type 2 diabetes, and progressively decreased (by approximately 4% per year), resulting in a worsening of hyperglycemia even when the degree of insulin resistance remained stable.[17]

The pathogenesis of type 2 diabetes involves both genetic and acquired (environmental) factors. A positive family history confers a twofold to fourfold increased risk for type 2 diabetes, and 15% to 25% of first-degree relatives of persons with type 2 diabetes develop impaired glucose tolerance or diabetes.[14] Despite the strong familial predisposition, the genetics of type 2 diabetes is poorly defined. This is probably because of the heterogeneous nature of the disorder as well as the difficulty in sorting out the contribution of acquired factors affecting insulin action and glycemic control.[15]

Among the acquired factors that predispose to type 2 diabetes, obesity and physical inactivity are paramount.[14,15,18] Approximately 90% of persons with type 2 diabetes are overweight. Obesity has profound effects on sensitivity of tissues to insulin, and as a consequence, on glucose homeostasis. As the body mass index (BMI) increases, the risk of developing diabetes increases. It is not only the absolute amount of fat, but also the distribution of body fat that has an effect on insulin resistance. It has been found that people with upper body (or central) obesity are at greater risk for developing type 2 diabetes and metabolic disturbances than persons with lower body (or peripheral) obesity (see Chapter 10). The increased insulin resistance has been attributed to the increased visceral (intra-abdominal) fat that can be detected on computed tomography scan and other imaging modalities.[19] Waist circumference and waist–hip ratio, which are both surrogate measures of central obesity, have been shown to correlate well with insulin resistance. Thus, measures such diet and exercise that reduce visceral adiposity are important in the management of persons with metabolic syndrome and obese type 2 diabetics.

Although many details of the relationship between adipose tissue and insulin resistance remain to be elucidated, several pathways have been proposed including the role of FFAs, adipose tissue cytokines (adipokines), and the peroxisome proliferator–activated receptor γ (PPAR-γ) that is expressed by adipocytes and plays an essential role in adipocyte differentiation. A large number of circulating hormones, cytokines, and metabolic fuels such as FFAs originate in fat cells and modify insulin action. It has been theorized that the insulin resistance and increased glucose production in obese people with type 2 diabetes may stem from an increased concentration of FFAs.[15,20] Visceral obesity is especially important because it is accompanied by an increase in fat storage and postprandial FFA concentrations. This has several consequences: first, excessive and chronic elevation of FFAs can cause beta cell dysfunction (lipotoxicity); second, FFAs also act at the level of the peripheral tissues to cause insulin resistance and glucose underutilization by inhibiting glucose uptake and glycogen storage; and third, the accumulation of FFAs and triglycerides reduces hepatic insulin sensitivity, leading to increased hepatic glucose production and hyperglycemia, especially in the fasting state. A further consequence is the diversion of excess FFAs to nonadipose tissues, including the liver, skeletal muscle, heart, and pancreatic beta cells.[21,22] In the liver, the uptake of FFAs from the portal blood can lead to hepatic triglyceride accumulation and nonalcoholic fatty liver disease (see Chapter 30).

In addition to the metabolic effects of visceral obesity, adipocytes are the source of a number of important factors (e.g., adiponectin, leptin, FFAs) involved in a wide range of other processes, including glucose and lipid metabolism, inflammation, and thrombosis.[15,21,22] In obesity and type 2 diabetes, there is a reduction in the production of some factors that are normally synthesized by adipocytes (i.e., adiponectin), whereas there is an accelerated release of other factors such as angiotensinogen, plasminogen activator inhibitor-1, leptin, and proinflammatory cytokines (e.g., tumor necrosis factor-α). Adiponectin, which is secreted by adipocytes and circulates in the blood, is the only known adipocyte-secreted factor that increases tissue sensitivity to insulin.[23] It has been shown that decreased levels of adiponectin coincide with insulin resistance in patients with obesity and type 2 diabetes. In skeletal muscle, adiponectin has been shown to decrease tissue triglyceride content by increasing the use of fatty acids as a fuel source. Adiponectin also appears to have antidiabetes, anti-inflammatory, and antiatherogenic effects.

Insulin Resistance and the Metabolic Syndrome. There is increasing evidence to suggest that when people with type 2 diabetes present predominantly with insulin resistance, the diabetes may represent only one aspect of a syndrome of metabolic disorders.[21,24] Hyperglycemia in these people is frequently associated with intra-abdominal obesity, high levels of plasma triglycerides and low levels of high-density lipoproteins (HDLs), hypertension, systemic inflammation (as detected by C-reactive protein [CRP] and other mediators), abnormal fibrinolysis, abnormal function of the vascular endothelium, and macrovascular disease (coronary artery, cerebrovascular, and peripheral arterial disease). This constellation of abnormalities often is referred to as the *insulin resistance syndrome, syndrome X,* or, the preferred term, *metabolic syndrome.*[22] In clinical practice, the definition of metabolic syndrome given in the Third Report of the National Cholesterol Education Program (NCEP III) is widely used[24] (Chart 33-1). Insulin resistance and increased risk of developing type 2 diabetes are also seen in women with polycystic ovary syndrome (see Chapter 40).

Other Specific Types of Diabetes

The category of other specific types of diabetes, formerly known as *secondary diabetes,* includes diabetes that is

CHART 33-1 NCEP ATP III Criteria for a Diagnosis of Metabolic Syndrome

Three or more of the following:

- Abdominal obesity: waist circumference >35 in (88 cm) in women or 40 in (102 cm) in men
- Triglycerides ≥150 mg/dL (1.7 mmol/L)
- High-density lipoproteins (HDL) <50 mg/dL (1.3 mmol/L) in women or <40 mg/dL (1.0 mmol/L) in men
- Blood pressure >130/85 mm Hg
- Fasting plasma glucose >100 mg/dL (5.6 mmol/L)

Developed from Grundy S. M., Panel Chair. (2001). *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).* NIH publication no. 01-3670. Bethesda, MD: National Institutes of Health.

associated with certain other conditions and syndromes. Such diabetes can occur with pancreatic disease or the removal of pancreatic tissue and with other endocrine diseases, such as acromegaly, Cushing syndrome, or pheochromocytoma. Endocrine disorders that produce hyperglycemia do so by increasing the hepatic production of glucose or decreasing the cellular use of glucose. Several specific types of diabetes are associated with monogenetic defects in beta cell function. These specific types of diabetes, which resemble type 2 diabetes but occur at an earlier age (usually before 25 years of age), were formerly referred to as *maturity-onset diabetes of the young* (MODY).[3]

Several diuretics—thiazide and loop diuretics—can elevate blood glucose. These diuretics increase potassium loss, which is thought to impair beta cell release of insulin. Other drugs and therapies known to cause hyperglycemia include diazoxide, glucocorticoids, oral contraceptives, antipsychotic agents, and total parenteral nutrition (i.e., hyperalimentation). Drug-related increases in blood glucose usually are reversed after the drug has been discontinued.

The advent of potent antiretroviral therapy (especially protease inhibitors) for the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) has significantly improved survival in these conditions. However, these people are now developing metabolic derangements with features similar to those seen in the metabolic syndrome (i.e., insulin resistance, high levels of plasma triglycerides, low levels of HDLs, hypertension, obesity, systemic inflammation [as detected by elevated levels of CRP and other mediators], abnormal fibrinolysis, abnormal endothelial dysfunction, and macrovascular disease).[25] In addition, changes in fat distribution (peripheral lipoatrophy and visceral obesity), sometimes referred to as *lipodystrophy,* often occur (see Chapter 16). These people should be aggressively treated to prevent cardiovascular complications resulting from the abnormal risk factors.

Gestational Diabetes

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance that begins or is first recognized during pregnancy. It occurs in 5% to 10% of pregnancies in the United States and is growing in prevalence.[26,27] The hyperglycemia varies in severity from glucose concentrations that would be diagnostic of diabetes apart from pregnancy to concentrations that are asymptomatic and only slightly above normal.[27] Factors that indicate a high risk for GDM include glycosuria, strong family history of type 2 diabetes, severe obesity, polycystic ovary disease, and prior history of GDM or delivery of a previous large-for-gestational-age infant.

All pregnant women should undergo risk assessment for diabetes during their first prenatal visit to determine the need for additional screening tests. Women who are younger than 25 years of age; were of normal body weight before pregnancy; have no family history of diabetes, prior history of GDM or large-for-gestational age infant, or presence of glycosuria; and are not members of a high-risk ethnic/racial group (e.g., Hispanic, Native American, Asian, African American) may not need to be screened.[11,26,27] Women at high risk for GDM should undergo glucose testing as soon as possible. An FPG greater than or equal to 126 mg/dL or a casual plasma glucose greater than or equal to 200 mg/dL meets the threshold for diagnosis of diabetes mellitus and should be confirmed on a subsequent day as soon as possible. Women of average or low risk, including those not found to have diabetes early in pregnancy, should undergo GDM testing at 24 to 28 weeks of gestation using a 50-g OGTT. This screening test consists of 50 g of glucose given without regard to the last meal, followed in 1 hour by a venous blood sample for glucose concentration. If the plasma glucose level is greater than 140 mg/dL (7.8 mmol/L), a 100-g 3-hour OGTT is indicated to establish the diagnosis of GDM.[27]

Diagnosis and careful medical management are essential because women with GDM are at higher risk for complications of pregnancy, mortality, and fetal abnormalities.[3] Fetal abnormalities include macrosomia (i.e., large body size), hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

Treatment of GDM includes close observation of mother and fetus because even mild hyperglycemia has been shown to be detrimental to the fetus.[26,27] Maternal fasting and postprandial blood glucose levels should be measured regularly. Fetal surveillance depends on the degree of risk for the fetus. The frequency of growth measurements and determinations of fetal distress depends on available technology and gestational age. All women with GDM require nutritional guidance because nutrition is the cornerstone of therapy. The nutrition plan should provide the necessary nutrients for maternal and fetal health, result in normoglycemia and proper weight gain, and prevent ketosis.[3] If dietary management alone does not achieve a capillary blood glucose of 90 to 99 mg/dL (5.0 to 5.50 mmol/L) or a 2-hour postprandial blood glucose less than 120 mg/dL (6.7 mmol/L), the Fifth International

Workshop on GDM recommends therapy with insulin.[28] Self-monitoring of blood glucose levels is essential.

Approximately 50% of women with GDM will develop type 2 diabetes within 5 to 10 years.[26] Predictors of future diabetes or prediabetes include maternal obesity, elevated FPG or OGTT, and diagnosis of GDM early in gestation. Women in whom GDM is diagnosed should be followed after delivery to detect diabetes early in its course. These women should be evaluated during their first postpartum visit with a 2-hour OGTT with a 75-g glucose load.

Clinical Manifestations of Diabetes

Diabetes mellitus may have a rapid or an insidious onset. In type 1 diabetes, signs and symptoms often arise suddenly. Type 2 diabetes usually develops more insidiously; its presence may be detected during a routine medical examination or when a patient seeks medical care for other reasons.

The most commonly identified signs and symptoms of diabetes are often referred to as the *three polys:* (1) polyuria (i.e., excessive urination), (2) polydipsia (i.e., excessive thirst), and (3) polyphagia (i.e., excessive hunger). These three symptoms are closely related to the hyperglycemia and glycosuria of diabetes. Glucose is a small, osmotically active molecule. When blood glucose levels are sufficiently elevated, the amount of glucose filtered by the glomeruli of the kidney exceeds the amount that can be reabsorbed by the renal tubules; this results in glycosuria accompanied by large losses of water in the urine. Thirst results from the intracellular dehydration that occurs as blood glucose levels rise and water is pulled out of body cells, including those in the hypothalamic thirst center. This early symptom may be easily overlooked in people with type 2 diabetes, particularly in those who have had a gradual increase in blood glucose levels. Polyphagia usually is not present in people with type 2 diabetes. In type 1 diabetes, it probably results from cellular starvation and the depletion of cellular stores of carbohydrates, fats, and proteins.

Weight loss despite normal or increased appetite is a common occurrence in people with uncontrolled type 1 diabetes. The cause of weight loss is twofold. First, loss of body fluids results from osmotic diuresis. Vomiting may exaggerate the fluid loss in ketoacidosis. Second, body tissue is lost because the lack of insulin forces the body to use its fat stores and cellular proteins as sources of energy. In terms of weight loss, there often is a marked difference between type 2 diabetes and type 1 diabetes. Weight loss is a frequent phenomenon in people with uncontrolled type 1 diabetes, whereas many people with uncomplicated type 2 diabetes often have problems with obesity.

Other signs and symptoms of hyperglycemia include recurrent blurred vision, fatigue, paresthesias, and skin infections. In type 2 diabetes, these often are the symptoms that prompt a person to seek medical treatment. Blurred vision develops as the lens and retina are exposed to hyperosmolar fluids. Lowered plasma volume produces weakness and fatigue. Paresthesias reflect a temporary dysfunction of the peripheral sensory nerves. Chronic skin infections can occur and are more common in people with type 2 diabetes. Hyperglycemia and glycosuria favor the growth of yeast organisms. Pruritus and vulvovaginitis due to *Candida* infections are common initial complaints in women with diabetes. Balanitis secondary to *Candida* infections can occur in men.

Diagnostic Tests

The diagnosis of diabetes mellitus is confirmed through the use of laboratory tests that measure blood glucose levels. Testing for diabetes should be considered in all individuals 45 years of age and older. Testing should be considered at a younger age in people who are obese, have a first-degree relative with diabetes, are members of a high-risk group, have delivered an infant weighing more than 9 pounds or been diagnosed with GDM, have hypertension or hyperlipidemia, or have met the criteria (IFG, IGT, elevated A1C) for increased risk of diabetes on previous testing.[28]

Blood Tests

Blood glucose measurements are used in both the diagnosis and management of diabetes. Diagnostic tests include the FPG, casual plasma glucose, the glucose tolerance test, and glycosylated hemoglobin (i.e., A1C).[10,11,28] Laboratory and capillary or finger-stick glucose tests are used for glucose management in people with diagnosed diabetes. Table 33-4 lists whole-blood and plasma glucose, as well as A1C values for glycemic control for people with diabetes.

Fasting Plasma Glucose. The FPG represents plasma glucose levels after food has been withheld for at least 8 hours. Advantages of the FPG are convenience, patient acceptability, and cost. An FPG level below 100 mg/dL (5.6 mmol/L) is considered normal (see Table 33-3).

TABLE 33-4 Correlation Between Hemoglobin A1C Level and Mean Plasma Glucose Levels

Hemoglobin A1C (%)	Mean Plasma Glucose, mg/dL (mmol/L)
6	126 (7.0)
7	154 (8.6)
8	183 (10.2)
9	212 (11.8)
10	240 (13.4)
11	269 (14.9)
12	298 (16.5)

From: American Diabetes Association. Standards of Medical Care—2010. *Diabetes Care 33*(Suppl 1), p. S19.

Casual Blood Glucose Test. A casual (or random) plasma glucose is one that is done without regard to the time of the last meal. A casual plasma glucose concentration that is unequivocally elevated (≥200 mg/dL [11.1 mmol/L]) in the presence of classic symptoms of diabetes such as polydipsia, polyphagia, polyuria, and blurred vision is diagnostic of diabetes mellitus at any age.

Oral Glucose Tolerance Test. The OGTT is an important screening test for diabetes. The test measures the body's ability to store glucose by removing it from the blood. In men and women, the test measures the plasma glucose response to 75 g of concentrated glucose solution at selected intervals, usually 1 and 2 hours. In pregnant women, a glucose load of 100 g is given with an additional 3-hour plasma glucose determination (see earlier section on gestational diabetes). In people with normal glucose tolerance, blood glucose levels return to normal within 2 to 3 hours after ingestion of a glucose load, in which case it can be assumed that sufficient insulin is present to allow glucose to leave the blood and enter body cells. Because a person with diabetes lacks the ability to respond to an increase in blood glucose by releasing adequate insulin to facilitate storage, blood glucose levels rise above those observed in normal people and remain elevated for longer periods.

Capillary Blood Glucose Monitoring. Technological advances have provided the means for monitoring blood glucose levels by using a drop of capillary blood. This procedure has provided health professionals with a rapid and economical means for monitoring blood glucose and has given people with diabetes a way of maintaining near-normal blood glucose levels through self-monitoring of blood glucose. These methods use a drop of capillary blood obtained by pricking the finger or forearm with a special needle or small lancet. Small trigger devices make use of the lancet virtually painless. The drop of capillary blood is placed on or absorbed by a reagent strip, and glucose levels are determined electronically using a glucose meter.

Laboratory tests that use plasma for measurement of blood glucose give results that are 10% to 15% higher than the finger-stick method, which uses whole blood.[28] Many blood glucose monitors approved for home use and some test strips now calibrate blood glucose readings to plasma values. It is important that people with diabetes know whether their monitors or glucose strips provide whole-blood or plasma test results.

Continuous glucose monitoring systems are becoming available to fine-tune glucose management. The various systems have small catheters implanted in the subcutaneous tissue to provide frequent samples. The variety and accuracy of these systems are continually improving. However, finger-stick glucose monitoring remains the standard of care.

Glycosylated Hemoglobin. Glycosylated hemoglobin, hemoglobin A_{1c} (HbA_{1c}), or A1C (the preferred term) are terms used to describe hemoglobin into which glucose has been incorporated. Hemoglobin normally does not contain glucose when it is released from the bone marrow. During its 120-day life span in the red blood cell, hemoglobin normally becomes glycosylated to form HbA_1. The major form of HbA_1 is hemoglobin HbA_{1C}, which makes up 2% to 6% of total hemoglobin.[3] Because glucose entry into red blood cells is not insulin dependent, the rate at which glucose becomes attached to the hemoglobin molecule depends on blood glucose levels. Glycosylation is essentially irreversible, and the level of A1C present in the blood provides an index of blood glucose levels over the previous 6 to 12 weeks. In uncontrolled diabetes or diabetes with hyperglycemia, there is an increase in the level of A1C. The American Diabetes Association (ADA) recommends initiating corrective measures for A1C levels greater than 7%. However, the goal has been redefined as lowering the A1C to less than 7%, or even achieving normal glycemic levels of less than 6%.[11]

Urine Tests

The ease, accuracy, and convenience of self-administered blood glucose monitoring techniques have made urine testing for glucose obsolete for most people with diabetes. These tests only reflect urine glucose levels and are influenced by such factors as the renal threshold for glucose, fluid intake and urine concentration, urine testing methodologies, and some drugs. It is recommended that all people with diabetes self-monitor their blood glucose. Urine ketone determinations remain an important part of monitoring diabetic control, particularly in people with type 1 diabetes who are at risk for development of ketoacidosis, and in pregnant diabetic women to check the adequacy of nutrition and glycemic control.[28]

Diabetes Management

The desired outcome of glycemic control in both type 1 and type 2 diabetes is normalization of blood glucose as a means of preventing short- and long-term complications. Treatment plans involve dietary management (medical nutrition therapy), exercise, and antidiabetic agents. People with type 1 diabetes require insulin therapy from the time of diagnosis. Weight loss and dietary management may be sufficient to control blood glucose levels in people with type 2 diabetes. However, they require follow-up care because insulin secretion from the beta cells may decrease or insulin resistance may persist or worsen, in which case oral antidiabetic agents are prescribed.

Among the methods used to achieve these treatment goals are education in self-management and problem solving. Individual treatment goals should take into account the person's age and other disease conditions, the person's capacity to understand and carry out the treatment regimen, and socioeconomic factors that might influence compliance with the treatment plan. Optimal control of both type 1 and type 2 diabetes is associated with prevention or delay of chronic diabetes complications.

Dietary Management

Dietary management usually is prescribed to meet the specific needs of each person with diabetes. Integral to

diabetes management is a prescribed plan for nutrition therapy.[29] Therapy goals include maintenance of near-normal blood glucose levels, achievement of optimal lipid levels, adequate calories to maintain and attain reasonable weights, prevention and treatment of chronic diabetes complications, and improvement of overall health through optimal nutrition.

The goals and principles of diet therapy differ between type 1 and type 2 diabetes, as well as for lean and obese people. For a person with type 1 diabetes, the usual food intake is assessed and used as a basis for adjusting insulin therapy to fit with the person's lifestyle. Eating consistent amounts and types of food at specific and routine times is encouraged. Home blood glucose monitoring is used to fine-tune the plan. Most people with type 2 diabetes are overweight. Nutrition therapy goals focus on achieving glucose, lipid, and blood pressure goals, and weight loss if indicated. Mild to moderate weight loss (5% to 10% of total body weight) has been shown to improve diabetes control, even if desirable weight is not achieved.

A coordinated team effort, including the person with diabetes, is needed to individualize the nutrition plan.[11,29] The diabetic diet has undergone marked changes over the years, particularly in the recommendations for distribution of calories among carbohydrates, proteins, and fats. There no longer is a specific diabetic or ADA diet but rather a dietary prescription based on nutrition assessment and treatment goals. Information is assessed regarding metabolic parameters and medical history of factors such as renal impairment and gastrointestinal autonomic neuropathy. Evaluating the effectiveness of the meal plan requires monitoring metabolic parameters such as blood glucose, A1C, lipids, blood pressure, body weight, and quality of life. Self-management education is essential to facilitate understanding of the associations among food, exercise, medication, and blood glucose.

Exercise

The benefits of exercise include cardiovascular fitness and psychological well-being. For many people with type 2 diabetes, the benefits of exercise include a decrease in body fat, better weight control, and improvement in insulin sensitivity.[11,30] Exercise is so important in diabetes management that a planned program of regular exercise usually is considered an integral part of the therapeutic regimen for every person with diabetes. In general, sporadic exercise has only transient benefits; a regular exercise or training program is the most beneficial. It is better for cardiovascular conditioning and can maintain a muscle–fat ratio that enhances peripheral insulin receptivity.

In people with diabetes, the beneficial effects of exercise are accompanied by an increased risk of hypoglycemia. Although muscle uptake of glucose increases significantly, the ability to maintain blood glucose levels is hampered by failure to suppress the absorption of injected insulin and activate the counterregulatory mechanisms that maintain blood glucose. Not only is there an inability to suppress insulin levels, but also insulin absorption may increase. This increased absorption is more pronounced when insulin is injected into the subcutaneous tissue of the exercised muscle, but it occurs even when insulin is injected into other body areas. Even after exercise ceases, insulin's lowering effect on blood glucose continues. In some people with type 1 diabetes, the symptoms of hypoglycemia occur several hours after cessation of exercise, perhaps because subsequent insulin doses (in people using multiple daily insulin injections) are not adjusted to accommodate the exercise-induced decrease in blood glucose. The cause of hypoglycemia in people who do not administer a subsequent insulin dose is unclear. It may be related to the fact that the liver and skeletal muscles increase their uptake of glucose after exercise as a means of replenishing their glycogen stores, or that the liver and skeletal muscles are more sensitive to insulin during this time. People with diabetes should be aware that delayed hypoglycemia can occur after exercise and that they may need to alter their diabetes medication dose, their carbohydrate intake, or both.

Although of benefit to people with diabetes, exercise must be weighed on the risk–benefit scale. Before beginning an exercise program, persons with diabetes should undergo an appropriate evaluation for macrovascular and microvascular disease.[30] The goal of exercise is safe participation in activities consistent with an individual's lifestyle. As with nutrition guidelines, exercise recommendations need to be individualized. Considerations include the potential for hypoglycemia, hyperglycemia, ketosis, cardiovascular ischemia and arrhythmias (particularly silent ischemic heart disease), exacerbation of proliferative retinopathy, and lower extremity injury. For those with chronic diabetes, the complications of vigorous exercise can be harmful and cause eye hemorrhage and other problems. For people with type 1 diabetes who exercise during periods of poor control (i.e., when blood glucose is elevated, exogenous insulin levels are low, and ketonemia exists), blood glucose and ketones rise to even higher levels because the stress of exercise is superimposed on preexisting insulin deficiency and increased counterregulatory hormone activity.

Oral and Injectable Antidiabetic Agents

Historically, two categories of antidiabetic agents existed: insulin injections and oral medications. However, this classification has become somewhat blurred owing to the introduction of new injectable antidiabetic agents (e.g., glucagon-like peptide-1 and amylin analogs). Because people with type 1 diabetes are deficient in insulin, they are in need of exogenous insulin replacement therapy from the start. People with type 2 diabetes can have increased hepatic glucose production; decreased peripheral utilization of glucose; decreased utilization of ingested carbohydrates; and, over time, impaired insulin secretion and excessive glucagon secretion from the pancreas (Fig. 33-8). The antidiabetic agents used in the treatment of type 2 diabetes (insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, and incretin-based agents) attack each one of these areas and sometimes all.[31,32] If good glycemic control cannot be achieved with one or a combination of antidiabetic agents, insulin can be added or used by itself.

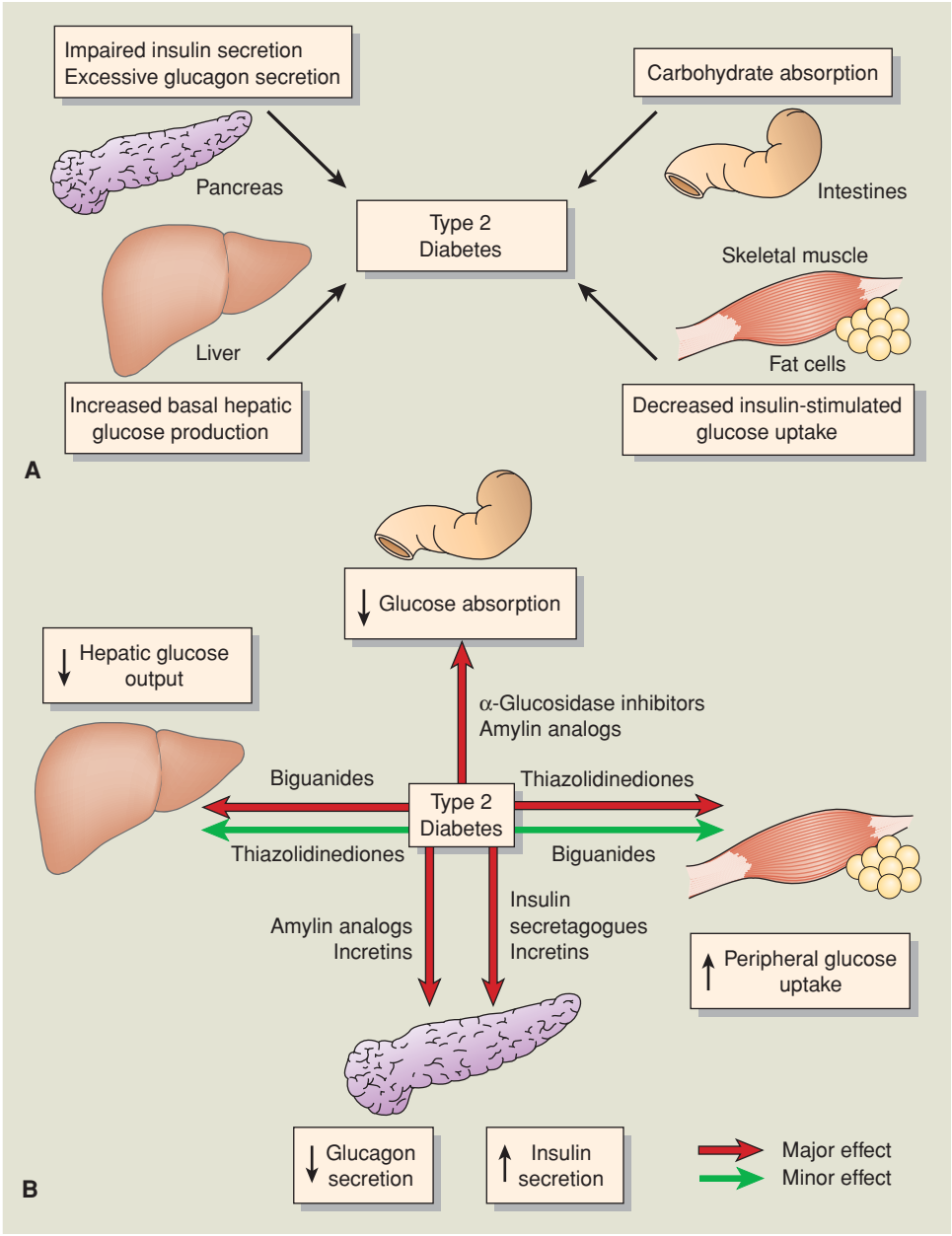


FIGURE 33-8. **(A)** Mechanisms of elevated blood glucose in type 2 diabetes mellitus. **(B)** Action sites of hypoglycemic agents and mechanisms of lowering blood glucose in type 2 diabetes. The incretins are the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists.

Insulin Secretagogues. The insulin secretagogues act at the level of the pancreatic beta cells to stimulate insulin secretion. There are two general classes of insulin secretagogues: sulfonylureas and meglitinides and related drugs.[32] Both types of secretagogues require the presence of functioning beta cells, are used only in the treatment of type 2 diabetes, and have the potential for producing hypoglycemia.

The control of insulin release from the pancreatic beta cells by glucose or the sulfonylurea drugs requires the generation of adenosine triphosphate (ATP), closing of an ATP-gated potassium channel, and opening of a transmembrane calcium channel.[32] The sulfonylureas (e.g., chlorpropamide, glipizide, glyburide, glimepiride) act by binding to a high-affinity sulfonylurea receptor on the beta cell that is linked to an ATP-sensitive potassium channel (Fig. 33-9). Binding of a sulfonylurea closes the channel, resulting in a coupled reaction that leads to an influx of calcium ions and insulin secretion. Because the sulfonylureas increase insulin levels and the rate at which glucose is removed from the blood, it is important to recognize that they can cause hypoglycemic reactions. This problem is more common in elderly people with impaired hepatic and renal function who are taking the longer-acting sulfonylureas.

The meglitinides (repaglinide) and related drugs (nateglinide) are relatively new insulin secretagogues that require the presence of glucose for their main action. These agents exert their action by closing the ATP-dependent potassium channel in the beta cells (see Fig. 33-9). Insulin

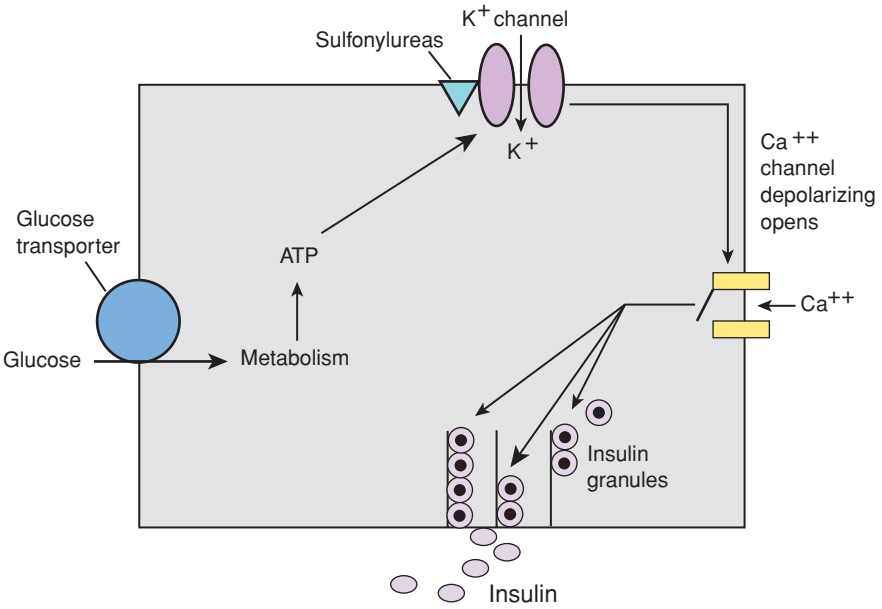


FIGURE 33-9. One model of control of release of insulin by the pancreatic beta cells and the action of the sulfonylurea agents. In the resting beta cell with low adenosine triphosphate (ATP) levels, potassium diffuses through the ATP-gated channels, maintaining the resting membrane potential. As blood glucose rises and is transported into the beta cell by the glucose transporter, ATP rises, causing the potassium channels to close and depolarization to occur. Depolarization results in opening of the voltage-gated calcium channels, which results in insulin secretion. (Modified from Karam J.H. [1992]. Type II diabetes and syndrome X. *Endocrinology and Metabolism Clinics of North America* 21, 339.)

release is glucose dependent and diminishes at low glucose levels. These agents, which are rapidly absorbed from the gastrointestinal tract, are taken shortly before meals (repaglinide 15 to 30 minutes and nateglinide 1 to 30 minutes). Both repaglinide and nateglinide can produce hypoglycemia; thus, proper timing of meals in relation to drug administration is essential.

Biguanides. *Metformin,* the only currently available biguanide, inhibits hepatic glucose production and increases the sensitivity of peripheral tissues to the actions of insulin. Secondary benefits of metformin therapy include weight loss and improved lipid profiles. Unlike the insulin secretagogues, whose primary action is to increase insulin secretion, metformin exerts its beneficial effects on glycemic control through decreased hepatic glucose production (main effect) and increased peripheral use of glucose. This medication does not stimulate insulin secretion; therefore, it does not produce hypoglycemia. Because of the risk for lactic acidosis, metformin is contraindicated in people with elevated serum creatinine levels, clinical and laboratory evidence of liver disease, or conditions associated with hypoxemia or dehydration.[32]

α-Glucosidase Inhibitors. The α-glucosidase inhibitors (acarbose, miglitol) block the action of intestinal brush border enzymes that break down complex carbohydrates.[32] In persons with type 2 diabetes, sulfonylureas, biguanides, or both may have beneficial effects on FPG levels. However, postprandial hyperglycemia persists in many persons and probably accounts for sustained increases in A1C levels. By delaying the breakdown of complex carbohydrates, the α-glucosidase inhibitors delay the absorption of carbohydrates from the gut and blunt the postprandial increase in plasma glucose and insulin levels. Although not a problem with monotherapy or combination therapy with a biguanide, hypoglycemia may occur with concurrent sulfonylurea treatment. If hypoglycemia does occur, it should be treated with glucose (dextrose) and not sucrose (table sugar), whose breakdown may be blocked by the action of the α-glucosidase inhibitors.

Thiazolidinediones. The thiazolidinediones (TZDs) or glitazones (e.g., pioglitazone, rosiglitazone) are the only class of drugs that directly target insulin resistance, a fundamental defect in the pathophysiology of type 2 diabetes. The TZDs improve glycemic control by increasing insulin sensitivity in the insulin-responsive tissues—liver, skeletal muscle, and fat—allowing the tissues to respond to endogenous insulin more efficiently without increased output from already dysfunctional beta cells.[3,32] Pioglitazone and rosiglitazone are both approved for use as monotherapy and in combination therapy. Because of the previous problem with liver toxicity in this class of drugs, liver enzymes should be monitored according to guidelines. Both agents can cause fluid accumulation and are therefore contraindicated in patients with New York Heart Association stage III and IV heart failure[33] (see Chapter 20, Table 20-1). In addition, there is increased risk of bone fractures with both compounds.[34]

The mechanism of action of the TZDs is complex and not fully understood. The action of the TZDs is associated with binding to PPAR-γ[32] (Fig. 33-10). Binding of the TZDs to PPAR-γ begins a cascade of events leading to regulation of genes involved in lipid and glucose metabolism. They result in an increase in the number of GLUT-4 transporters and increased insulin-mediated uptake of glucose in the peripheral tissues. *Adiponectin* is produced by adipocytes and directly sensitizes the body to the actions of insulin, and may be a part of the missing link in explaining insulin resistance in persons with type 2 diabetes.[32] The TZDs are thought to decrease insulin resistance, at least in part by increasing adipocyte production

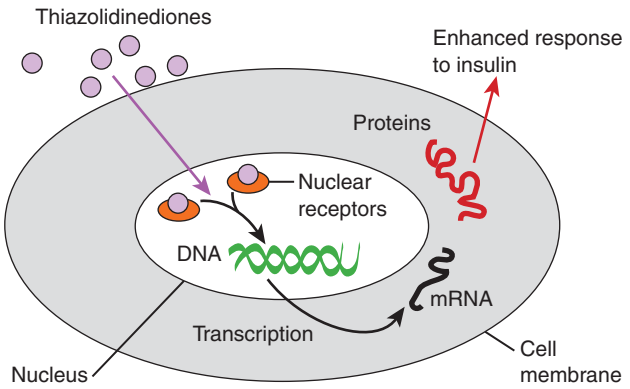


FIGURE 33-10. Action of the thiazolidinediones on activation of the nuclear peroxisome proliferator–activated receptor γ (PPAR-γ) that regulates gene transcription of proteins that regulate glucose uptake and reduce fatty acid release. mRNA, messenger ribonucleic acid.

of adiponectin. Additional effects of TZDs are numerous and include correction of many of the abnormal metabolic features associated with type 2 diabetes. This includes a decrease in FFA and triglycerides, microalbuminuria, blood pressure, inflammatory mediators (e.g., fibrinogen and CRP), and procoagulation factors.[35]

Incretin-Based Agents. Incretins are hormones released into the circulation by the gastrointestinal tract after a meal, especially one high in carbohydrates, that amplify the glucose-induced release of insulin (see Chapter 28).[3,6] The main incretins secreted are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[3,36] Both GLP-1 and GIP are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). DPP-4 enzyme inhibitors work by inhibiting the DPP-4 enzyme and increasing GLP-1 and GIP levels, which then increase insulin release. GLP-1 also helps to suppress glucagon release.

Exenatide is a synthetic analog of GLP-1 that is resistant to DPP-4 degradation. Approved in 2005, exenatide was the first type of incretin to become available for treatment of diabetes.[36] Exenatide is approved as an injectable adjunctive therapy for people with type 2 diabetes treated with metformin or sulfonylureas who still have suboptimal glycemic control. The drug has been shown to have multiple actions such as potentiation of glucose-mediated insulin release, slowed gastric emptying, and a central loss of appetite. Exenatide is injected subcutaneously 60 minutes before a meal. When added to preexisting sulfonylurea therapy, the oral hypoglycemic dosage may need to be lowered to prevent hypoglycemia. The major side effects are nausea and weight loss.[36] Although exenatide was the first GLP-1 agonist to be developed and approved, other agents and formulations are in development.

Sitagliptin, approved in 2006, is an oral DPP-4 inhibitor indicated for adjunctive therapy for persons with type 2 diabetes.[36] The drug is given once daily, and may be given in combination with metformin or a thiazolidinedione. Another DPP-4 inhibitor, saxagliptin, was approved in 2009 for treatment of persons with type 2 diabetes either as monotherapy or in combination with metformin, a sulfonylurea, or a thiazolidinedione.[36]

Insulin

Type 1 diabetes mellitus always requires treatment with insulin, and many people with type 2 diabetes eventually require insulin therapy. Insulin is destroyed in the gastrointestinal tract and must be administered by injection or inhalation. An inhaled form of insulin (Exubera) was on the market for a short time in the United States but was withdrawn for commercial reasons. Other inhaled insulin formulations are in clinical development.

During the past several decades, many pharmaceutical companies have entered the insulin manufacturing market. After much research, human insulin has become widely available, providing an alternative to previous forms of insulin that were obtained from bovine and porcine sources. The manufacture of human insulin uses recombinant deoxyribonucleic acid (DNA) technology. More recently, insulin analogs have become available that offer even better and more reproducible release characteristics.[37] In these agents, the human insulin sequence has been modified to improve their pharmacologic properties.

Insulin types are classified by length and peaking of action.[32,37] There are four principal types of insulin: short acting, rapid acting, intermediate acting, and long acting. *Short-acting insulin* (regular) is a soluble crystalline insulin whose effects begin within 30 minutes after subcutaneous injection and generally last for 5 to 8 hours. The *rapid-acting insulins* (lispro, aspart, and glulisine) are produced by recombinant technology with an amino acid substitution. These insulins have a more rapid onset, peak, and duration of action than short-acting regular insulin. The rapid-acting insulins, which are used in combination with intermediate or long-acting insulins, are usually administered immediately before a meal. *Intermediate- to long-acting insulins* include NPH, glargine, and detemir. These insulins have slower onsets and a longer duration of action. They require several hours to reach therapeutic levels, so their use in type 1 diabetes requires supplementation with rapid- or short-acting insulin. *Glargine* and *detemir* have a slower, more prolonged absorption than NPH insulin and provide a relatively constant concentration over 12 to 24 hours. All forms of insulin have the potential to produce hypoglycemia or "insulin reaction" as a side effect (to be discussed).

Two intensive treatment regimens—multiple daily injections and continuous subcutaneous infusion of insulin—closely simulate the normal pattern of insulin secretion by the body. With each method, a basal insulin level is maintained, and bolus doses of short- or rapid-acting insulin are delivered before meals. The choice of management is determined by the person with diabetes in collaboration with the health care team.

With *multiple daily injections* (MDIs), the basal insulin requirements are met by an intermediate- or long-acting insulin administered once or twice daily. Boluses of rapid- or short-acting insulin are used before meals. The development of convenient injection devices (e.g.,

pen injectors) has made it easier for people with diabetes to comply with algorithms for these insulins that are administered before meals.

The *continuous subcutaneous insulin infusion* (CSII) method uses an insulin pump. With this method, the basal insulin requirements are met by continuous infusion of subcutaneous insulin, the rate of which can be varied to accommodate diurnal variations.[38] The CSII technique involves the insertion of a small needle or plastic catheter into the subcutaneous tissue of the abdomen. Tubing from the catheter is connected to a syringe set into a small infusion pump worn on a belt or in a jacket pocket. The computer-operated pump then delivers one or more set basal amounts of insulin. In addition to the basal amount delivered by the pump, a bolus amount of insulin may be delivered when needed (e.g., before a meal) by pushing a button. Although the pump's safety has been proven, strict attention must be paid to signs of hypoglycemia. Self-monitoring of blood glucose levels is a necessity when using the CSII method of management. Hyperglycemia and ketotic episodes caused by pump failure, catheter clogging, and infections at the needle site also are possible complications. Candidate selection is crucial to the successful use of the insulin pump. Only people who are highly motivated to do frequent blood glucose tests and make daily insulin adjustments are candidates for this method of treatment.[38]

Pancreas or Islet Cell Transplantation

Pancreas or islet cell transplantation is not a lifesaving procedure. It does, however, afford the potential for significantly improving the quality of life. The most serious problems are the requirement for immunosuppression and the need for diagnosis and treatment of rejection. Investigators are looking for methods of transplanting islet cells and protecting the cells from destruction without the use of immunosuppressive drugs.[39]

Management of Diabetes in Children

Children with diabetes differ from adults in many respects, including changes in insulin sensitivity related to sexual maturity and physical growth, their ability to provide self-care and need for supervision in child care and school, and vulnerability to hypoglycemia and diabetic ketoacidosis.[11] While current standards of care for diabetes management reflect the need to maintain glucose levels as near normal as possible, glycemic goals need to take into account that children younger than 6 to 7 years of age have a form of "hypoglycemic unawareness."[11] Their counterregulatory mechanisms are immature and they lack the cognitive capacity to recognize and respond to hypoglycemic symptoms, placing them at greater risk for hypoglycemia and its sequelae. Also, unlike adults, young children under 5 years of age are at risk for permanent cognitive impairment after episodes of severe hypoglycemia.[11] Thus, the glycemic goals for children must consider the benefits of long-term health outcomes against the risks of hypoglycemia and the difficulties in achieving normoglycemia in children.

Acute Complications

The three major acute complications of impaired blood glucose regulation are diabetic ketoacidosis, hyperosmolar hyperglycemic state, and hypoglycemia. All are life-threatening conditions that demand immediate recognition and treatment. The Somogyi effect and dawn phenomenon, which result from the mobilization of counterregulatory hormones, contribute to difficulties with diabetic control.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA), characterized by hyperglycemia, ketosis, and metabolic acidosis, is an acute life-threatening complication of uncontrolled diabetes.[40–42] DKA primarily affects persons with type 1 diabetes, but may also occur in persons with type 2 diabetes when severe stress such as sepsis or trauma is present. It may be an initial manifestation of previously undiagnosed type 1 diabetes or may result from increased insulin requirements in type 1 diabetes during stress situations such as infection or trauma that increase the release of stress hormones. For example, a mother may bring a child into the clinic or emergency department with reports of lethargy, vomiting, and abdominal pain, unaware that the child has diabetes. In clinical practice, ketoacidosis also occurs with the omission or inadequate use of insulin.

Ketoacidosis reflects the effect of insulin deficiency at multiple sites (Fig. 33-11). Insulin lack results in the rapid breakdown of energy stores from muscle and fat depots, leading to increased movement of amino acids to the liver for conversion to glucose and of fatty acids for conversion to ketones. In the presence of ketosis, the levels of glucagon and counterregulatory hormones (i.e., corticosteroids, epinephrine, and growth hormone) are consistently increased. Furthermore, in the absence of insulin, peripheral utilization of glucose and ketones is reduced. Metabolic acidosis is caused by the excess ketoacids that require buffering by bicarbonate ions; this leads to a marked decrease in serum bicarbonate levels.

The definitive diagnosis of DKA consists of *hyperglycemia* (blood glucose levels >250 mg/dL [13.8 mmol/L]), low serum bicarbonate, low arterial pH, and positive urine and serum ketones. It can be further subdivided into *mild DKA* (serum bicarbonate of 15 to 18 mEq/dL [15 to 18 mmol/L], pH 7.25 to 7.30); *moderate DKA* (serum bicarbonate 10 to <15 mEq/dL [10 to <15 mmol/L], pH 7.00 to 7.24): and *severe DKA* (serum bicarbonate <10 mEq/dL [<10 mmol/L], pH <7.00).[40,41] Hyperglycemia leads to osmotic diuresis, dehydration, and a critical loss of electrolytes. Hyperosmolality of extracellular fluids from hyperglycemia leads to a shift of water and potassium from the intracellular to the extracellular compartment. Extracellular sodium concentration frequently is low or normal despite enteric water losses because of an intracellular–extracellular fluid shift. This dilutional effect is referred to as *pseudohyponatremia*. Serum potassium levels may also be normal or elevated, despite total potassium depletion resulting from protracted polyuria and vomiting.

The development of DKA is commonly preceded by a day or more of polyuria, polydipsia, nausea, vomiting,

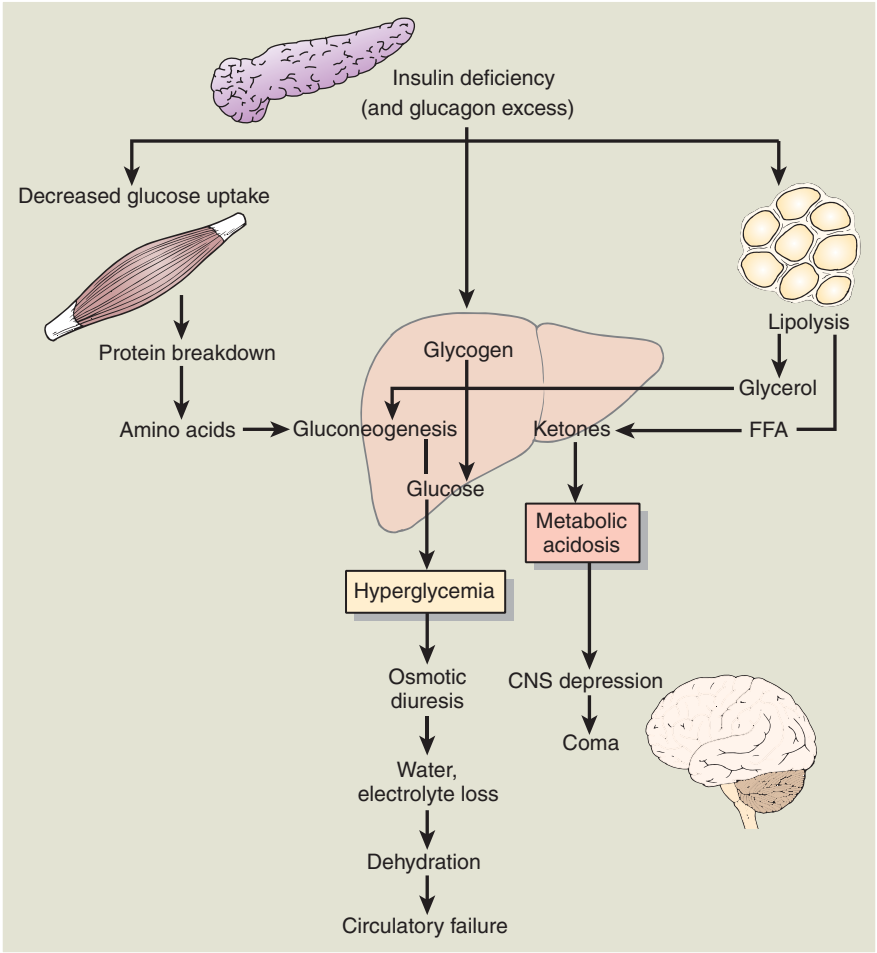


FIGURE 33-11. Mechanisms of diabetic ketoacidosis. Diabetic ketoacidosis is associated with very low insulin levels and extremely high levels of glucagon, catecholamines, and other counterregulatory hormones. Increased levels of glucagon and the catecholamines lead to mobilization of substrates for gluconeogenesis and ketogenesis by the liver. Gluconeogenesis in excess of that needed to supply glucose for the brain and other glucose-dependent tissues produces a rise in blood glucose levels. Mobilization of free fatty acids (FFAs) from triglyceride stores in adipose tissue leads to accelerated ketone production and ketosis. CNS, central nervous system.

and marked fatigue, with eventual stupor that can progress to coma. Abdominal pain and tenderness may be experienced without abdominal disease. The breath has a characteristic fruity smell because of the presence of the volatile ketoacids. Hypotension and tachycardia may be present because of a decrease in blood volume. A number of the signs and symptoms that occur in DKA are related to compensatory mechanisms. The heart rate increases as the body compensates for a decrease in blood volume, and the rate and depth of respiration increase (i.e., Kussmaul respiration) as the body attempts to prevent further decreases in pH. Metabolic acidosis is discussed further in Chapter 8.

The goals in treating DKA are to improve circulatory volume and tissue perfusion, decrease blood glucose, and correct the acidosis and electrolyte imbalances. These objectives usually are accomplished through the administration of insulin and intravenous fluid and electrolyte replacement solutions. Because insulin resistance accompanies severe acidosis, low-dose insulin therapy is used. An initial loading dose of regular insulin often is given intravenously, followed by continuous low-dose infusion. Frequent laboratory tests are used to monitor blood glucose and serum electrolyte levels and to guide fluid and electrolyte replacement. It is important to replace fluid and electrolytes and correct pH while bringing the blood glucose concentration to a normal level. Too rapid a drop in blood glucose may cause hypoglycemia. A sudden change in the osmolality of extracellular fluid can also occur when blood glucose levels are lowered too rapidly, and this can cause cerebral edema. Cerebral and other autoregulatory mechanisms may not be as well developed in younger children, placing them at particular risk for development of cerebral edema.[42] Serum potassium levels often fall as acidosis is corrected and potassium moves from the extracellular into the intracellular compartment. Thus, it may be necessary to add potassium to the intravenous infusion. Identification and treatment of the underlying cause, such as infection, also are important.

Hyperosmolar Hyperglycemic State

The hyperosmolar hyperglycemic state (HHS) is characterized by hyperglycemia (blood glucose >600 mg/dL [33.3 mmol/L]), hyperosmolarity (plasma osmolarity >320 mOsm/L) and dehydration, the absence of ketoacidosis, and depression of the sensorium.[40] HHS may occur in various conditions, including type 2 diabetes, acute pancreatitis, severe infection, myocardial infarction, and treatment with oral or parenteral nutrition solutions. It is seen most frequently in people with type 2 diabetes.

A partial or relative insulin deficiency may initiate the syndrome by reducing glucose utilization while inducing hyperglucagonemia and increasing hepatic glucose output. With massive glycosuria, obligatory water loss occurs. If the person is unable to maintain adequate fluid intake because of associated acute or chronic illness or has excessive fluid loss, dehydration develops. As the plasma volume contracts, renal insufficiency develops and the resultant limitation of renal glucose losses leads to increasingly higher blood glucose levels and severity of the hyperosmolar state.

In hyperosmolar states, the increased serum osmolarity has the effect of pulling water out of body cells, including brain cells. The condition may be complicated by thromboembolic events arising because of the high serum osmolality. The most prominent manifestations are weakness, dehydration, polyuria, neurologic signs and symptoms, and excessive thirst. The neurologic signs include hemiparesis, Babinski reflexes, aphasia, muscle fasciculations, hyperthermia, hemianopia, nystagmus, visual hallucinations, seizures, and coma. The onset of HHS often is insidious, and because it occurs most frequently in older people, it may be mistaken for a stroke.

The treatment of HHS requires judicious medical observation and care as water moves back into brain cells, posing a threat of cerebral edema. Extensive potassium losses that also have occurred during the diuretic phase of the disorder require correction. Because of the problems encountered in the treatment and the serious nature of the disease conditions that cause HHS, the prognosis for this disorder is less favorable than that for ketoacidosis.

Hypoglycemia

Hypoglycemia, or an insulin reaction, occurs from a relative excess of insulin in the blood and is characterized by below-normal blood glucose levels.[43,44] It occurs most commonly in people treated with insulin injections, but prolonged hypoglycemia also can result from some oral hypoglycemic agents. There are many factors that can precipitate an insulin reaction in a person with type 1 diabetes, including error in insulin dose, failure to eat, increased exercise, decreased insulin need after removal of a stress situation, medication changes, and a change in insulin injection site. Alcohol decreases liver gluconeogenesis, and people with diabetes need to be cautioned about its potential for causing hypoglycemia, especially if it is consumed in large amounts or on an empty stomach.

Hypoglycemia usually has a rapid onset and progression of symptoms. The signs and symptoms of hypoglycemia can be divided into two categories: (1) those caused by altered cerebral function and (2) those related to activation of the autonomic nervous system. Because the brain relies on blood glucose as its main energy source, hypoglycemia produces behaviors related to altered cerebral function. Headache, difficulty in problem solving, disturbed or altered behavior, coma, and seizures may occur. At the onset of the hypoglycemic episode, activation of the parasympathetic nervous system often causes hunger. The initial parasympathetic response is followed by activation of the sympathetic nervous system; this causes anxiety, tachycardia, sweating, and constriction of the skin vessels (i.e., the skin is cool and clammy).

The signs and symptoms of hypoglycemia are highly variable, and not everyone manifests all or even most of the symptoms. The manifestations are particularly variable in children and in elderly people. Elderly people may not display the typical autonomic responses associated with hypoglycemia but frequently develop signs of impaired function of the central nervous system, including mental confusion. Some people develop hypoglycemic unawareness. Unawareness of hypoglycemia should be suspected in people who do not report symptoms when their blood glucose concentrations are less than 50 to 60 mg/dL (2.8 to 3.3 mmol/L). This occurs most commonly in people who have a longer duration of diabetes and A1C levels within the normal range.[43] Some medications, such as β-adrenergic blocking drugs, interfere with the sympathetic response normally seen in hypoglycemia. If hypoglycemia occurs with α-glucosidase inhibitors, it should be treated with glucose (dextrose) and not sucrose (table sugar), whose breakdown may be blocked by the action of the α-glucosidase inhibitors.

The most effective treatment of an insulin reaction is the immediate administration of 15 to 20 g of glucose in a concentrated carbohydrate source, which can be repeated as necessary. Monosaccharides such as glucose, which can be absorbed directly into the bloodstream, work best. Complex carbohydrates can be administered after the acute reaction has been controlled to sustain blood glucose levels. It is important not to overtreat hypoglycemia and cause hyperglycemia. Alternative methods for increasing blood glucose may be required when the person having the reaction is unconscious or unable to swallow. Glucagon may be given intramuscularly or subcutaneously. Glucagon acts by hepatic glycogenolysis to raise blood glucose. Because the liver contains only a limited amount of glycogen (approximately 75 g), glucagon is ineffective in people whose glycogen stores have been depleted. In situations of severe or life-threatening hypoglycemia, it may be necessary to administer glucose (20 to 50 mL of a 50% solution) intravenously.

The Somogyi Effect and Dawn Phenomenon

The *Somogyi effect* describes a cycle of insulin-induced posthypoglycemic episodes. In 1924, Joslin and associates noticed that hypoglycemia was associated with alternate episodes of hyperglycemia. It was not until 1959 that Somogyi presented the results of his 20 years of studies, which confirmed the observation that "hypoglycemia begets hyperglycemia."[45] In people with diabetes, insulin-induced hypoglycemia produces a compensatory increase in blood levels of catecholamines, glucagon, cortisol, and growth hormone. These counterregulatory hormones cause blood glucose to become elevated and produce some degree of insulin resistance. The cycle begins when the increase in blood glucose and insulin resistance is treated with larger insulin doses. The hypoglycemic

episode often occurs during the night or at a time when it is not recognized, rendering the diagnosis of the phenomenon more difficult.

Research suggests that even rather mild insulin-associated hypoglycemia, which may be asymptomatic, can cause hyperglycemia in people with type 1 diabetes through the recruitment of counterregulatory mechanisms, although the insulin action does not wane. A waning of insulin's effects when it occurs (i.e., end of the duration of action) causes an exacerbation of the posthypoglycemic hyperglycemia that occurs and accelerates its development. These findings may explain the labile nature of the disease in some people with diabetes. Measures to prevent hypoglycemia and the subsequent activation of counterregulatory mechanisms include a redistribution of dietary carbohydrates and an alteration in insulin dose or time of administration.[46]

The *dawn phenomenon* is characterized by increased levels of fasting blood glucose or insulin requirements, or both, between 5 and 9 AM without antecedent hypoglycemia. It occurs in people with type 1 or type 2 diabetes. It has been suggested that a change in the normal circadian rhythm for glucose tolerance, which usually is higher during the later part of the morning, is altered in people with diabetes.[47] Growth hormone has been suggested as a possible factor. When the dawn phenomenon occurs alone, it may produce only mild hyperglycemia, but when it is combined with the Somogyi effect, it may produce profound hyperglycemia.

Chronic Complications

The chronic complications of diabetes include disorders of the microvasculature (i.e., neuropathies, nephropathies, and retinopathies), macrovascular complications (i.e., coronary artery, cerebral vascular, and peripheral vascular disease), and foot ulcers (Fig. 33-12). The level of chronic hyperglycemia is the best-established concomitant factor associated with diabetic complications.[48,49] The Diabetes Control and Complications Trial (DCCT), which was conducted with 1441 patients with type 1 diabetes, demonstrated that the incidence of retinopathy, nephropathy, and neuropathy can be reduced by intensive diabetic treatment.[49] Similar results have been demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS) in 5000 patients with type 2 diabetes.[50]

Theories of Pathogenesis

The interest among researchers in explaining the causes and development of chronic lesions in a person with diabetes has led to a number of theories. At least three distinct metabolic pathways have been implicated in long-term complications of diabetes: intracellular hyperglycemia and disturbance in polyol pathways, formation of advanced glycation end products, and activation of protein kinase C.[3,48,51]

Polyol Pathway. A polyol is an organic compound that contains three or more hydroxyl (OH) groups. The polyol pathway refers to the intracellular mechanisms responsible for changing the number of hydroxyl units on a glucose molecule. In the sorbitol pathway, glucose is transformed first to sorbitol and then to fructose. This process is activated by the enzyme aldose reductase. Although glucose is converted readily to sorbitol, the rate at which sorbitol can be converted to fructose and then metabolized is limited. Sorbitol is osmotically active, and it has been hypothesized that the presence of excess intracellular amounts may alter cell function in those tissues that use this pathway (e.g., lens, kidneys, nerves, blood vessels). In the lens, for example, the osmotic effects of sorbitol cause swelling and opacity. Increased sorbitol also is associated with a decrease in myoinositol and reduced adenosine triphosphatase activity. The reduction of these compounds may contribute to the pathogenesis

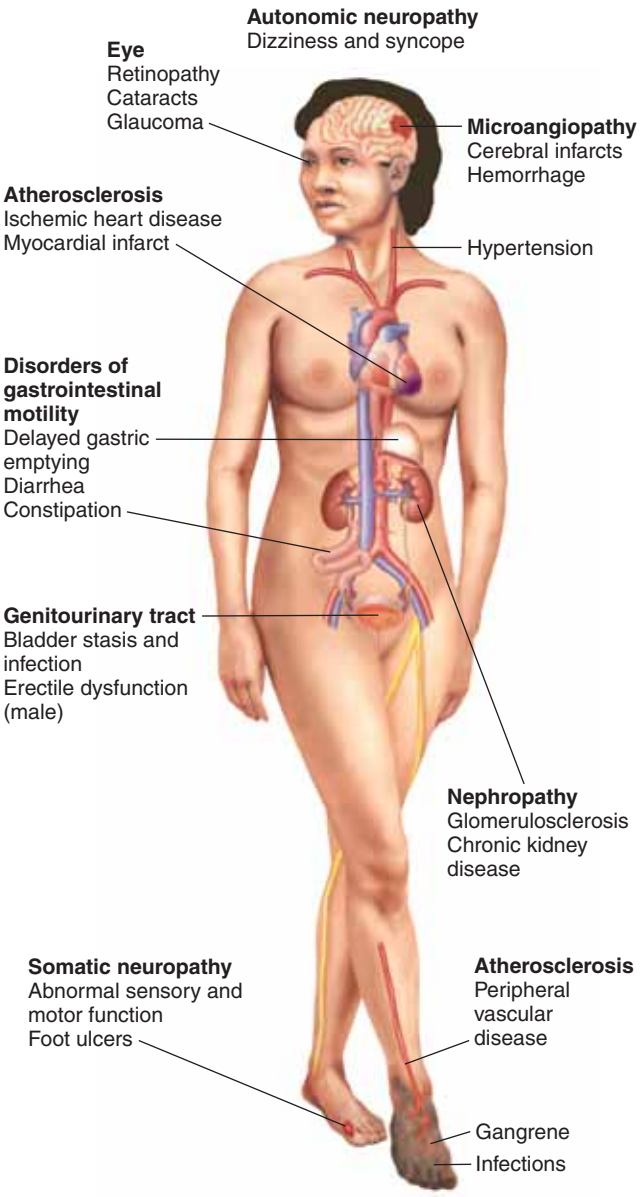


FIGURE 33-12. Long-term complications of diabetes mellitus.

Chronic Complications of Diabetes

- The chronic complications of diabetes result from elevated blood glucose levels and associated impairment of lipid and other metabolic pathways.
- Diabetic nephropathy, which is a leading cause of chronic kidney disease, is associated with the increased work demands and microalbuminuria imposed by poorly controlled blood glucose levels.
- Diabetic retinopathy, which is a leading cause of blindness, is closely linked to elevations in blood glucose and hyperlipidemia seen in persons with uncontrolled diabetes.
- Diabetic neuropathies, which can affect the somatic and autonomic nervous systems, result from the demyelinating effect of long-term uncontrolled diabetes.
- Macrovascular disorders such as coronary heart disease, stroke, and peripheral vascular disease reflect the combined effects of unregulated blood glucose levels, elevated blood pressure, and hyperlipidemia.
- The chronic complications of diabetes are best prevented by measures aimed at tight control of blood glucose levels, maintenance of normal lipid levels, and control of hypertension.

of neuropathies caused by Schwann cell damage. Aldose reductase inhibitors are in development with the aim of reducing complications resulting from this pathway; however, to date none of them has been successful for a variety of reasons.

Formation of Advanced Glycation End Products. Glycoproteins, or what could be called *glucose proteins*, are normal components of the basement membrane in smaller blood vessels and capillaries. These glycoproteins are also termed *advanced glycation end products* (AGEs). It has been suggested that the increased intracellular concentration of glucose associated with uncontrolled blood glucose levels in diabetes favors the formation of AGEs. These abnormal glycoproteins are thought to produce structural defects in the basement membrane of the microcirculation and to contribute to eye, kidney, and vascular complications. Some of the altered cellular functions resulting from AGEs are due to binding to specific receptors for AGEs (RAGEs).

Protein Kinase C. Diacylglycerol (DAG) and protein kinase C (PKC) are critical intracellular signaling molecules that can regulate many vascular functions, including permeability, vasodilator release, endothelial activation, and growth factor signaling. Levels of DAG and PKC are elevated in diabetes. Activation of PKC in blood vessels of the retina, kidney, and nerves can produce vascular damage. A PKC inhibitor is currently in clinical trials for diabetic retinopathy and neuropathy, but has shown variable results.[3]

Neuropathies

Although the incidence of neuropathies is high among people with diabetes, it is difficult to document exactly how many people are affected by these disorders because of the diversity in clinical manifestations and because the condition often is far advanced before it is recognized. Results of the DCCT study showed that intensive diabetic therapy can reduce the incidence of clinical neuropathy by 60% compared with conventional therapy.[52]

Two types of pathologic changes have been observed in connection with diabetic neuropathies. The first is a thickening of the walls of the nutrient vessels that supply the nerve, leading to the assumption that vessel ischemia plays a major role in the development of these neural changes. The second finding is a segmental demyelinization process that affects the Schwann cell. This demyelinization process is accompanied by a slowing of nerve conduction.

Although there are several methods for classifying the diabetic peripheral neuropathies, a simplified system divides them into the somatic and autonomic nervous system neuropathies (Chart 33-2).

Somatic Neuropathy. A distal symmetric polyneuropathy, in which loss of function occurs in a stocking–glove pattern, is the most common form of peripheral neuropathy. Somatic sensory involvement usually occurs first and usually is bilateral and symmetric, and associated with diminished perception of vibration, pain, and temperature, particularly in the lower extremities.[53] In addition to the discomforts associated with the loss of sensory or motor function, lesions in the peripheral nervous system predispose a person with diabetes to other complications. The loss of feeling, touch, and position sense increases the risk of falling. Impairment of temperature and pain sensation increases the risk of serious burns and injuries to the feet. Denervation of the small muscles of the foot result in clawing of the toes and displacement of the submetatarsal fat pad anteriorly. These changes, together with joint and connective tissue changes, alter the biomechanics of the foot, increasing plantar pressure and predisposing to development of foot trauma and ulcers.[53]

Painful diabetic neuropathy involves the somatosensory neurons that carry pain impulses. This disorder, which causes hypersensitivity to light touch and occasionally severe "burning pain," particularly at night, can become physically and emotionally disabling.[53]

Autonomic Neuropathy. The autonomic neuropathies involve disorders of sympathetic and parasympathetic nervous system function. There may be disorders of vasomotor function, decreased cardiac responses, inability to

CHART 33-2 Classification of Diabetic Neuropathies

Somatic

Polyneuropathies (bilateral sensory)
- Paresthesias, including numbness and tingling
- Impaired pain, temperature, light touch, two-point discrimination, and vibratory sensation
- Decreased ankle and knee-jerk reflexes

Mononeuropathies
- Involvement of a mixed nerve trunk that includes loss of sensation, pain, and motor weakness

Amyotrophy
- Associated with muscle weakness, wasting, and severe pain of muscles in the pelvic girdle and thigh

Autonomic

Impaired vasomotor function
- Postural hypotension

Impaired gastrointestinal function
- Gastric atony
- Diarrhea, often postprandial and nocturnal

Impaired genitourinary function
- Paralytic bladder
- Incomplete voiding
- Erectile dysfunction
- Retrograde ejaculation

Cranial nerve involvement
- Extraocular nerve paralysis
- Impaired pupillary responses
- Impaired special senses

empty the bladder, gastrointestinal motility problems, and sexual dysfunction.[54] Defects in vasomotor reflexes can lead to dizziness and syncope due to postural hypotension when the person moves from the supine to the standing position (see Chapter 18). Incomplete emptying of the bladder predisposes to urinary stasis and bladder infection and increases the risk of renal complications.

Gastrointestinal motility disorders are common in persons with long-standing diabetes. The symptoms vary in severity and include gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis (delayed emptying of stomach) is commonly seen in persons with diabetes.[55] The disorder is characterized by complaints of epigastric discomfort, nausea, postprandial vomiting, bloating, and early satiety. Abnormal gastric emptying also jeopardizes the regulation of the blood glucose level. Diarrhea is another common symptom seen mostly in persons with poorly controlled type 1 diabetes and autonomic neuropathy.[56] The pathogenesis is thought to be multifactorial. Diabetic diarrhea is typically intermittent, watery, painless, and nocturnal and may be associated with fecal incontinence.

In the male, disruption of sensory and autonomic nervous system function may cause sexual dysfunction (see Chapter 39). Diabetes is the leading physiologic cause of erectile dysfunction, and it occurs in both type 1 and type 2 diabetes. Of the 7.8 million men with diabetes in the United States, 30% to 60% have erectile dysfunction.[54]

Nephropathies

Diabetic nephropathy, a term used to describe the combination of lesions that occur concurrently in the diabetic kidney, is the leading cause of chronic kidney disease in persons starting renal replacement therapy (see Chapter 26).[57] Not all people with diabetes develop clinically significant nephropathy; for this reason, attention is focusing on risk factors for the development of this complication. Among the suggested risk factors are genetic and familial predisposition, elevated blood pressure, poor glycemic control, smoking, hyperlipidemia, and microalbumuria.[11,58] Diabetic nephropathy occurs in family clusters, suggesting a familial predisposition, although this does not exclude the possibility of environmental factors shared by siblings. The risk for development of kidney disease is greater among Native Americans, Hispanic Americans (especially Mexican Americans), and African Americans.[11,58]

The most common kidney lesions in people with diabetes are those that affect the glomeruli. Various glomerular changes may occur in people with diabetic nephropathy, including capillary basement membrane thickening, diffuse glomerular sclerosis, and nodular glomerulosclerosis (see Chapter 25). Nodular glomerulosclerosis, also called *intercapillary glomerulosclerosis* or *Kimmelstiel-Wilson syndrome*, is a form of glomerulosclerosis that involves the development of nodular lesions in the glomerular capillaries of the kidneys, causing impaired blood flow with progressive loss of kidney function and, eventually, renal failure. Nodular glomerulosclerosis is thought to occur only in people with diabetes. Changes in the basement membrane in diffuse nodular glomerulosclerosis allow plasma proteins to escape in the urine, causing albuminuria, hypoalbuminemia, edema, and other signs of impaired kidney function.

Kidney enlargement, nephron hypertrophy, and hyperfiltration are early accompaniments of diabetes, reflecting the increased work performed by the kidneys in reabsorbing excessive amounts of glucose. One of the first manifestations of diabetic nephropathy is an increase in urinary albumin excretion (i.e., microalbuminuria), which is easily assessed by laboratory methods. Microalbuminuria is defined as a urine protein loss between 30 and 300 mg/day or an albumin-to-creatinine ratio (A/C ratio) between 30 and 300 μg/mg (normal <30 μg/mg) from a spot urine collection.[58] It is recommended that the A/C ratio be the preferred screen for microalbuminuria. Both systolic and diastolic forms of hypertension accelerate the progression of diabetic nephropathy. Even moderate lowering of blood pressure can decrease the risk of chronic kidney disease.[11]

Measures to prevent diabetic nephropathy or its progression in persons with diabetes include achievement of glycemic control, maintenance of blood pressure control (<130/80 mm Hg), prevention or reduction in the level of proteinuria (using angiotensin-converting enzyme

inhibitors or angiotensin receptor blockers, or protein restriction in selected patients), treatment of hyperlipidemia, and smoking cessation in people who smoke.[11,57] Smoking increases the risk of chronic kidney disease in both persons with and without diabetes. People with type 2 diabetes who smoke have a greater risk of microalbuminuria, and their rate of progression to chronic kidney disease is approximately twice as rapid as in those who do not smoke.[11]

Retinopathies

Diabetes is the leading cause of acquired blindness in the United States.[58,59] Although people with diabetes are at increased risk for development of cataracts and glaucoma, retinopathy is the most common pattern of eye disease. Diabetic retinopathy is estimated to be the most frequent cause of newly diagnosed blindness among Americans between the ages of 20 and 74 years.[59]

Diabetic retinopathy is characterized by abnormal retinal vascular permeability, microaneurysm formation, neovascularization and associated hemorrhage, scarring, and retinal detachment[59] (see Chapter 38). Twenty years after the onset of diabetes, nearly all people with type 1 diabetes and more than 60% of people with type 2 diabetes have some degree of retinopathy. Pregnancy, puberty, and cataract surgery can accelerate these changes.[59] Although there has been no extensive research on risk factors associated with diabetic retinopathy, they appear to be similar to those for other complications. Among the suggested risk factors associated with diabetic retinopathy are poor glycemic control, elevated blood pressure, and hyperlipidemia. The strongest case for control of blood glucose comes from the DCCT and UKPDS studies, which demonstrated a reduction in retinopathy with improved glucose control.[49,50]

Because of the risk of retinopathy, it is important that people with diabetes have regular dilated eye examinations. The recommendation for follow-up examinations is based on the type of examination that was done and the findings of that examination. People with persistently elevated glucose levels or proteinuria should be examined yearly.[59] Women who are planning a pregnancy should be counseled on the risk of development or progression of diabetic retinopathy. Women with diabetes who become pregnant should be followed closely throughout pregnancy. This does not apply to women in whom GDM develops because such women are not at risk for development of diabetic retinopathy.

People with macular edema, moderate to severe nonproliferative retinopathy, or any proliferative retinopathy should receive the care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. Methods used in the treatment of diabetic retinopathy include the destruction and scarring of the proliferative lesions with laser photocoagulation. The use of antagonists to growth factors (e.g., vascular endothelial growth factor) may also play a role in management.

Macrovascular Complications

Diabetes mellitus is a major risk factor for atherosclerotic coronary artery disease, cerebrovascular disease, and peripheral vascular disease. The prevalence of these macrovascular complications is increased twofold to fourfold in people with diabetes.

Multiple risk factors for macrovascular disease, including obesity, hypertension, hyperglycemia, hyperinsulinemia, hyperlipidemia, altered platelet function, endothelial dysfunction, systemic inflammation (as evidenced by increased CRP), and elevated fibrinogen levels, frequently are found in people with diabetes. There appear to be differences between type 1 and type 2 diabetes in terms of duration of disease and development of macrovascular disease. In people with type 2 diabetes, macrovascular disease may be present at the time of diagnosis. Indeed, approximately 50% of people with type 2 diabetes have some form of complication at presentation (either microvascular or macrovascular). The reason for these discrepancies has been attributed to the associated cardiovascular risk factors that are part of the metabolic syndrome.[19,20]

Aggressive management of cardiovascular risk factors should include smoking cessation, hypertension, lipid lowering, diabetes control, and antiplatelet agents (aspirin or clopidogrel) if not contraindicated[11,19] (see Chapter 18). If treatment is warranted for peripheral vascular disease, the peroneal arteries between the knees and ankles commonly are involved in diabetes, making revascularization difficult.

Diabetic Foot Ulcers

Foot problems are common among people with diabetes and may become severe enough to cause ulceration, infection, and, eventually, the need for amputation.[60,61] Foot problems have been reported as the most common complication leading to hospitalization among people with diabetes. In people with diabetes, lesions of the feet represent the effects of neuropathy and vascular insufficiency. Approximately 60% to 70% of people with diabetic foot ulcers have neuropathy without vascular disease, 15% to 20% have vascular disease, and 15% to 20% have neuropathy and vascular disease.[60]

Distal symmetric neuropathy is a major risk factor for foot ulcers. People with sensory neuropathies have impaired pain sensation and often are unaware of the constant trauma to the feet caused by poorly fitting shoes, improper weight bearing, hard objects or pebbles in the shoes, or infections such as athlete's foot. Neuropathy prevents people from detecting pain; they are unable to adjust their gait to avoid walking on an area of the foot where pressure is causing trauma and necrosis. Motor neuropathy with weakness of the intrinsic muscles of the foot may result in foot deformities, which lead to focal areas of high pressure. When the abnormal focus of pressure is coupled with loss of sensation, a foot ulcer can occur. Common sites of trauma are the back of the heel, the plantar metatarsal area, or the great toe, where weight is borne during walking (Fig. 33-13).

All persons with diabetes should receive a full foot examination at least once a year. This examination

FIGURE 33-13. Neuropathic ulcers occur on pressure points in areas with diminished sensation in diabetic polyneuropathy. Pain is absent (and therefore the ulcer may go unnoticed). (From Bates B.B. [1995]. *A guide to physical examination and history taking* [6th ed.]. Philadelphia: J.B. Lippincott.)

should include assessment of protective sensation, foot structure and biomechanics, vascular status, and skin integrity.[3,61] Evaluation of neurologic function should include a somatosensory test using either the Semmes-Weinstein monofilament or vibratory sensation. The Semmes-Weinstein monofilament is a simple, inexpensive device for testing sensory status (Fig. 33-14). The monofilament is held in the hand or attached to a handle at one end. When the unattached or unsupported end of the monofilament is pressed against the skin until it buckles or bends slightly, it delivers 10 g of pressure at the point of contact.[61] The test consists of having the person being tested report at which of two moments he or she is being touched by the monofilament. For example, the examiner will call out "one" and then "two" and briefly touch the monofilament to the site at one of the two test times. Between 4 and 10 sites per foot are touched. An incorrect response at even one site indicates increased risk of neuropathy and foot complications.

Because of the constant risk of foot problems, it is important that people with diabetes wear shoes that have been fitted correctly and inspect their feet daily, looking for blisters, open sores, and fungal infection (e.g., athlete's foot) between the toes. If their eyesight is poor, a family member should do this for them. In the event a lesion is detected, prompt medical attention is needed to prevent serious complications. Specially designed shoes have been demonstrated to be effective in preventing relapses in people with previous ulcerations.[61] Smoking should be avoided because it causes vasoconstriction and contributes to vascular disease. Because cold produces vasoconstriction, appropriate foot coverings should be used to keep the feet warm and dry. Toenails should be cut straight across to prevent ingrown toenails. The toenails often are thickened and deformed, requiring the services of a podiatrist.

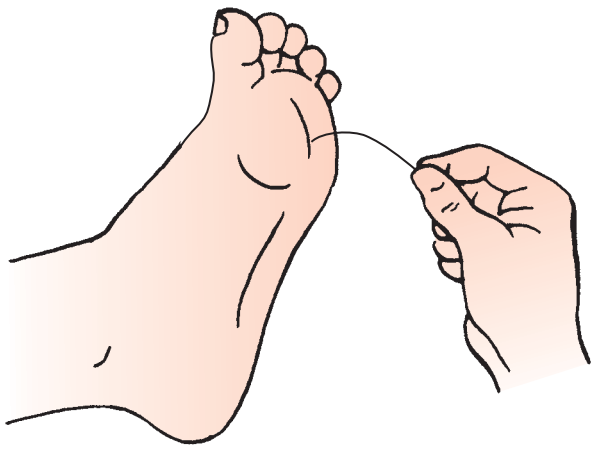


FIGURE 33-14. Use of a monofilament in testing for impaired sensation in the foot of a person with diabetes.

Persons with diabetes mellitus develop more extensive and rapidly progressive peripheral vascular disease than do individuals without diabetes. Cardiovascular risk factors should be addressed in patients with diabetic ulcers and peripheral vascular disease. Ulcers that are resistant to standard therapy may respond to application of growth factors. Growth factors provide a means by which cells communicate with each other and can have profound effects on cell proliferation, migration, and extracellular matrix synthesis. Becaplermin, a topical preparation of recombinant human platelet-derived growth factor (PDGF), is used in the treatment of neuropathic lower extremity ulcers.

Infections

Although not specifically an acute or a chronic complication, infections are a common concern of people with diabetes. Certain types of infections occur with increased frequency in people with diabetes: soft tissue infections of the extremities, osteomyelitis, urinary tract infections and pyelonephritis, candidal infections of the skin and mucous surfaces, dental caries and periodontal disease, and tuberculosis.[62,63] Controversy as to whether infections are more common in people with diabetes or whether infections seem more prevalent because they often are more serious in people with diabetes.

Suboptimal response to infection in a person with diabetes is caused by the presence of chronic complications, such as vascular disease and neuropathies, and by the presence of hyperglycemia and altered neutrophil function. Sensory deficits may cause a person with diabetes to ignore minor trauma and infection, and vascular disease may impair circulation and delivery of blood cells and other substances needed to produce an adequate inflammatory response and effect healing. Pyelonephritis and urinary tract infections are relatively common in persons with diabetes, and it has been suggested that these infections may bear some relation to the presence of a neurogenic bladder or nephrosclerotic changes in the kidneys. Hyperglycemia and glycosuria may influence the growth of microorganisms and increase the severity of the infection. Diabetes and elevated blood glucose levels also may impair host defenses such as the function of neutrophils and immune cells. Polymorphonuclear leukocyte function, particularly adherence, chemotaxis, and phagocytosis, is depressed in persons with diabetes, particularly those with poor glycemic control.

In summary, diabetes mellitus is a disorder of carbohydrate, protein, and fat metabolism resulting from an imbalance between insulin availability and insulin need. The disease can be classified as type 1 diabetes, in which there is destruction of beta cells and an absolute insulin deficiency, or type 2 diabetes, in which there is a lack of insulin availability or effectiveness. Type 1 diabetes can be further subdivided into type 1A immune-mediated diabetes, which is thought to be caused by autoimmune mechanisms, and type 1B idiopathic diabetes, for which the cause is unknown. Other specific types of diabetes include secondary forms of carbohydrate intolerance, which occur secondary to some other condition that destroys beta cells (e.g., pancreatic disorders) or endocrine diseases that cause increased production of glucose by the liver and decreased use of glucose by the tissues (e.g., Cushing syndrome). Gestational diabetes develops during pregnancy, and although glucose tolerance often returns to normal after childbirth, it indicates an increased risk for the development of diabetes. The metabolic syndrome represents a constellation of metabolic abnormalities characterized by obesity, insulin resistance, high triglyceride levels and low HDL levels, hypertension, cardiovascular disease, and increased risk for development of type 2 diabetes.

The most commonly identified symptoms of type 1 diabetes are polyuria, polydipsia, polyphagia, and weight loss despite normal or increased appetite. Although persons with type 2 diabetes may present with one or more of these symptoms, they are often asymptomatic initially. The diagnosis of diabetes mellitus is based on clinical signs of the disease, fasting blood glucose levels, random plasma glucose measurements, and results of the glucose tolerance test. Glycosylation involves the irreversible attachment of glucose to the hemoglobin molecule; the measurement of glycosylated hemoglobin (A1C) provides an index of blood glucose levels over several months. Self-monitoring provides a means of maintaining near-normal blood glucose levels through frequent testing of blood glucose and adjustment of insulin dosage.

Dietary management focuses on maintaining a well-balanced diet, controlling calories to achieve and maintain an optimum weight, and regulating the distribution of carbohydrates, proteins, and fats. Two types of antidiabetic agents are used in the management of diabetes: injectable insulin (and newer injectable agents including amylin and GLP-1 analogs) and oral diabetic drugs. Type 1 diabetes, and sometimes type 2, requires treatment with injectable insulin. Oral antidiabetic drugs include the insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, and DPP-4 enzyme inhibitors. These drugs require a functioning pancreas and may be used in the treatment of type 2 diabetes.

The metabolic disturbances associated with diabetes affect almost every body system. The acute complications of diabetes include diabetic ketoacidosis, hyperglycemic hyperosmolar state, and hypoglycemia in people with insulin-treated diabetes. The chronic complications of diabetes affect the microvascular system (including the retina, kidneys, and peripheral nervous system) and the macrovascular system (coronary, cerebrovascular, and peripheral arteries). The diabetic foot is usually a combination of both microvascular and macrovascular dysfunction. Infection is also a frequent cofactor in the diabetic foot.

REVIEW EXERCISES

1. A 6-year-old boy is admitted to the emergency department with nausea, vomiting, and abdominal pain. He is very lethargic; his skin is warm, dry, and flushed; his pulse is rapid; and he has a sweet smell to his breath. His parents relate that he has been very thirsty during the past several weeks, his appetite has been poor, and he has been urinating frequently. His initial plasma glucose is 420 mg/dL (23.1 mmol/L), and a urine test for ketones is strongly positive.

A. What is the most likely cause of this boy's elevated blood glucose and ketonuria?
B. Explain his presenting signs and symptoms in terms of the elevated blood glucose and metabolic acidosis.
C. What type of treatment will this boy require?

2. A 53-year-old accountant presents for his routine yearly examination. His history indicates that he was found to have a fasting glucose of 120 mg/dL (6.7 mmol/L) on two prior occasions. Currently, he is asymptomatic. He has no other medical problems and does not use any medications. He neither smokes nor drinks alcohol. His father had type 2 diabetes at age 60 years. His physical examination reveals a blood pressure of 125/80 mm Hg, BMI of 32 kg/m^2, and waist circumference of 45 in (114 cm). Laboratory study results are as follows: complete blood count (CBC), thyroid-stimulating hormone (TSH), and alanine aminotransferase (ALT) are within normal limits. The lipid panel shows that his HDL cholesterol (30 mg/dL [0.8 mmol/L]) and LDL cholesterol (136 mg/dL [3.5 mmol/L]) are within the normal range, and triglycerides are elevated (290 mg/dL [2.3 mmol/L]; normal is <165 mg/dL [1.9 mmol/L]).

A. What is this man's probable diagnosis?
B. Based on this man's blood glucose level and the ADA diabetes classification system, what diabetic status would you place this man in? Does he need a 75-g OGTT for further assessment of his IFG?
C. His OGTT test result reveals a 2-hour glucose value of 175 mg/dL (9.63 mmol/L). What is the diagnosis? What type of treatment would be appropriate for this man?

REFERENCES

1. National Diabetes Information Clearing House. (2007). *Diabetes statistics*. [Online] Available: http://diabetes.niddk.nih.gov/DM/PUBS/statistics/#allages. Accessed February 4, 2010.
2. Guyton A., Hall J.E. (2006). *Medical physiology* (11th ed., pp. 961–977). Philadelphia: Elsevier Saunders.
3. Masharani U., German M.S. (2007). Pancreatic hormones and diabetes mellitus. In Gardner D.G., Shoback D. (Eds.), *Greenspan's basic and clinical endocrinology* (8th ed., pp. 661–747). New York: Lange Medical Books/McGraw-Hill.
4. Shepard P.R., Kahn B. (1999). Glucose transporters and insulin action. *New England Journal of Medicine* 341, 248–256.
5. Riddle M.C., Drucker D.J. (2006). Emerging therapies mimicking the effects of amylin and glucagon-like peptide-1. *Diabetes Care* 29, 435–449.
6. Drucker D.J. (2006). The biology of incretin hormones. *Cell Metabolism* 3, 153–165.
7. Goldfine I.R., Youngren J.F. (1998). Contributions of the *American Journal of Physiology* to the discovery of insulin. *American Journal of Physiology: Endocrinology and Metabolism* 274, E207–E209.
8. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (1997). Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 10, 1183–1197.
9. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (2003). Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26(11), 3160–3167.
10. American Diabetes Association. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33(Suppl 1), S62–S69.
11. American Diabetes Association. (2010). Standards of medical care in diabetes—2010. *Diabetes Care* 33(Suppl 1), S11–S61.
12. Jones K.L. (2008). Role of obesity in complicating and confusing the diagnosis and treatment of diabetes in children. *Pediatrics* 121(2), 361–368.
13. The International Diabetes Federation Consensus Workshop. (2004). Type 2 diabetes in the young: The evolving epidemic. *Diabetes Care* 27, 1798–1811.
14. Stumvolt M., Goldstein B.J., van Haeften T.W. (2005). Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet* 365, 1333–1346.
15. Gerich J.E. (2003). Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes. *Mayo Clinic Proceedings* 78, 447–456.
16. DeFronzo R.A. (2004). Pathogenesis of type 2 diabetes mellitus. *Medical Clinics of North America* 88, 787–835.
17. Matthews D.R., Cull C.A., Stratton I.M., et al., United Kingdom Prospective Diabetes Study (UKPDS) Group. (1998). UKPDS 26: Sulfonylurea failure in non-insulin-dependent diabetic patients over six years. *Diabetes Medicine* 15, 297–303.
18. Kahn S.E., Hull R.L., Utzschneider K.M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 444, 840–846.
19. Gallagher E.J., LeRoith D., Karnieli E. (2008). The metabolic syndrome—From insulin resistance to obesity and diabetes. *Endocrinology and Metabolism Clinics of North America* 37, 559–579.
20. Matfin G. (2007). Challenges in developing drugs for the metabolic syndrome. *British Journal of Diabetes and Vascular Disease* 7, 152–156.
21. Grundy S.M., Panel Chair. (2001). *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. NIH publication no. 01-3670. Bethesda, MD: National Institutes of Health.
22. Guven S., El-Bershawi A., Sonnenberg G.E., et al. (1999). Persistent elevation in plasma leptin level in ex-obese with normal body mass index: Relation to body composition and insulin sensitivity. *Diabetes* 48, 347–352.
23. Bays H., Mandarino L., DeFronzo R.A. (2004). Role of adipocyte, free fatty acid, and ectopic fat in pathogenesis of type 2 diabetes: Peroxisomal proliferator-activated receptor agonists provide a rationale therapeutic approach. *Journal of Clinical Endocrinology and Metabolism* 89, 463–478.
24. Kadowaki T., Yamauchi T., Kubota N., et al. (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *Journal of Clinical Investigation* 116, 1784–1792.
25. Kuritzkes D.R., Currier J. (2003). Cardiovascular risk factors and antiretroviral therapy. *New England Journal of Medicine* 348, 679–680.
26. Serlin D.C., Lash R.W. (2009). Diagnosis and management of gestational diabetes. *American Family Physician* 80(1), 57–62.
27. Metzger B.E., Bucanan T.A., Coustan D.R., et al. (2007). Summary and recommendations of the Fifth International Workshop—Conference on Gestational Diabetes. *Diabetes Care* 30(Suppl 2), S251–S260.
28. American Diabetes Association. (2004). Tests of glycemia in diabetes. *Diabetes Care* 27(Suppl 1), S91–S93.
29. Bantle J.P., Wylie-Rosett J., Albright A.L., et al. (2006). Nutritional recommendations and interventions for diabetes—2006: A position statement of the American Diabetes Association. *Diabetes Care* 29, 2140–2157.
30. American Diabetes Association. (2004). Physical activity/exercise and diabetes mellitus. *Diabetes Care* 27(Suppl 1), S55–S59.
31. Nathan D.M., Buse J.B., Davidson M.B., et al. (2006). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29, 1963–1972.
32. Nolte M.S., Karam J.H. (2007). Pancreatic hormones and antidiabetic drugs. In Katzung B.G. (Ed.), *Basic and clinical pharmacology* (10th ed., pp. 683–703). New York: McGraw-Hill Medical.
33. Erdmann E., Wilcox R.G. (2008). Weighing up cardiovascular benefits of thiazolidinedione therapy: The impact of increased risk of heart failure. *European Heart Journal* 29, 12–20.
34. Meier B.M., Kraenzlin M.E., Meier C.R. (2009). Risk of fractures with glitazones: A critical review of evidence to date. *Drug Safety* 32(7), 539–547.
35. Zangeneh F., Kudva Y.C., Basu A. (2003). Insulin sensitizers. *Mayo Clinic Proceedings* 78, 471–479.
36. Davidson J.A. (2009). Advances in therapy of type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors. *Cleveland Clinic Journal of Medicine* 75(Suppl 5), S28–S38.
37. Hirsch I. (2005). Insulin analogs. *New England Journal of Medicine* 352, 174–183.
38. American Diabetes Association. (2004). Continuous subcutaneous insulin infusion. *Diabetes Care* 27(Suppl 1), S110.
39. American Diabetes Association. (2004). Pancreas transplantation for patients with type 1 diabetes. *Diabetes Care* 27(Suppl 1), S105.
40. American Diabetes Association. (2004). Hyperglycemic crises in patients with diabetes mellitus. *Diabetes Care* 27(Suppl 1), S94–S102.
41. Wilson J.F. (2010). In the clinic. Diabetes ketoacidosis. *Annals of Internal Medicine* 152(1), ITC1-1–ITC1-16.
42. American Diabetes Association. (2006). Diabetic ketoacidosis in infants, children and adolescents. *Diabetes Care* 29, 1150–1159.
43. Masharani U., Gitelman S.E. (2007). Hypoglycemic disorders. In Gardner D.G., Shoback D. (Eds.), *Greenspan's basic and clinical endocrinology* (8th ed., pp. 748–769). New York: Lange Medical Books/McGraw-Hill.

44. American Diabetes Association Workgroup on Hypoglycemia. (2005). Defining and reporting hypoglycemia in diabetes: A report of the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 28, 1245–1249.
45. Somogyi M. (1959). Exacerbation of diabetes in excess insulin action. *American Journal of Medicine* 26, 169–191.
46. Bolli G.B., Gotterman I.S., Campbell P.J. (1984). Glucose counterregulation and waning of insulin in the Somogyi phenomenon (posthypoglycemic hyperglycemia). *New England Journal of Medicine* 311, 1214–1219.
47. Bolli G.B., Gerich J.E. (1984). The dawn phenomenon: A common occurrence in both non-insulin and insulin dependent diabetes mellitus. *New England Journal of Medicine* 310, 746–750.
48. Sheetz M.J., King G.L. (2002). Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *Journal of the American Medical Association* 288, 2579–2588.
49. The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensified treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* 329, 955–977.
50. Stratton I.M., Adler A.I., Neil H.A., et al. (2000). Association of glycaemia with macrovascular and microvascular complications in type 2 diabetes (UKPDS 35): Prospective observational study. *British Medical Journal* 321, 405–412.
51. Maitra A. (2010). The endocrine system. In Kumar V., Abbas A.K., Fausto N., et al. *Robbins and Cotran pathologic basis of diseases* (8th ed., pp. 1130–1146). Philadelphia: Saunders Elsevier.
52. Boulton A.J.M., Vinik A.I., Arezzo J.C., et al. (2005). Diabetic neuropathies. *Diabetes Care* 28, 956–962.
53. Boulton A.J.M., Malik R.A. (2004). Diabetic somatic neuropathies. *Diabetes Care* 27, 1458–1486.
54. AACE Male Sexual Dysfunction Taskforce. (2003). AACE medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: A couple's problem—2003 update. *Endocrine Practice* 9, 77–95.
55. Camilleri M. (2007). Diabetic gastroparesis. *New England Journal of Medicine* 356, 820–829.
56. Shakil A., Church R.J., Rao S.S. (2008). Gastrointestinal complications of diabetes. *American Family Physician* 77(12), 1703–1704.
57. Gross J.L., DeAzevedo M.J., Silveiro S.P., et al. (2005). Diabetic nephropathy: Diagnosis, prevention, and management. *Diabetes Care* 28, 176–188.
58. American Diabetes Association. (2004). Diabetic retinopathy. *Diabetes Care* 27(Suppl 1), S84–S87.
59. Mohamed Q., Gillies M.C., Wong T.Y. (2007). Management of diabetic retinopathy: A systematic review. *Journal of the American Medical Association* 298(8), 902–916.
60. Anderson C.A., Roukis T.S. (2007). The diabetic foot. *Surgical Clinics of North America* 87, 1149–1177.
61. American Diabetes Association. (2004). Preventative foot care in people with diabetes. *Diabetes Care* 27(Suppl 1), S63–S64.
62. Joshi N., Caputo G.M., Weitekamp M.R., et al. (1999). Infections in patients with diabetes mellitus. *New England Journal of Medicine* 341, 1906–1912.
63. Gupta S., Koirala J., Khardori R., et al. (2007). Infections in diabetes mellitus and hyperglycemia. *Infectious Disease Clinics of North America* 21, 617–638.

UNIT 10

Nervous System

Nervous Tissue Cells
- *Neurons*
- *Supporting Cells*
  - Supporting Cells of the Peripheral Nervous System
  - Supporting Cells of the Central Nervous System
- *Metabolic Requirements of Nervous Tissue*

Nerve Cell Communication
- *Action Potentials*
- *Synaptic Transmission*
  - Chemical Synaptic Transmitters

Developmental Organization of the Nervous System
- *Embryonic Development*
  - Neural Tube Defects
- *Segmental Organization*
  - Cell Columns
  - Longitudinal Tracts

Spinal Cord and Brain
- *The Spinal Cord*
  - Spinal Nerves
  - Spinal Reflexes
- *The Brain*
  - Hindbrain
  - Midbrain
  - Forebrain
  - Meninges
  - Ventricular System and Cerebrospinal Fluid
  - Blood-Brain and Cerebrospinal Fluid–Brain Barriers

The Autonomic Nervous System
- *Autonomic Efferent Pathways*
  - Sympathetic Nervous System
  - Parasympathetic Nervous System
- *Central Integrative Pathways*
- *Autonomic Neurotransmission*
  - Acetylcholine and Cholinergic Receptors
  - Catecholamines and Adrenergic Receptors

Chapter 34

Organization and Control of Neural Function

The nervous system, in coordination with the endocrine system, provides the means by which cell and tissue functions are integrated into a solitary, surviving organism. It controls skeletal muscle movement and helps to regulate cardiac and visceral smooth muscle activity. The nervous system enables the reception, integration, and perception of sensory information; it provides the substratum necessary for intelligence, anticipation, and judgment; and it facilitates adjustment to an ever-changing external environment.

Nervous Tissue Cells

The nervous system can be divided into two basic components: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and spinal cord, which is protected by the skull and vertebral column, whereas the PNS is found outside these structures. Inherent in the basic design of the nervous system is the provision for the concentration of computational and control functions in the CNS, with the PNS relaying somatic and visceral sensory (afferent) input to the CNS for processing and transmitting efferent or motor output from the CNS to effector organs throughout the body (Fig. 34-1). Functionally, the nervous system is divided into the somatic and visceral or autonomic nervous systems. The somatic (Greek *soma*, "body") nervous system provides sensory and motor innervation for all parts of the CNS and PNS except viscera, smooth muscle, and glands. The autonomic nervous system

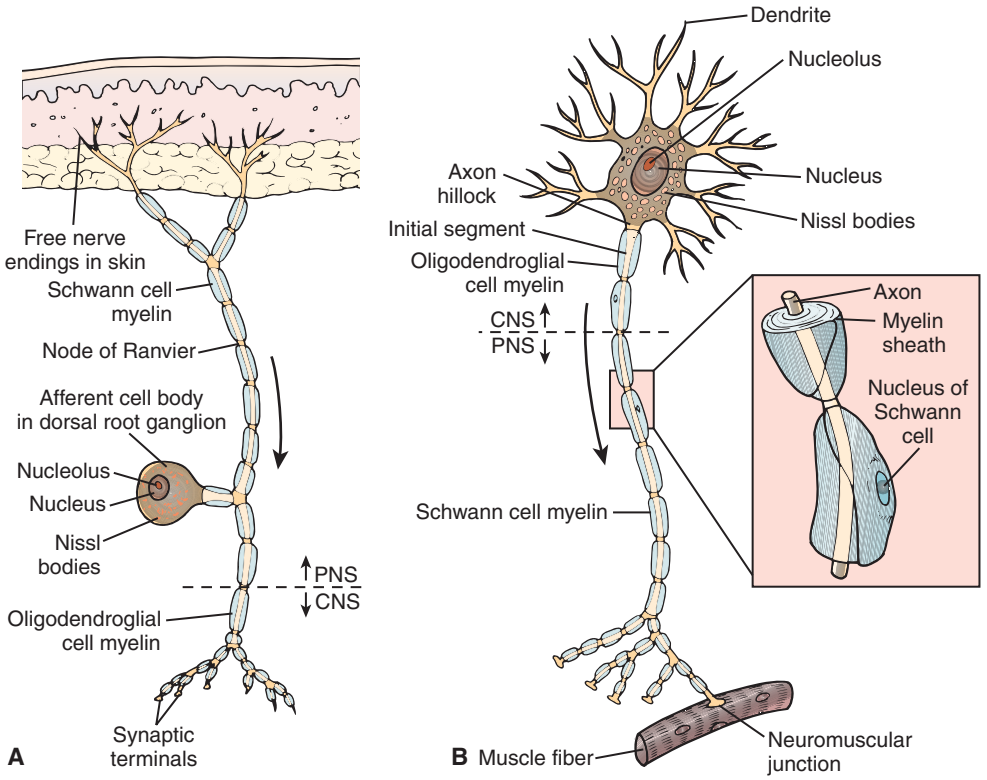


FIGURE 34-1. Afferent **(A)** and efferent neurons **(B),** showing the soma or cell body, dendrites, and axon. *Arrows* indicate the direction for conduction of action potentials.

(ANS) provides efferent motor innervation to smooth muscle, the conducting system of the heart, and glands. The ANS is further divided into a sympathetic division and a parasympathetic division.

Nervous tissue consists of two principal types of cells, neurons and supporting cells. The neurons are the functional cells of the nervous system. They exhibit membrane excitability and conductivity and secrete neurotransmitters and hormones, such as epinephrine and antidiuretic hormone. The supporting cells, such as the Schwann cells in the PNS and the glial cells in the CNS, protect the nervous system and provide metabolic support for the neurons.

Neurons

Neurons, which are the functioning cells of the nervous system, have three distinct parts: the cell body and its cytoplasm-filled processes, the dendrites and axons (Fig. 34-1). The axonal and dendritic processes form the functional connections, or synapses, with other nerve cells, receptor cells, or effector cells. Afferent, or sensory, neurons of the PNS transmit information to the CNS (see Fig. 34-1A), whereas efferent, or motor, neurons carry information away from the CNS (see Fig. 34-1B). Interspersed between the afferent and efferent neurons is a network of interconnecting neurons (also called *interneurons* or *internuncial* neurons) that modulate and control the body's response to changes in the internal and external environments.

The *cell body* of a neuron, also known as the *soma*, contains a large vesicular nucleus with one or more distinct nucleoli and a well-developed rough endoplasmic reticulum. A neuron's nucleus has the same deoxyribonucleic acid (DNA) and genetic code content that is present in other cells of the body, and its nucleolus, which is composed of portions of several chromosomes, produces ribonucleic acid (RNA) associated with protein synthesis. The cytoplasm contains large masses of ribosomes that are

The Structural Organization of the Nervous System

- The nervous system is divided into two parts: the central nervous system (CNS), consisting of the brain and spinal cord, which are located in the skull and spinal column, and the peripheral nervous system (PNS), which is located outside these structures.
- The nervous system contains two major types of cells: neurons, which are functioning cells of the nervous system, and supporting cells, which protect the nervous system and supply metabolic support.
- There are two types of neurons: afferent neurons or sensory neurons, which carry information to the CNS, and efferent neurons or motoneurons, which carry information from the CNS to the effector organs.

prominent in most neurons. These acidic RNA masses, which are involved in protein synthesis, stain as dark Nissl bodies with basic histologic stains (see Fig. 34-1B). The Nissl bodies and free ribosomes extend into the dendrites, but not into the axon. This area of the cell body, called the *axon hillock,* is free of large cytoplasmic organelles and serves as a landmark to distinguish between axons and dendrites in microscopic preparations.

The *dendrites* (from the Greek *dendron,* "tree") are multiple, branched extensions of the nerve cell body; they conduct information toward the cell body and are the main source of information for the neuron. The dendrites and cell body are studded with synaptic terminals that communicate with axons and dendrites of other neurons.

Axons are long efferent processes that project from the cell body and carry impulses away from the cell. Most neurons have only one axon; however, axons may exhibit multiple branching that results in many axonal terminals. The cytoplasm of the cell body extends to fill the dendrites and the axon. The proteins and other materials used by the axon are synthesized in the cell body and then flow down the axon through its cytoplasm.

The cell body of the neuron is equipped for a high level of metabolic activity. This is necessary because the cell body must synthesize the cytoplasmic and membrane constituents required to maintain the function of the axon and its terminals. Some of these axons extend for a distance of 1 to 1.5 m and have a volume that is 200 to 500 times greater than the cell body itself. Two axonal transport systems, one slow and one rapid, move molecules from the cell body through the cytoplasm of the axon to its terminals. Replacement proteins and nutrients slowly diffuse from the cell body, where they are transported, down the axon, moving at the rate of approximately 1 mm/day. Other molecules, such as some neurosecretory granules (e.g., neurotransmitters, neuromodulators, and neurohormones) or their precursors, are conveyed by a rapid, energy-dependent active transport system, moving at the rate of approximately 400 mm/day. For example, antidiuretic hormone and oxytocin, which are synthesized by neurons in the hypothalamus, are carried by rapid axonal transport to the posterior pituitary, where the hormones are released into the blood. A reverse rapid (i.e., retrograde) axonal transport system moves materials, including target cell messenger molecules, from axonal terminals back to the cell body.

Supporting Cells

The supporting cells of the nervous system, the Schwann cells of the PNS and the several types of glial cells of the CNS, give the neurons protection and metabolic support. The supporting cells segregate the neurons into isolated metabolic compartments, which are required for normal neural function.

The many-layered wrappings of the Schwann cells of the PNS and the oligodendroglia of the CNS produce myelin sheaths that serve to increase the velocity of nerve impulse conduction in axons. Myelin has a high lipid content, which gives it a whitish color, and hence the name *white matter* is given to the masses of myelinated fibers of the spinal cord and brain. Besides its role in increasing conduction velocity, the myelin sheath is essential for the survival of larger neuronal processes, perhaps by the secretion of neurotrophic compounds.

In some pathologic conditions, such as multiple sclerosis in the CNS and Guillain-Barré syndrome in the PNS, the myelin may degenerate or be destroyed, leaving a section of the axonal process without myelin while leaving the nearby Schwann or oligodendroglial cells intact. Unless remyelination takes place, the axon eventually dies.

Supporting Cells of the Peripheral Nervous System

Schwann cells are the supporting cells in the PNS. They produce the myelin sheath that isolates axons of neurons in the PNS from the surrounding extracellular compartment, ensure rapid conduction of nerve impulses, and aid in cleaning up PNS debris and guide the regrowth of PNS axons. During the process of myelination, the Schwann cell wraps around each nerve process several times in a "jelly roll" fashion (Fig. 34-2). Schwann cells line up along the neuronal process, and each of these cells forms its own discrete myelin segment. Successive Schwann cells are separated by short extracellular fluid gaps, called the *nodes of Ranvier,* where the myelin is missing and voltage-gated sodium channels are concentrated. The nodes of Ranvier increase nerve conduction by allowing the impulse to jump from node to node through the extracellular fluid in a process called *saltatory conduction* (from the Latin *saltare,* "to jump"). In this way, the impulse can travel more rapidly than it could if it were required to move systematically along the entire nerve process. This increased conduction velocity greatly reduces reaction time, or time between the application of a stimulus and the subsequent motor response. The short reaction time is especially important in peripheral nerves with long distances (sometimes 1 to 1.5 m) for conduction between the CNS and distal effector organs.

Each of the Schwann cells along a peripheral nerve is encased in a continuous tube of basement membrane, which in turn is surrounded by a multilayered sheath of loose connective tissue known as the *endoneurium* (see Fig. 34-2). The endoneurial sheath, which is essential to the regeneration of peripheral nerves, provides a collagenous tube through which a regenerating axon can again reach its former target. The endoneurial sheath does not penetrate the CNS. The absence of the endoneurial sheaths is thought to be a major factor in the limited axonal regeneration of CNS nerves compared with those of the PNS.

The endoneurial sheaths are bundled with blood vessels into small clusters of nerves called *fascicles*. In the nerve, the fascicles consisting of bundles of nerve fibers are surrounded by another protective covering called the *perineurium*. Usually, several fascicles are further surrounded by the heavy, protective *epineurial sheath* of the peripheral nerve. The protective layers that surround the peripheral nerve processes are continuous with the connective tissue capsule of the sensory nerve endings and the connective tissue that surrounds the effector structures, such as the skeletal muscle cell. Centrally, the connective tissue

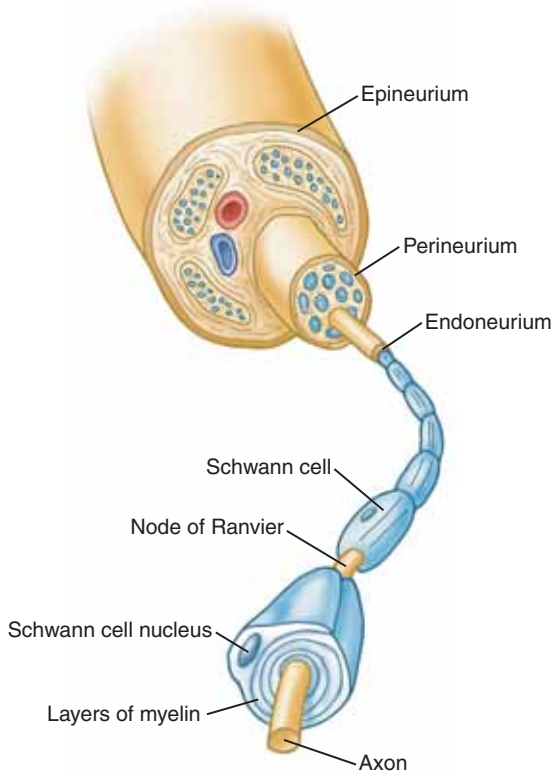


FIGURE 34-2. Section of a peripheral nerve containing both afferent (sensory) and efferent (motor) neurons. Schwann cells form a myelin sheath around the larger nerve fibers in the peripheral nervous system. Successive Schwann cells are separated by short extracellular fluid gaps called the *nodes of Ranvier,* where the myelin is missing and the voltage-gated sodium channels are concentrated.

layers continue along the dorsal and ventral roots of the nerve and fuse with the meninges that surround the spinal cord and brain.

Supporting Cells of the Central Nervous System

Supporting cells of the CNS consist of the oligodendrocytes, astrocytes, microglia, and ependymal cells (Fig. 34-3). The *oligodendrocytes* form the myelin in the CNS. Instead of forming a myelin covering for a single axon, these cells reach out with several processes, each wrapping around and forming a multilayered myelin segment around several different axons. As with peripheral myelinated fibers, the covering of axons in the CNS increases the velocity of nerve conduction.

Astrocytes are the largest and most numerous of neuroglial cells and are particularly prominent in the gray matter of the CNS. They form a network within the CNS and communicate with neurons to support and modulate their activities. Astrocytes have many processes, some stretching their processes from blood vessels to neurons and others filling most of the intercellular space within the CNS. It is now thought that astrocytes play an important role in the movement of metabolites and wastes to and from neurons and regulate ionic concentrations in the intercellular compartment. In addition, astrocytes take up neurotransmitters from synaptic zones after their release and thereby help regulate synaptic activity. They also have a role in maintaining the tight junctions of capillaries that form the blood-brain barrier. Astrocytes are also the principal cells responsible for repair and scar formation in the brain. They can fill their

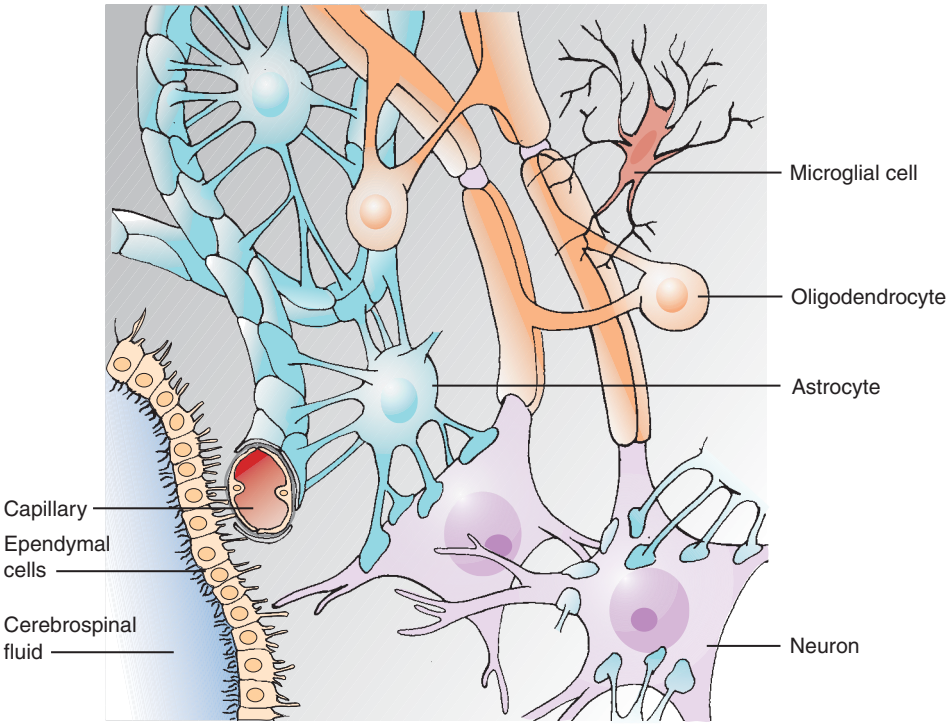


FIGURE 34-3. The supporting cells of the central nervous system (CNS). Diagrammatic view of relationships between the glial elements (astrocyte, oligodendrocyte, microglial cell, and the ependymal cells), the capillaries, the cerebrospinal fluid, and the cell bodies of CNS neurons.

cytoplasm with microfibrils (i.e., fibrous astrocytes), and masses of these cells form the special type of scar tissue that develops in the CNS when tissue is destroyed, a process called *gliosis*.

A third type of neuroglial cell, the *microglia,* is a small phagocytic cell that is available for cleaning up debris after cellular damage, infection, or cell death. The fourth type of cell, the *ependymal cell,* forms the lining of the neural tube cavity, the ventricular system. In some areas, these cells combine with a rich vascular network to form the *choroid plexus,* where production of the cerebrospinal fluid (CSF) takes place.

Metabolic Requirements of Nervous Tissue

Nervous tissue has a high rate of metabolism. Although the brain makes up only 2% of the body's weight, it receives approximately 15% of the resting cardiac output and consumes 20% of its oxygen. Despite its substantial energy requirements, the brain can neither store oxygen nor engage in anaerobic metabolism. An interruption in the blood or oxygen supply to the brain rapidly leads to clinically observable signs and symptoms. Without oxygen, brain cells continue to function for approximately 10 seconds. Unconsciousness occurs almost simultaneously with cardiac arrest, and the death of brain cells begins within 4 to 6 minutes. Interruption of blood flow also leads to the accumulation of metabolic by-products that are toxic to neural tissue.

Glucose is the major fuel source for the nervous system. Unlike muscle cells, neurons have no glycogen stores and must rely on glucose from the blood or the glycogen stores of supporting glial cells to meet their energy needs. Persons receiving insulin for diabetes may experience signs of neural dysfunction and unconsciousness (i.e., insulin reaction or shock) when blood glucose drops because of insulin excess (see Chapter 33).

In summary, the nervous system can be divided into two basic components: the CNS or brain and spinal cord, which are located within the skull and vertebral column, and the PNS, which is located outside these structures. Inherent in the basic design of the nervous system is the provision for the concentration of computational and control functions in the CNS, with the PNS relaying input to the CNS for processing and transmitting output from the CNS to effector organs throughout the body.

Nervous tissue consists of two types of cells: neurons and supporting cells. Neurons, which are the functional components of the nervous system, are composed of three parts: a cell body, which controls cell activity; the dendrites, which conduct information toward the cell body; and the axon, which carries impulses from the cell body. The supporting cells consist of Schwann cells of the PNS and the oligodendrocytes, astrocytes, microglial cells, and ependymal cells of the CNS. The supporting cells protect and provide metabolic support for the neurons and aid in segregating them into isolated compartments, which is necessary for normal neuronal function. The Schwann cells of the PNS and the oligodendroglial cells of the CNS form the myelin sheath that allows for rapid conduction of impulses.

The nervous system has a high level of metabolic activity, requiring a continuous supply of oxygen and glucose. Although the brain makes up only 2% of the body's weight, it receives approximately 15% of the resting cardiac output and consumes 20% of its oxygen.

Nerve Cell Communication

Neurons are characterized by the ability to communicate with other neurons and body cells through electrical impulses or action potentials, which are abrupt, pulsatile changes in the membrane potential that last a few ten thousandths to a few thousandths of a second. The frequency and pattern of action potentials constitute the code used by neurons to transfer information from one location to another.

Action Potentials

The cell membranes of excitable tissue, including those of nerve and muscle cells, contain ion channels that are responsible for generating action potentials (see Chapter 1, Fig. 1-13). These ion channels are guarded by voltage-dependent gates that open and close with changes in the membrane potential. Separate voltage-gated channels exist for the sodium, potassium, and calcium ions. Each type of ion channel has a characteristic membrane potential that opens and closes its channels. Also present are ligand-gated channels that respond to chemical messengers such as neurotransmitters, mechanically gated channels that respond to physical changes in the cell membrane, and light-gated channels that respond to fluctuations in light levels.

Action potentials can be divided into three phases: the resting or polarized state, depolarization, and repolarization (Fig. 34-4). The *resting membrane potential* (approximately −90 mV for large nerve fibers) is the undisturbed period of the action potential during which the nerve is not transmitting impulses (discussed in Chapter 1). During this period, the membrane is said to be *polarized* because of the large separation of charge (i.e., positive on the outside and negative on the inside). The resting phase of the membrane potential continues until some event causes the membrane to increase its permeability to sodium. A *threshold potential* (approximately −60 mV in large nerve fibers) represents the membrane potential at which neurons or other excitable tissues are stimulated to fire. When the threshold potential is reached, the gate-like structures in the ion channels open. Below the threshold potential, these gates remain tightly closed. The gates function on an all-or-none basis; they are either

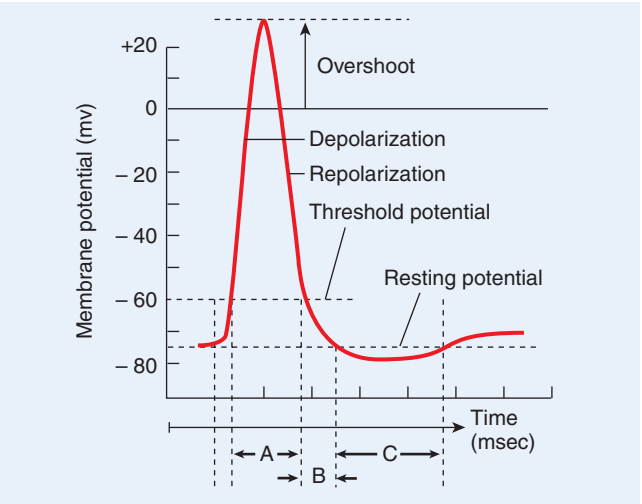


FIGURE 34-4. Time course of the action potential recorded at one point of an axon with one electrode inside and one outside the plasma membrane. The rising part of the action potential is called the *spike.* The rising phase plus approximately the first half of the repolarization phase is the absolute refractory period **(A)**. The portion of the repolarization phase that extends from the threshold to the resting membrane potential represents the relative refractory period **(B)**. The remaining portion of the repolarization phase to the resting membrane potential is the negative afterpotential **(C)**.

fully open or fully closed. Under ordinary circumstances, the threshold stimulus is sufficient to open many ion channels, triggering massive depolarization of the membrane (the action potential).

Depolarization is characterized by the flow of electrically charged ions. During the depolarization phase, the membrane suddenly becomes permeable to sodium ions; the rapid inflow of sodium ions produces local currents that travel through the adjacent cell membrane, causing the sodium channels in this part of the membrane to open. In neurons, sodium ion gates remain open for approximately a quarter of a millisecond. During this phase of the action potential, the inner face of the membrane becomes positive (approximately +30 to +45 mV).

Repolarization is the phase during which the polarity of the resting membrane potential is reestablished. This is accomplished with closure of the sodium channels and opening of the potassium channels. The outflow of positively charged potassium ions across the cell membrane returns the membrane potential to negativity. The sodium/potassium–adenosine triphosphatase (Na^+/K^+-ATPase) pump gradually reestablishes the resting ionic concentrations on each side of the membrane. Membranes of excitable cells must be sufficiently repolarized before they can be reexcited. During repolarization, the membrane remains refractory (i.e., does not fire) until repolarization is approximately one-third complete. This period, which lasts approximately one half of a millisecond, is called the *absolute refractory period.* During one portion of the recovery period, the membrane can be excited, although only by a stronger-than-normal stimulus. This period is called the *relative refractory period.*

The excitability of neurons can be affected by conditions that alter the resting membrane potential, moving it either closer to or farther from the threshold potential. *Hypopolarization* increases the excitability of the postsynaptic neuron by bringing the membrane potential closer to the threshold potential so that a smaller subsequent stimulus is needed to cause the neuron to fire. *Hyperpolarization* brings the membrane potential further from the threshold and has the opposite, inhibitory effect, decreasing the likelihood that an action potential will be generated.

Synaptic Transmission

Neurons communicate with each other through structures known as *synapses.* Two types of synapses are found in the nervous system: electrical and chemical. *Electrical synapses* permit the passage of current-carrying ions through small openings called *gap junctions* that penetrate the cell junction of adjoining cells and allow current to travel in either direction. The gap junctions allow an action potential to pass directly and quickly from one neuron to another and often serve to link neurons having close functional relationships into circuits.

The most common type of synapse is the *chemical synapse.* Chemical synapses involve special presynaptic and postsynaptic membrane structures, separated by a synaptic cleft. The presynaptic terminal secretes one and often several chemical transmitter molecules (i.e., neurotransmitters or neuromodulators). The secreted neurotransmitters diffuse into the synaptic cleft and bind to receptors on the postsynaptic membrane. In contrast to an electrical synapse, a chemical synapse serves as a rectifier, permitting only one-way communication. Chemical synapses are divided into two types: excitatory and inhibitory. In excitatory synapses, binding of the neurotransmitter to the receptor produces depolarization of the postsynaptic membrane. Binding of the neurotransmitter to the receptor in an inhibitory synapse reduces the postsynaptic neuron's ability to generate an action potential.

A neuron's cell body and dendrites are covered by thousands of synapses, any or many of which can be active at any moment. Because of the interaction of this rich synaptic input, each neuron resembles a little integrator, in which circuits of many neurons interact with one another. It is the complexity of these interactions and the subtle integrations involved in producing behavioral responses that give rise to the nervous system's intelligence.

Chemical Synaptic Transmitters

The function of the nervous system relies on chemical substances that function as synaptic transmitters. These messengers include the neurotransmitters, neuromodulators, and neurotrophic or nerve growth factors.

Neurotransmitters. Neurotransmitters are small molecules that incorporate a positively charged nitrogen atom; they include several amino acids, peptides, and

monoamines. The amino acids glutamine, glycine, and γ-aminobutyric acid (GABA) serve as neurotransmitters at most CNS synapses. GABA mediates most synaptic inhibition in the CNS. Drugs such as the benzodiazepines (e.g., the tranquilizer diazepam) and the barbiturates exert their action by binding to their own distinct receptor on a GABA-operated ion channel. The drugs by themselves do not open the channel, but they change the effect that GABA has when it binds to the channel at the same time as the drug. *Peptides* are low–molecular-weight molecules that are made up of two or more amino acids. They include substance P and the endorphins and enkephalins, which are involved in pain sensation and perception (see Chapter 35). A *monoamine* is an amine molecule containing one amino group (NH_2). Serotonin, dopamine, norepinephrine, and epinephrine are monoamines synthesized from amino acids.

The process of neurotransmission involves the synthesis, storage, and release of a neurotransmitter; the reaction of the neurotransmitter with a receptor; and termination of the receptor action. Neurotransmitters are synthesized in the cytoplasm of the axon terminal. The synthesis of transmitters may require one or more enzyme-catalyzed steps (e.g., one for acetylcholine and three for norepinephrine). Neurons are limited as to the type of transmitter they can synthesize by their enzyme systems. After synthesis, the neurotransmitter molecules are stored in the axon terminal in tiny, membrane-bound sacs called *synaptic vesicles*. These vesicles protect the neurotransmitters from enzyme destruction in the nerve terminal. There may be thousands of vesicles in a single terminal, each containing 10,000 to 100,000 transmitter molecules. The arrival of an impulse at a nerve terminal causes the vesicles to move to the cell membrane and release their transmitter molecules into the synaptic space.

Neurotransmitters exert their actions through specific proteins, called *receptors,* embedded in the postsynaptic membrane. These receptors are tailored precisely to match the size and shape of the transmitter. In each case, the interaction between a transmitter and receptor results in a specific physiologic response. The action of a transmitter is determined by the type of receptor (excitatory or inhibitory) to which it binds. For example, acetylcholine is excitatory when it is released at a myoneural junction, and it is inhibitory when it is released at the sinoatrial node in the heart. Receptors are named according to the type of neurotransmitter with which they interact. For example, a *cholinergic receptor* is a receptor that binds acetylcholine.

Rapid removal of a transmitter, once it has exerted its effects on the postsynaptic membrane, is necessary to maintain precise control of neural transmission. A released transmitter can undergo one of three fates: (1) it can be broken down into inactive substances by enzymes, (2) it can be taken back up into the presynaptic neuron in a process called *reuptake,* or (3) it can diffuse away into the intercellular fluid until its concentration is too low to influence postsynaptic excitability. For example, acetylcholine is rapidly broken down by acetylcholinesterase into acetic acid and choline, with the choline being taken back into the presynaptic neuron for reuse in acetylcholine synthesis. The catecholamines are largely taken back into the neuron in an unchanged form for reuse. Catecholamines also can be degraded by enzymes in the synaptic space or in the nerve terminals.

Neuromodulators. Other classes of messenger molecules, known as *neuromodulators,* also may be released from axon terminals. Neuromodulator molecules react with presynaptic or postsynaptic receptors to alter the release of or response to neurotransmitters. Neuromodulators may act on postsynaptic receptors to produce slower and longer-lasting changes in membrane excitability. This alters the action of the faster-acting neurotransmitter molecules by enhancing or decreasing their effectiveness. By combining with autoreceptors on its own presynaptic membrane, a transmitter can act as a neuromodulator to augment or inhibit further nerve activity. In some nerves, such as the peripheral sympathetic nerves, a messenger molecule can have both transmitter and modulator functions. For example, norepinephrine can activate an α_1-adrenergic postsynaptic receptor to produce vasoconstriction or stimulate an α_2-adrenergic presynaptic receptor to inhibit further norepinephrine release.

Neurotrophic Factors. Neurotrophic or nerve growth factors are required to maintain the long-term survival of the postsynaptic cell and are secreted by axon terminals independent of action potentials. Examples include neuron-to-neuron trophic factors in the sequential synapses of CNS sensory neurons. Trophic factors from target cells that enter the axon and are necessary for the long-term survival of presynaptic neurons also have been demonstrated. Target cell–to–neuron trophic factors probably have great significance in establishing specific neural connections during normal embryonic development.

In summary, neurons communicate with other neurons and body cells through pulsed electrical signals called *action potentials.* The cell membranes of neurons contain ion channels that are responsible for generating action potentials. Action potentials are divided into three parts: the resting membrane potential, during which the membrane is polarized but no electrical activity occurs; the depolarization phase, during which sodium channels open, allowing rapid inflow of the sodium ions that generate the electrical impulse; and the repolarization phase, during which the membrane is permeable to the potassium ion, allowing for the efflux of potassium ions and return to the resting membrane potential.

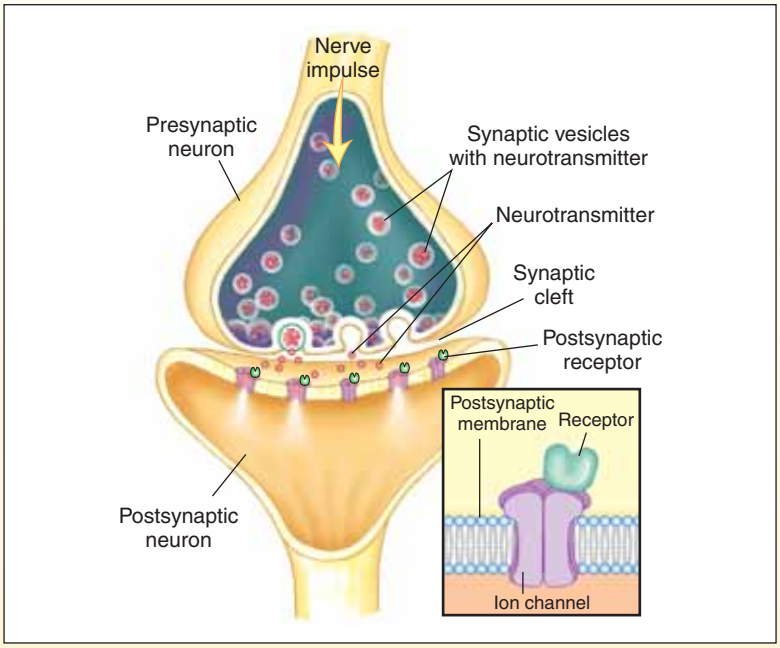
Synapses are structures that permit communication between neurons. Two types of synapses have been identified: electrical and chemical. Electrical synapses consist of gap junctions between adjacent cells that allow action potentials to move rapidly from one cell to another. Chemical synapses involve special presynaptic and postsynaptic structures, separated by a synaptic cleft. They rely on chemical messengers, released from the presynaptic neuron, that cross the synaptic cleft and then interact with receptors on the postsynaptic neuron.

UNDERSTANDING → Synaptic Transmission

Neurons communicate with each other through chemical synapses and the use of neurotransmitters. Chemical synapses consist of a presynaptic neuron, a synaptic cleft, and a postsynaptic neuron. The communication process relies on (1) synthesis and release of the neurotransmitter from a presynaptic neuron, (2) binding of the neurotransmitter to receptors in the postsynaptic neuron, and (3) removal of the neurotransmitter from the receptor site.

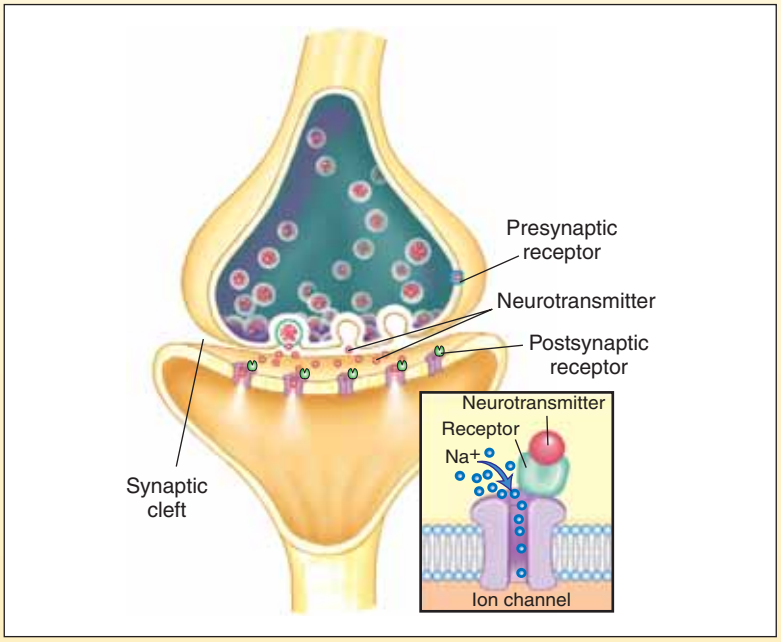
1

Neurotransmitter Synthesis and Release. Neurotransmitters are synthesized in the presynaptic neuron, and then stored in synaptic vesicles. Communication between the two neurons begins with a nerve impulse that stimulates the presynaptic neuron, followed by movement of the synaptic vesicles to the cell membrane and release of neurotransmitter into the synaptic cleft.

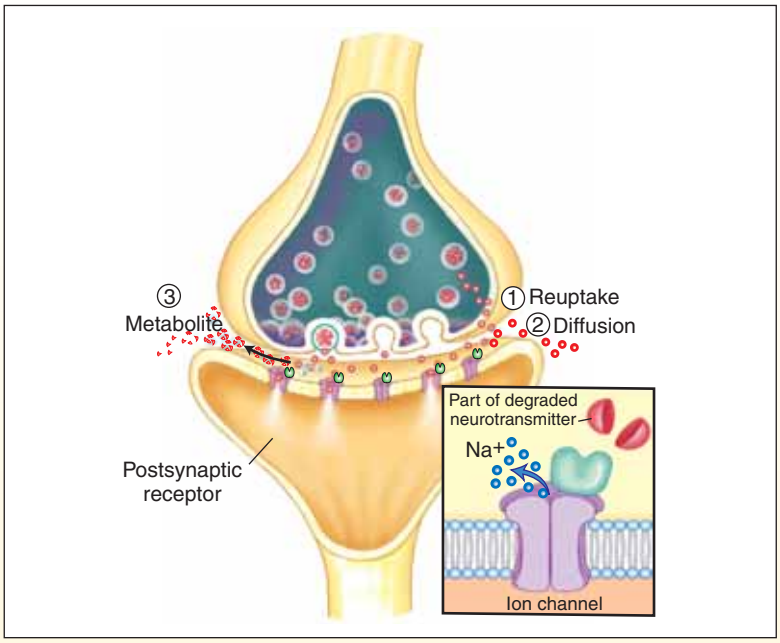


2

Receptor Binding. Once released from the presynaptic neuron, the neurotransmitter moves across the synaptic cleft and binds to receptors on the postsynaptic neuron. The action of a neurotransmitter is determined by the type of receptor (excitatory or inhibitory) to which it binds. Binding of a neurotransmitter to a receptor with an excitatory function often results in the opening of an ion channel, such as the sodium channel. Many presynaptic neurons also have receptors to which a neurotransmitter binds. The presynaptic receptors function in a negative feedback manner to inhibit further release of the neurotransmitter.



3 **Neurotransmitter Removal.** Precise control of synaptic function relies on the rapid removal of the neurotransmitter from the receptor site. A released neurotransmitter can (1) be taken back up into the neuron in a process called reuptake, (2) diffuse out of the synaptic cleft, or (3) be broken down by enzymes into inactive substances or metabolites. The action of norepinephrine is largely terminated by the reuptake process, in which the neurotransmitter is taken back into the neuron in an unchanged form and reused. It can also be broken down by enzymes in the synaptic cleft or in the nerve terminals. The neurotransmitter acetylcholine is rapidly broken down by the enzyme acetylcholinesterase.



Neurotransmitters are chemical messengers that control neural function; they selectively cause excitation or inhibition of action potentials. Three major types of neurotransmitters are known: amino acids such as glutamic acid and GABA, peptides such as the endorphins and enkephalins, and monoamines such as epinephrine and norepinephrine. Neurotransmitters interact with cell membrane receptors to produce either excitatory or inhibitory actions. Neuromodulators are chemical messengers that react with membrane receptors to produce slower and longer-acting changes in membrane permeability. Neurotrophic or growth factors, also released from presynaptic terminals, are required to maintain the long-term survival of postsynaptic neurons.

Developmental Organization of the Nervous System

The organization of the nervous system can be described in terms of its embryonic development, in which newer functions and greater complexity result from the modification and enlargement of earlier developed structures. Thus, the rostral or front end of the CNS, which is the last to develop, is more specialized in its functions than the brain stem and spinal cord, which are the first to develop. The dominance of the front end of the CNS is reflected in what has been termed a *hierarchy of control*, with the forebrain having control over the brain stem and the brain stem having control over the spinal cord. In the developmental process, newer functions were added to the surface of earlier developed systems. As newer functions became concentrated at the rostral end of the nervous system, they also became more vulnerable to injury. Nothing exemplifies this principle better than the persistent vegetative state (discussed in Chapter 37) that occurs when severe brain injury causes irreversible damage to higher cortical centers, while lower stem centers such as those that control breathing remain functional.

Embryonic Development

The nervous system appears very early in embryonic development (22 to 23 days). This early development is essential because it influences the development and organization of many other body systems, including the axial skeleton, skeletal muscles, and sensory organs such as the eyes and ears. Throughout life, the organization of the nervous system retains many patterns that were established during embryonic life. It is this early pattern of segmental development in the embryo that is presented as a framework for understanding the nervous system.

During the second week of development, embryonic tissue consists of two layers, the endoderm and the ectoderm.

The Developmental Organization of the Nervous System

- Embryologically, the nervous system begins its development as a hollow tube, the cephalic portion of which becomes the brain and the more caudal part the spinal cord.
- In the process of development, the basic organizational pattern is that of a longitudinal series of segments, each repeating the same basic fundamental organizational pattern: a body wall or soma containing the axial skeleton and a neural tube, which develops into the nervous system.
- On cross-section, the embryonic neural tube develops into a central canal surrounded by gray matter or cellular portion (cell columns) and the white matter, or tract system of the central nervous system (CNS).
- As the nervous system develops, it becomes segmented, with a repeating pattern of afferent neuron axons forming the dorsal roots of each succeeding segmental nerve, and the exiting efferent neurons forming the ventral roots of each succeeding segmental nerve.
- The nerve cells in the gray matter are arranged longitudinally in cell columns, with afferent sensory neurons located in the dorsal columns and efferent motor neurons located in the ventral columns.
- The axons of the cell column neurons project out into the white matter of the CNS, forming the longitudinal tract systems.

At the beginning of week 3, the ectoderm begins to invaginate and migrates between the two layers, forming a third layer called the *mesoderm* (Fig. 34-5). Mesoderm along the entire midline of the embryo forms a specialized rod of embryonic tissue called the *notochord*. The notochord and adjacent mesoderm provide the necessary induction signal for the overlying ectoderm to differentiate and form a thickened structure called the *neural plate*, the primordium of the nervous system. Within the neural plate an axial groove (i.e., neural groove) develops and sinks into the underlying mesoderm, allowing its walls to fuse across the top and form an ectodermal tube called the *neural tube*. This process, called *closure*, occurs during the later third and fourth weeks of gestation and is vital to the survival of the embryo.

During embryonic development, the neural tube develops into the CNS, while the notochord becomes the foundation around which the vertebral column ultimately develops. The surface ectoderm separates from the neural tube and fuses over the top to become the outer layer of skin. Initial closure of the neural tube begins at the cervical and high thoracic levels and zippers rostrally toward the cephalic end of the embryo and caudally toward the sacrum. Complete closure occurs at the rostral-most end of the brain (i.e., anterior neuropore) around day 25 and at about day 27 in the lumbosacral region (i.e., posterior neuropore).

As the neural tube closes, ectodermal cells called *neural crest cells* migrate away from the dorsal surface of the neural tube to become the progenitors of the neurons and supporting cells of the PNS. During this period of embryonic development, neural cell adhesive molecules (N-CAMs) are produced to decrease migration of neural crest cells. In addition, fibronectin molecules are produced to increase the formation of pathways that guide the neural crest cells during their migration. Some of these cells gather into clusters to form the *dorsal root ganglia* at the sides of each spinal cord segment and the *cranial ganglia* that are present in most brain segments. Neurons of these ganglia become the afferent or sensory neurons of the PNS. Other neural crest cells become the pigment cells of the skin or contribute to the formation of the meninges, many structures of the face, and the peripheral ganglion cells of the autonomic nervous system, including those of the adrenal cortex.

During development, the more rostral portions of the embryonic neural tube—approximately 10 segments—undergo extensive modification and enlargement to form the brain (Fig. 34-6). In the early embryo, 3 swellings, or primary vesicles, develop, subdividing these 10 segments into the prosencephalon, or forebrain, containing the first 2 segments; the mesencephalon, or midbrain, which develops from segment 3; and the rhombencephalon, or hindbrain, which develops from segments 4 to 10. In the prosencephalon or forebrain, two pairs of lateral outpouchings develop: the optic cup, which becomes the optic nerve and retina, and the telencephalic vesicles, which become the cerebral hemispheres. Within the prosencephalon, the hollow central canal expands to become enlarged CSF-filled cavities, the first and second (lateral) ventricles. The remaining diencephalic portion of the neural tube develops into the thalamus and hypothalamus. The neurohypophysis (posterior pituitary) grows as a midline ventral outgrowth at the junctions of segments 1 and 2. A dorsal outgrowth, the pineal body, develops between segments 2 and 3.

Neural Tube Defects

The major morphogenic defects of the spine and spinal cord are due to the abnormal formation or closure of the neural tube and surrounding tissues. These neural tube defects can involve neural tissue, the meninges that cover the spinal cord, muscle tissue, skin, and the vertebral column. Severe neural tube defects occur in approximately 1 in 1000 births. These defects range from spina bifida occulta to spina bifida with myeloschisis. In spina bifida occulta, the lamina (neural arches) of lumbar (L) 5 and/or sacral (S) 1 fail to develop and spinal cord and surrounding meninges lie within the incomplete vertebral column. The defect is concealed by the overlying skin, but its location is often marked by a patch of hair in the lumbar region. Most people with spina bifida occulta have no back problems. In severe types of spina bifida,

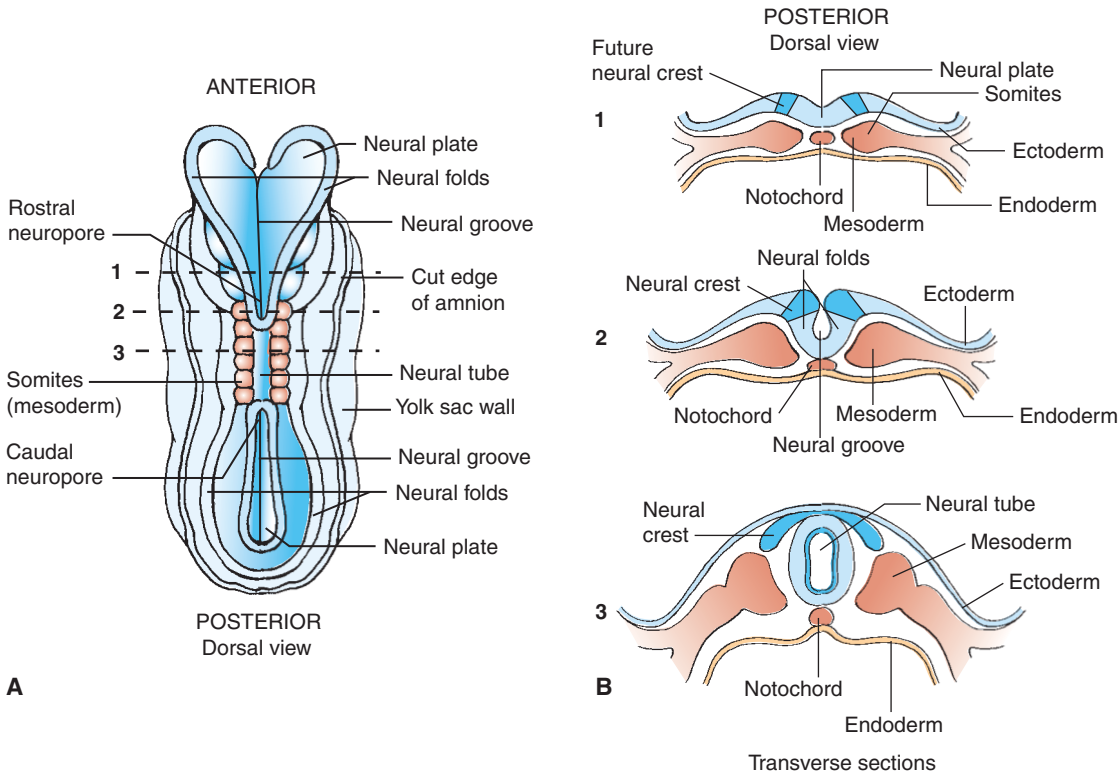


FIGURE 34-5. Folding of the neural tube. **(A)** Dorsal view of a six-somite embryo (22 to 23 days) showing the neural folds, neural groove, and fused neural tube. The anterior neuropore closes at about day 25 and the posterior neuropore at about day 27. **(B)** Three cross-sections taken at the levels indicated in A. The sections indicate where the neural tube is just beginning to form.

one or more of the vertebral arches may fail to develop completely. In spina bifida cystica, there is herniation of the meninges (meningocele, a spina bifida associated with a meningeal cyst) and/or the spinal cord (meningomyelocele) (Fig. 34-7).

Clinical neurologic dysfunction is related to abnormalities in the cord itself and to superimposed infections that extend from the thin overlying skin. Meningomyeloceles occur most commonly in the lumbosacral region and produce clinical deficits referable to motor and sensory function in the lower extremities as well as disturbances in bowel and bladder control. The etiology of neural tube defects is unknown. Folate deficiency during the initial weeks of gestation has been implicated as a risk factor, possibly interacting with host and environmental factors. Antenatal diagnosis has been facilitated by ultrasonographic imaging and maternal blood sampling for elevated α-fetoprotein (see Chapter 6).

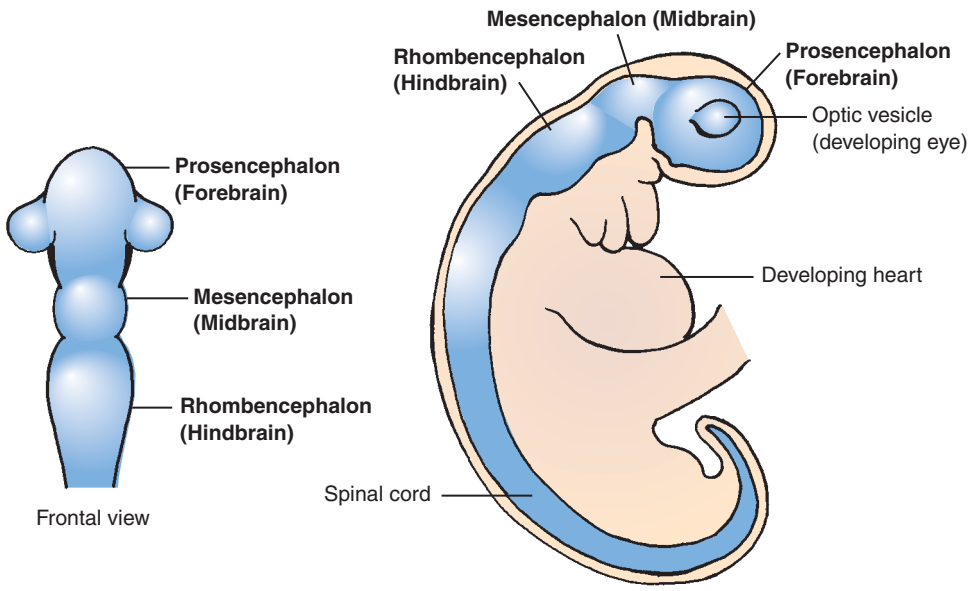


FIGURE 34-6. Frontal and lateral views of a 5-week-old embryo showing the brain vesicles and three embryonic divisions of the brain and brain stem.

FIGURE 34-7. Posterior view of spina bifida cystica. (From Moore K.L., Dalley A.F. [2006]. *Clinically oriented anatomy* [5th ed., p. 497]. Philadelphia: Lippincott Williams & Wilkins.)

Segmental Organization

Developmentally, the basic organizational pattern of the body is that of a longitudinal series of segments, each repeating the same fundamental pattern. Although the early muscular, skeletal, vascular, and excretory systems and the nerves that supply the somatic and visceral structures have the same segmental pattern, it is the nervous system that most clearly retains this organization in postnatal life. The CNS and its associated peripheral nerves consist of approximately 43 segments, 33 of which form the spinal cord and spinal nerves, and 10 of which form the brain and its cranial nerves.

The basic pattern of the CNS is that seen in the spinal cord—a central cavity surrounded by an inner core of gray matter and a superficial layer of white matter (Fig. 34-8). The brain retains this organization, but it also contains additional regions of gray matter that are not evident in the spinal cord. The gray matter is functionally divided into longitudinal columns of nerve cell bodies called the *cell columns*. The superficial white matter region contains the longitudinal tract systems of the CNS. The dorsal half or dorsal horn of the gray matter contains afferent neurons. The ventral portion, or *ventral horn,* contains efferent neurons that communicate by way of the ventral roots with effector cells of the body segment. Many CNS neurons develop axons that grow longitudinally as tract systems that communicate between neighboring and distal segments of the neural tube.

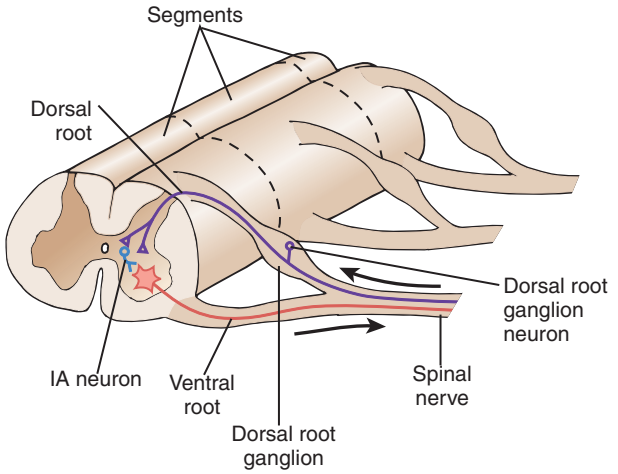


FIGURE 34-8. In this diagram of three segments of the spinal cord, three dorsal roots enter the dorsal lateral surface of the cord, and three ventral roots exit. The dorsal root ganglion contains dorsal root ganglion cells, whose axons bifurcate: one process enters the spinal cord in the dorsal root, and the other extends peripherally to supply the skin and muscle of the body. The ventral root is formed by axons from motoneurons in the spinal cord. IA, input association.

Each segment of the CNS is accompanied by bilateral pairs of bundled nerve fibers, or roots, a dorsal pair and a ventral pair. The paired dorsal roots connect a pair of dorsal root ganglia and their corresponding CNS segment. The dorsal root ganglia contain many afferent nerve cell bodies, each having two axonlike processes—one that ends in a peripheral receptor and the other that enters the dorsal horn of its respective CNS segment. The paired ventral roots of each segment contain fibers supplying skeletal muscles and visceral structures of the body segment.

All brain segments, except segment 2, retain some portion of the basic segmental organization of the nervous system in which each segment has multiple paired branches containing a grouping of component axons. The classic pattern of spinal nerve organization, which consists of a pair of dorsal and a pair of ventral roots, is a later development that has not occurred in the cranial nerves. Consequently, the cranial nerves, which are arbitrarily numbered 1 through 12, retain the early pattern of development, with more than one cranial nerve branching from a single segment. The truly segmental nerve pattern of the cranial nerves is altered because all branches from segment 2 and most of the branches from segment 1 are missing. Cranial nerve 2, also called the *optic nerve,* is not a segmental nerve. It is a brain tract connecting the retina (modified brain) with the first forebrain segment from which it developed.

Cell Columns

The body is organized into soma (e.g., skin, muscles, and skeletal structures of the body wall) and viscera (e.g., internal organs and blood vessels). The organizational structure of the nervous system can be best explained and simplified as a pattern in which functionally specific PNS and CNS afferent and efferent somatic and visceral neurons are repeated as parallel cell columns running lengthwise along the nervous system. In this organizational pattern, afferent neurons, dorsal horn cells, and ventral horn cells are organized as a bilateral series of 11 cell columns.

The cell columns on each side can be further grouped according to their location in the PNS: four in the dorsal root ganglia that contain sensory neurons, four in the dorsal horn containing sensory input association neurons, and three in the ventral horn that contain motor neurons (Fig. 34-9). The axonlike process that enters the dorsal horn communicates with a neuron called an *input association (IA) neuron.* The IA neurons distribute afferent information to local reflex circuitry and to more rostral segments of the CNS. The ventral horns contain *output association* (OA) neurons and lower motor neurons,

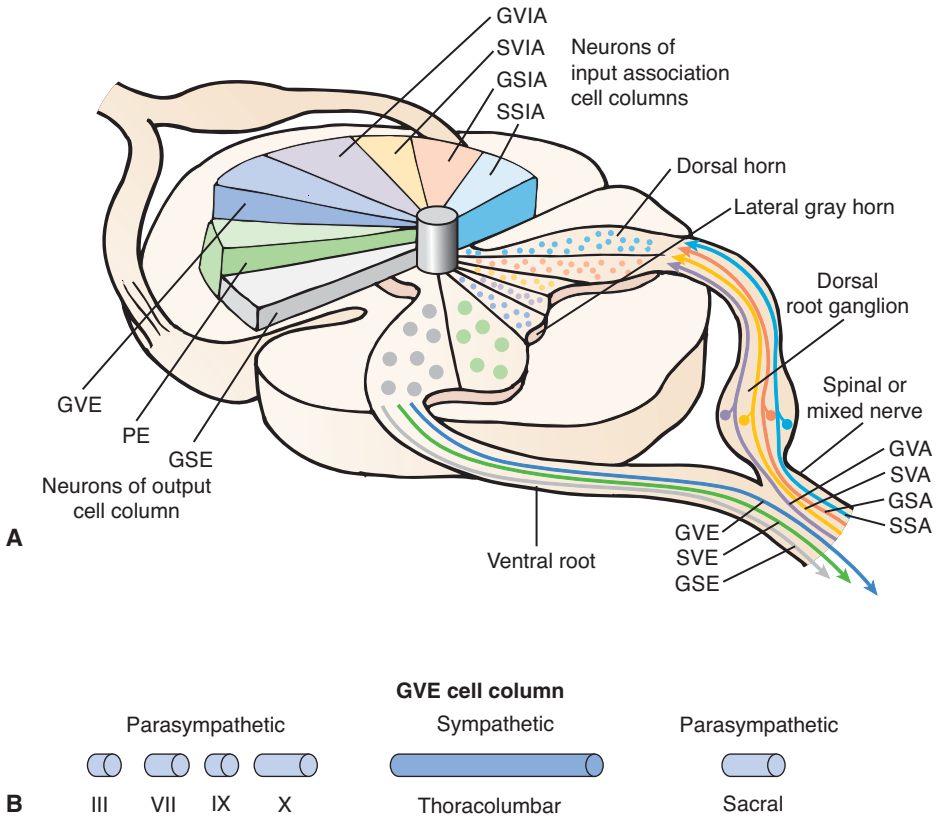


FIGURE 34-9. **(A)** Cell columns of the central nervous system. The cell columns in the dorsal horn contain input association (IA) neurons for the general visceral afferent (GVA), special visceral afferent (SVA), special sensory afferent (SSA), and general somatic afferent (GSA) neurons with cell bodies in the dorsal root ganglion. The cell columns in the ventral horn contain the general visceral efferent (GVE), pharyngeal efferent (PE), and general somite efferent (GSE) neurons and their output association (OA) neurons. **(B)** Schematic of the GVE cell column showing both parasympathetic and sympathetic components. The column is not continuous but is interrupted in the brain stem because only the nuclei of cranial nerves III, VII, IX, and X contain preganglionic parasympathetic neurons. The column again is interrupted until levels T1 to L1 or L2, where the preganglionic neurons of the sympathetic portion are found in the lateral horn of the spinal cord. Another gap is evident until the sacral portion of the parasympathetic nervous system.

which project to the effector muscles. The afferent and efferent cell columns of the PNS and CNS, their projections, and the type of information they transmit are summarized in Table 34-1.

Between the IA neurons and the OA neurons are networks of small internuncial neurons arranged in complex circuits. Internuncial neurons provide the discreteness, appropriateness, and intelligence of responses to stimuli. Most of the billions of CNS cells in the spinal cord and brain gray matter are internuncial neurons.

Dorsal Horn Cell Columns. Four columns of afferent (sensory) neurons in the dorsal root ganglia directly innervate four corresponding columns of IA neurons in the dorsal horn (see Fig. 34-9). These columns are categorized as special (special somatic and special visceral) and general (general somatic and general visceral) afferent neurons.

The special somatic afferent (SSA) fibers are concerned with internal sensory information such as joint and tendon sensation (i.e., proprioception). Neurons in the special sensory IA cell columns relay their information to local reflexes concerned with posture and movement. These neurons also relay information to the cerebellum, contributing to coordination of movement, and to the forebrain, contributing to experience. Afferents innervating the vestibular system of the inner ear also belong to the special somatic afferent category. *Special visceral afferent* (SVA) neurons innervate specialized gut-related visceral receptors, such as the taste buds and receptors of the olfactory mucosa. Their central processes communicate with special visceral IA column neurons that project to reflex circuits producing salivation, chewing, swallowing, and other responses. Forebrain projection fibers from these association cells provide sensations of taste (i.e., gustation) and smell (i.e., olfaction).

General somatic afferent (GSA) neurons innervate the skin and other somatic structures, responding to stimuli such as those that produce pressure or pain. General sensory IA column neurons relay information to protective and other local reflex circuits and project the information to the forebrain, where it is perceived as painful, warm, cold, and the like. *General visceral afferent* (GVA) neurons innervate visceral structures such as the gastrointestinal tract, urinary bladder, and heart and great vessels; they project to the general visceral IA column, which relays information to vital reflex circuits and sends information to the forebrain regarding visceral sensations such as stomach fullness and bladder pressure.

Ventral Horn Cell Columns. The ventral horn contains three longitudinal cell columns: the general visceral efferent, pharyngeal efferent, and general somatic efferent (see Fig. 34-9). The efferent neurons for the OA in the ventral horn originate in brain centers (motor cortex and ANS centers) that control skeletal muscle and visceral function. Each of these cell columns contains OA and efferent neurons. The OA neurons coordinate and integrate the function of the efferent motor neurons of its column.

The *general visceral efferent* (GVE) neurons transmit the efferent output of the ANS and are called *preganglionic neurons*. These neurons are structurally and

TABLE 34-1 The Segmental Nerves and Their Components

Segment and Nerve	Component	Innervation	Function
1. Forebrain			
I. Olfactory	SVA	Receptors in olfactory mucosa	Reflexes, olfaction (smell)
2. II. Optic nerve		Optic nerve and retina (part of brain system, not a peripheral nerve)	
3. Midbrain			
V. Trigeminal (V_1) ophthalmic division	SSA	Muscles: upper face: forehead, upper lid	Facial expression, proprioception
	GSA	Skin, subcutaneous tissue; conjunctiva; frontal/ethmoid sinuses	Somesthesia Reflexes (blink)
III. Oculomotor	GVE	Iris sphincter	Pupillary constriction
		Ciliary muscle	Accommodation
	GSE	Extrinsic eye muscles	Eye movement, lid movement
4. Pons			
V. Trigeminal (V_2) maxillary division	SSA	Muscles: facial expression	Proprioception Reflexes (sneeze), somesthesia
	GSA	Skin, oral mucosa, upper teeth, hard palate, maxillary sinus	
V. Trigeminal (V_3) mandibular division	SSA	Lower jaw, muscles: mastication	Proprioception, jaw jerk
	GSA	Skin, mucosa, teeth, anterior ⅔ of tongue	Reflexes, somesthesia
	PE	Muscles: mastication tensor tympani tensor veli palatini	Mastication: speech Protects ear from loud sounds Tenses soft palate
IV. Trochlear	GSE	Extrinsic eye muscle	Moves eye down and in
5. Caudal Pons			
VIII. Vestibular, cochlear (vestibulocochlear)	SSA	Vestibular end organs	Reflexes, sense of head position
		Organ of Corti	Reflexes, hearing
VII. Facial nerve, intermedius portion	GSA	External auditory meatus	Somesthesia
	GVA	Nasopharynx	Gag reflex: sensation
	SVA	Taste buds of anterior ⅔ of tongue	Reflexes: gustation (taste)
	GVE	Nasopharynx	Mucus secretion, reflexes
		Lacrimal, sublingual, submandibular glands	Lacrimation, salivation
Facial nerve	PE	Muscles: facial expression, stapedius	Facial expression Protects ear from loud sounds
VI. Abducens	GSE	Extrinsic eye muscle	Lateral eye deviation
6. Middle Medulla			
IX. Glossopharyngeal	SSA	Stylopharyngeus muscle	Proprioception
	GSA	Posterior external ear	Somesthesia
	SVA	Taste buds of posterior ⅓ of tongue	Gustation (taste)
	GVA	Oral pharynx	Gag reflex: sensation
	GVE	Parotid gland; pharyngeal mucosa	Salivary reflex: mucus secretion
	PE	Stylopharyngeus muscle	Assists swallowing
7,8,9,10. Caudal Medulla			
X. Vagus	SSA	Muscles: pharynx, larynx	Proprioception
	GSA	Posterior external ear	Somesthesia
	SVA	Taste buds, pharynx, larynx	Reflexes, gustation
	GVA	Visceral organs (esophagus to midtransverse colon, liver, pancreas, heart, lungs)	Reflexes, sensation
	GVE	Visceral organs as above	Parasympathetic efferent
	PE	Muscles: pharynx, larynx	Swallowing, phonation, emesis
XII. Hypoglossal	GSE	Muscles of tongue	Tongue movement, reflexes
Spinal Segments			
C1–C4 Upper Cervical	PE	Muscles: sternocleidomastoid, trapezius	Head, shoulder movement
XI. Spinal accessory nerve			
Spinal nerves	SSA	Muscles of neck	Proprioception, DTRs
	GSA	Neck, back of head	Somesthesia
	GSE	Neck muscles	Head, shoulder movement
C5–C8 Lower Cervical	SSA	Upper limb muscles	Proprioception, DTRs
	GSA	Upper limbs	Reflexes, somesthesia
	GSE	Upper limb muscles	Movement, posture

Segment and Nerve	Component	Innervation	Function
Spinal Segments *(continued)*			
T1–L2 Thoracic, Upper Lumbar	SSA	Muscles: trunk, abdominal wall	Proprioception
	GSA	Trunk, abdominal wall	Reflexes, somesthesia
	GVA	All of viscera	Reflexes and sensation
	GVE	All of viscera	Sympathetic reflexes, vasomotor control, sweating, piloerection
	GSE	Muscles: trunk, abdominal wall, back	Movement, posture, respiration
L2–S1 Lower Lumbar, Upper Sacral	SSA	Lower limb muscles	Proprioception, DTRs
	GSA	Lower trunk, limbs, back	Reflexes, somesthesia
	GSE	Muscles: trunk, lower limbs, back	Movement, posture
S2–S4 Lower Sacral	SSA	Muscles: pelvis, perineum	Proprioception
	GSA	Pelvis, genitalia	Reflexes, somesthesia
	GVA	Hindgut, bladder, uterus	Reflexes, sensation
	GVE	Hindgut, visceral organs	Visceral reflexes, defecation, urination, erection
S5–Co2 Lower Sacral, Coccygeal	SSA	Perineal muscles	Proprioception
	GSA	Lower sacrum, anus	Reflexes, somesthesia
	GSE	Perineal muscles	Reflexes, posture

Afferent (sensory) components: SSA, special somatic afferent; GSA, general somatic afferent; SVA, special visceral afferent; GVA, general visceral afferent.

Efferent (motor) components: GVE, general visceral efferent (autonomic nervous system); PE, pharyngeal efferent; GSE, general somatic efferent; DTRs, deep tendon reflexes.

functionally divided between either the sympathetic or the parasympathetic nervous systems (discussed later in this chapter). Their axons project through the segmental ventral roots to innervate smooth and cardiac muscle and glandular cells of the body, most of which are in the viscera. In the viscera, three additional cell columns are present on each side of the body. These become the postganglionic neurons of the ANS. In the sympathetic nervous system, the columns are represented by the paravertebral or sympathetic chain ganglia and the prevertebral series of ganglia (e.g., celiac ganglia) associated with the dorsal aorta. For the parasympathetic nervous system, these become the enteric plexus in the wall of the gut-derived organs and a series of ganglia in the head.

The *pharyngeal efferent* (PE) neurons innervate the muscles of mastication and facial expression, as well as the muscles of the pharynx and larynx. PE neurons also innervate the muscles responsible for moving the head. The *general somatic efferent* (GSE) neurons supply skeletal muscles of the body and head, including those of the trunk, limbs, and tongue and the extrinsic eye muscles. These efferent neurons of the PNS transmit the commands of the CNS to peripheral effectors, the skeletal muscles. They are the "final common pathway neurons" in the sequence leading to motor activity. They often are called *lower motor neurons* (LMNs) because they are under the control of *upper motor neurons* (UMNs) that have their origin in the CNS.

Longitudinal Tracts

The gray matter of the cell columns in the CNS is surrounded by bundles of myelinated axons (i.e., white matter) and unmyelinated axons that travel longitudinally along the length of the neural axis. This white matter can be divided into three layers: an inner, middle, and outer layer (Fig. 34-10). The inner layer contains short fibers that project for a maximum of approximately five segments before reentering the gray matter. The middle layer projects to six or more segments. The inner and middle layer fibers have many branches, or collaterals, that enter the gray matter of intervening segments. The outer layer contains large-diameter axons that can travel the entire length of the nervous system (Table 34-2). *Suprasegmental* is a term that refers to higher levels of the CNS, such as the brain stem and cerebrum and structures above a given CNS segment. The middle and outer layer fibers have suprasegmental projections.

The longitudinal layers are arranged in bundles, or fiber tracts, that contain axons that have either the same destination, origin, or function (Fig. 34-11). These longitudinal

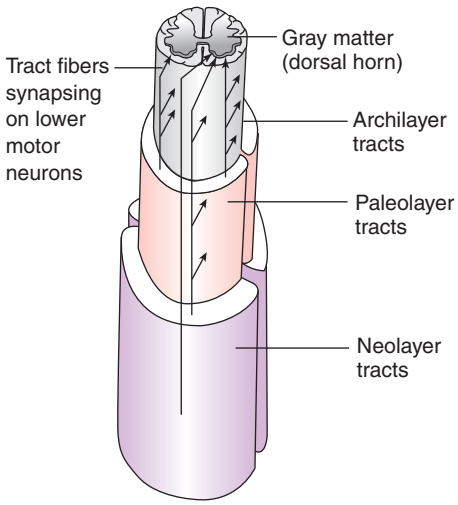


FIGURE 34-10. The three concentric subdivisions of the tract systems of the white matter. Migration of neurons into the archilayer converts it into the reticular formation of the white matter.

TABLE 34-2 Characteristics of the Concentric Subdivisions of the Longitudinal Tracts in the White Matter of the Central Nervous System

Characteristics	Archilayer Tracts	Paleolayer Tracts	Neolayer Tracts
Segmental span	Intersegmental (<5 segments)	Suprasegmental (≥5 segments)	Suprasegmental
Number of synapses	Multisynaptic	Multisynaptic but fewer than archilayer tracts	Monosynaptic with target structures
Conduction velocity	Very slow	Fast	Fastest
Examples of functional systems	Flexor withdrawal reflex circuitry	Spinothalamic tracts	Corticospinal tracts

tracts are named systematically to reflect their origin and destination; the origin is named first, and the destination is named second. For example, the spinothalamic tract originates in the spinal cord and terminates in the thalamus. The corticospinal tract originates in the cerebral cortex and ends in the spinal cord.

The Inner Layer. The inner layer of white matter contains the axons of neurons that connect neighboring segments of the nervous system. Axons of this layer permit the pool of motor neurons of several segments to work together as a functional unit. They also allow the afferent neurons of one segment to trigger reflexes that activate motor units in neighboring and in the same segments. It is the most primitive of the three layers, and it is sometimes called the *archilayer.* It is the first of the longitudinal layers to become functional, and its circuitry may be limited to reflex types of movements, including reflex movements of the fetus (i.e., quickening) that begin during the fifth month of intrauterine life.

The inner layer of the white matter differs from the other two layers in one important aspect. Many neurons in the embryonic gray matter migrate out into this layer, resulting in a rich mixture of neurons and local fibers called the *reticular formation.* The circuitry of most reflexes is contained in the reticular formation. In the brain stem, the reticular formation becomes quite large and contains major portions of vital reflexes, such as those controlling respiration, cardiovascular function, swallowing, and vomiting. A functional system called the *reticular activating system* (RAS) operates in the lateral portions of the reticular formation of the medulla, pons, and especially the midbrain. Information converging from all sensory modalities, including those of the somesthetic, auditory, visual, and visceral afferent nerves, bombards the neurons of this system.

The RAS has descending and ascending portions. The descending portion communicates with all spinal segmental levels through middle-layer reticulospinal tracts and serves to facilitate many cord-level reflexes. For example, it speeds reaction time and stabilizes postural reflexes. The ascending portion accelerates brain activity, particularly thalamic and cortical activity. This is reflected by the appearance of awake brain-wave patterns. Sudden stimuli result in protective and attentive postures and cause increased awareness.

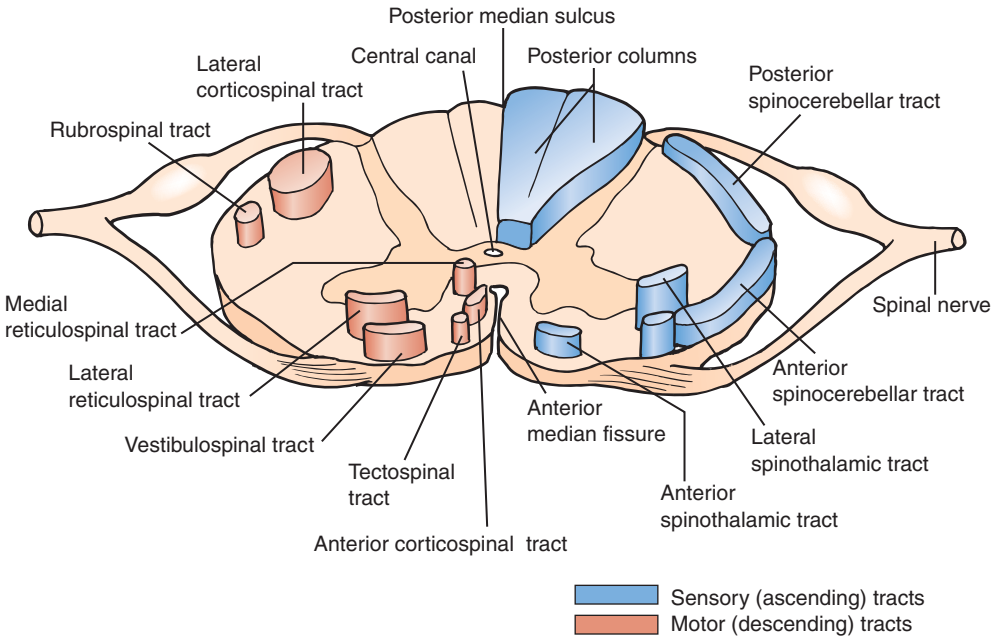


FIGURE 34-11. Transverse section of the spinal cord showing selected sensory and motor tracts. The tracts are bilateral but are indicated only on one half of the cord.

The Middle Layer. The middle layer of the white matter, sometimes called the *paleolayer,* contains most of the major fiber tract systems required for sensation and movement. It contains the ascending spinoreticular and spinothalamic tracts. This layer consists of larger-diameter and longer suprasegmental fibers, which ascend to the brain stem and are largely functional at birth. It facilitates many primitive functions, such as the auditory startle reflex, which occurs in response to loud noises. This reflex consists of turning the head and body toward the sound, dilating the pupils of the eyes, catching of the breath, and quickening of the pulse.

The Outer Layer. The outer layer of the tract systems is the newest of the three layers with respect to development, and it is sometimes called the *neolayer.* This pathway, which becomes functional at about 2 years of age, contains the pathways needed for bladder training. Myelination of these suprasegmental tracts, which include many pathways required for delicate and highly coordinated skills, is not complete until approximately the fifth year of life. This includes the development of tracts needed for fine manipulative skills, such as the finger–thumb coordination required for using tools and the toe movements needed for acrobatics. Being the last to be most developed and more superficial, the neolayer tracts are the most vulnerable to injury.

Collateral Communication Pathways. Axons in the archilayer and paleolayer characteristically possess many collateral branches that move into the gray cell columns or synapse with fibers of the reticular formation as the axon passes each succeeding CNS segment. Should a major axon be destroyed at some point along its course, these collaterals provide multisynaptic alternative pathways that bypass the local damage. Damage usually is followed by slow return of function, presumably through the collateral connections.

Neolayer tracts do not possess these collaterals but instead project mainly to the target neurons with which they communicate. When neolayer tracts are damaged, the paleolayer and archilayer tracts often remain functional, and rehabilitation methods can result in effective use of the older systems. Delicacy and refinement may be lost, but basic function remains. For example, when the corticospinal system, an important neolayer system that permits the fine manipulative control required for writing, is damaged, the remaining paleolayer systems, if intact, permit the grasping and holding of objects. The hand can still be used to perform its basic function, but the individual manipulation of the fingers is permanently lost.

In summary, the organization of the nervous system retains many early patterns of segmental development that were established during early embryonic life. Developmentally, the basic organizational pattern of the body is that of a longitudinal series of segments, each repeating the same fundamental pattern—a central cavity surrounded by an inner core of gray matter made up of nerve cells and a superficial layer of white matter containing axons of the longitudinal tract systems.

The 43 or more body segments are connected to their corresponding CNS or neural tube segments by segmental afferent and efferent PNS neurons. Afferent neuronal processes that carry sensory information enter the CNS through the dorsal root ganglia and are of four types: general somatic, special sensory, general visceral, and special visceral. Each of these afferent neurons synapses with its appropriate input association neurons in the cell columns of the dorsal horn. There are three cells columns of output association neurons in the ventral horn that synapse with lower motor neurons that exit the CNS in the ventral roots: general somatic efferent neurons that innervate skeletal muscles, pharyngeal efferent neurons that innervate pharyngeal muscles, and general visceral neurons that innervate visceral structures.

Longitudinal communication between CNS segments is provided by tracts that are arranged in three layers: an inner, a middle, and an outer layer. The inner layer of white matter contains the axons of neurons that connect neighboring segments of the nervous system. It contains a mixture of nerve cells and axons called the *reticular formation* and is the site of many important spinal cord and brain stem reflex circuits. The middle layer tracts provide the longitudinal communication between more distant segments of the nervous system; it contains most of the major fiber tract systems required for sensation and movement. The outer or neolayer systems, which become functional during infancy and childhood, provide the means for very delicate and discriminative function.

Spinal Cord and Brain

The Spinal Cord

In the adult, the spinal cord is found in the upper two thirds of the spinal canal of the vertebral column (Fig. 34-12A). It extends from the foramen magnum at the base of the skull to a cone-shaped termination, the conus medullaris, usually at the level of the first or second lumbar vertebra (L1 or L2) in the adult. The dorsal and ventral roots of the more caudal portions of the cord elongate during development and angle downward from the cord, forming what is called the *cauda equina* (from the Latin for "horse's tail"). The filum terminale, which is composed of nonneural tissues and the pia mater, continues caudally and attaches to the second sacral vertebra (S2).

The spinal cord is somewhat oval on transverse section, with the gray matter that forms the dorsal and ventral horns having the appearance of a butterfly or the letter "H" (see Fig. 34-12B). The central portion of the cord, which connects the dorsal and ventral horns, is called the *intermediate gray matter.* The intermediate gray matter surrounds the central canal. In the thoracic area, the small,

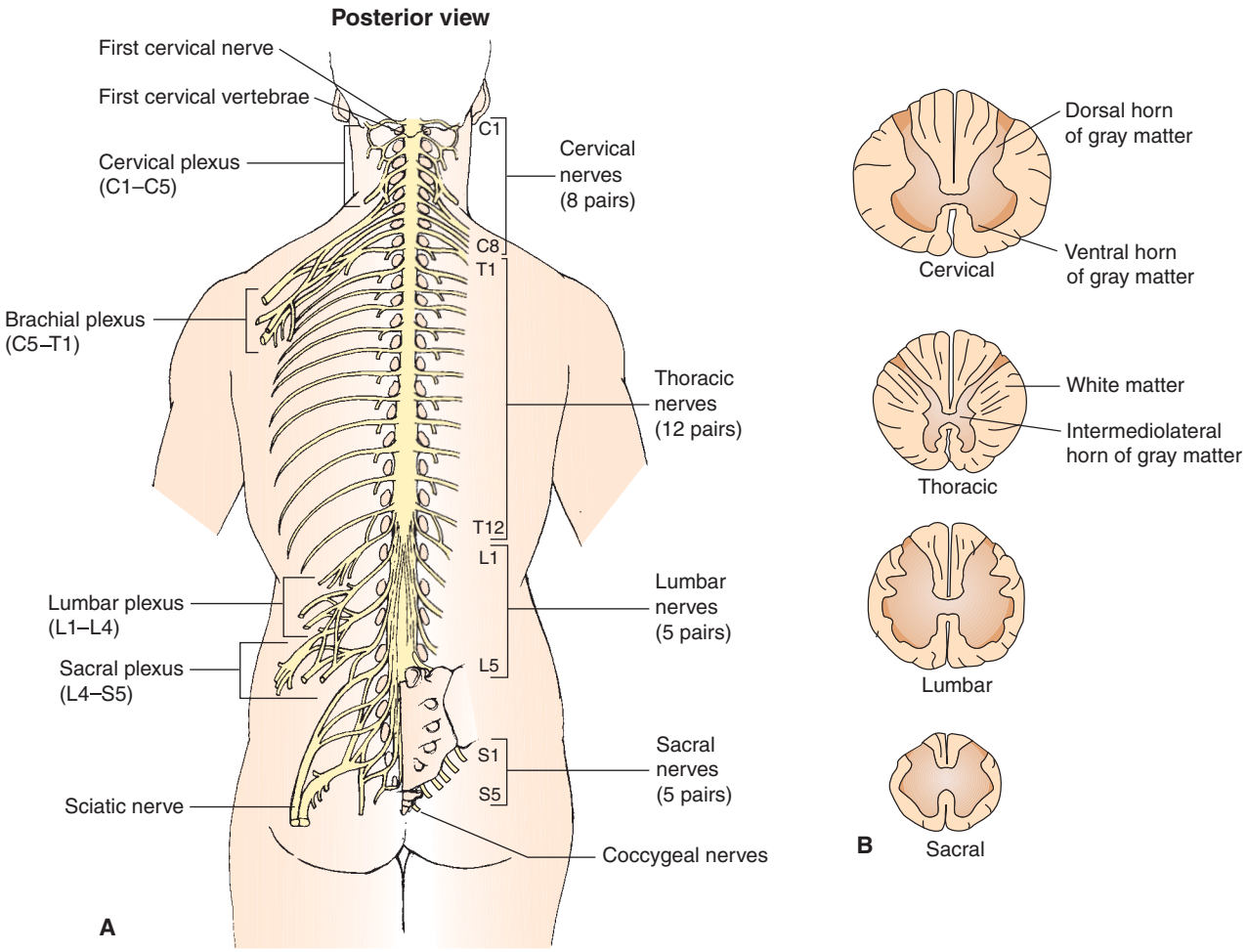


FIGURE 34-12. **(A)** Posterior view of the spinal cord, including portions of the major spinal nerves and some of the components of the major nerve plexuses. **(B)** Cross-sectional views of the spinal cord, showing regional variations in gray matter and increasing white matter as the cord ascends.

slender projections that emerge from the intermediate gray matter are called the *intermediolateral columns* of the horns. These columns contain the visceral OA neurons and the efferent neurons of the sympathetic nervous system.

The gray matter is proportional to the amount of tissue innervated by a given segment of the cord (see Fig. 34-12B). Larger amounts of gray matter are present in the lower lumbar and upper sacral segments, which supply the lower extremities, and in the fifth cervical segment to the first thoracic segment, which supply the upper limbs. The white matter in the spinal cord also increases progressively toward the brain because ever more ascending fibers are added and the number of descending axons is greater.

The spinal cord and the dorsal and ventral roots are covered by a connective tissue sheath, the pia mater, which also contains the blood vessels that supply the white and gray matter of the cord (Fig. 34-13). On the lateral sides of the spinal cord, extensions of the pia mater, the denticulate ligaments, attach the sides of the

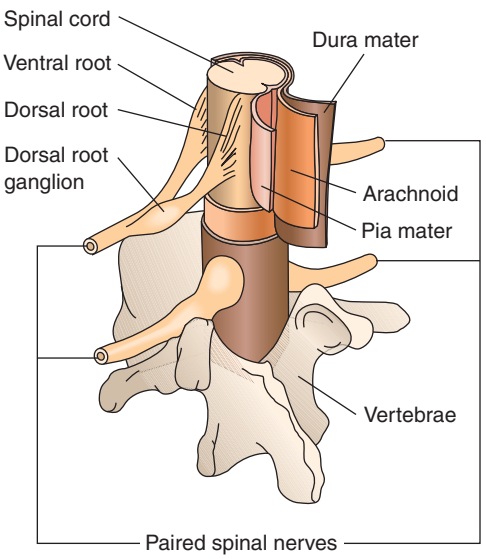


FIGURE 34-13. Spinal cord and meninges.

spinal cord to the bony walls of the spinal canal. Thus, the cord is suspended by both the denticulate ligaments and the segmental nerves. A fat- and vessel-filled epidural space intervenes between the spinal dura mater and the inner wall of the spinal canal.

The spinal cord, spinal nerves, and their supporting structures are protected by the vertebral column. The vertebral body is the anterior, more massive part of the bone that gives strength to the vertebral column and supports body weight. Each vertebral body has two pedicles that extend posteriorly and support the laterally oriented transverse processes of the laminae, which arch medially and fuse to continue as the spinal processes. The vertebral arch and posterior surface of the vertebral body form the wall of the vertebral foramen. The succession of vertebral foramina in the articulated spinal column forms the vertebral canal (spinal canal), which contains the spinal cord, meninges, fat, and spinal nerve roots. The spaces between the vertebral bodies are filled with fibrocartilaginous discs and stabilized with tough ligaments. A gap, the intervertebral foramen, occurs between each two succeeding pedicles, allowing for the exit of the segmental nerves and passage of blood vessels. Supporting structures of the spinal cord are discussed further in Chapter 36.

Early in fetal life, the spinal cord extends the entire length of the vertebral column and the spinal nerves exit through the intervertebral foramina (openings) near their level of origin. Because the vertebral column and spinal dura grow at a faster rate than the spinal cord, a disparity develops between each succeeding cord segment and the exit of its dorsal and ventral nerve roots through the corresponding intervertebral foramina. In the newborn, the cord terminates at the level of L2 or L3. In the adult, the cord usually terminates in the inferior border of L1, and the arachnoid and its enclosed subarachnoid space, which is filled with CSF, do not close down on the filum terminale until they reach the level of S2. This results in the formation of a pocket of CSF, the *dural cisterna spinalis,* which extends from approximately L2 to S2. Because this area contains an abundant supply of CSF and the spinal cord does not extend this far, the area often is used for sampling the CSF. A procedure called a *spinal tap,* or puncture, can be done by inserting a special needle into the dural sac at L3 or L4. The spinal roots, which are covered with pia mater, are in little danger of trauma from the needle used for this purpose.

Spinal Nerves

The peripheral nerves that carry information to and from the spinal cord are called *spinal nerves*. There are 32 or more pairs of spinal nerves (i.e., 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 2 or more coccygeal); each pair is named for the segment of the spinal cord from which it exits. Because the first cervical spinal nerve exits the spinal cord just above the first cervical vertebra (C1), the nerve is given the number of the bony vertebra just below it (see Fig. 34-12A). However, the numbering is changed for all lower levels. An extra cervical nerve, the C8 nerve, exits above the T1 vertebra, and each of the subsequent nerves are numbered for the vertebra just above its point of exit.

Each spinal cord segment communicates with its corresponding body segment through the paired segmental spinal nerves. Each spinal nerve, accompanied by the blood vessels supplying the spinal cord, enters the spinal canal through an intervertebral foramen, where it divides into two branches, or roots. One branch enters the dorsolateral surface of the cord (i.e., dorsal root), carrying the axons of afferent neurons into the CNS. The other branch leaves the ventrolateral surface of the cord (i.e., ventral root), carrying the axons of efferent neurons into the periphery. These two branches or roots fuse at the intervertebral foramen, forming the mixed spinal nerve—"mixed" because it has both afferent and efferent axons.

After emerging from the vertebral column, the spinal nerve divides into two branches or *rami* (singular, *ramus*): a small dorsal primary ramus and a larger ventral primary ramus (Fig. 34-14). The thoracic and upper lumbar spinal nerves also lead to a third branch, the ramus communicans, which contains sympathetic axons supplying the blood vessels, the genitourinary system, and the gastrointestinal system. The dorsal ramus contains sensory fibers from the skin and motor fibers to muscles of the back. The ventral primary ramus contains motor fibers that innervate the skeletal muscles of the anterior body wall and the legs and arms.

Spinal nerves do not go directly to skin and muscle fibers; instead, they form complicated nerve networks called *plexuses* (see Fig. 34-12A). A plexus is a site of intermixing nerve branches. Many spinal nerves enter a plexus and connect with other spinal nerves before exiting from the plexus. Nerves emerging from a plexus form progressively smaller branches that supply the skin and muscles of the various parts of the body. The PNS contains four major plexuses: the cervical plexus, the brachial plexus, the lumbar plexus, and the sacral plexus.

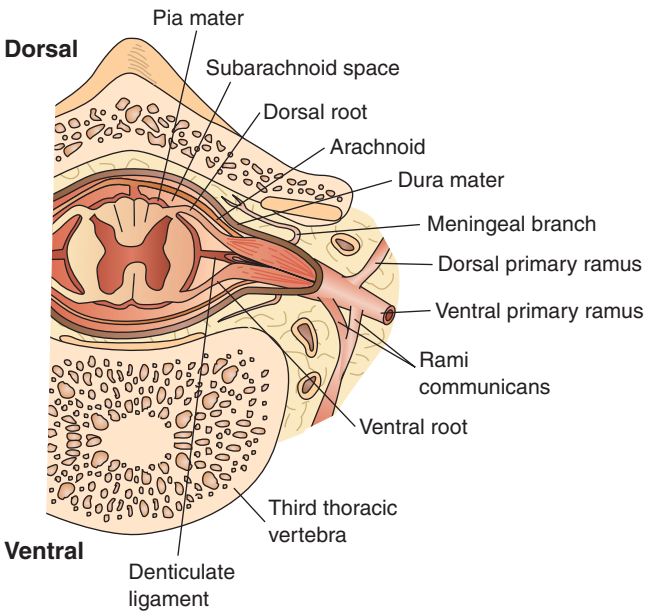


FIGURE 34-14. Cross-section of vertebral column at the level of the third thoracic vertebra, showing the meninges, the spinal cord, and the origin of a spinal nerve and its branches or rami.

Spinal Reflexes

A *reflex* is a highly predictable relationship between a stimulus and an elicited motor response. Its anatomic basis consists of an afferent neuron, the connection or synapse with CNS interneurons that communicate with the effector neuron, and the effector neuron that innervates a muscle or organ. Reflexes are essentially "wired in" to the CNS in that normally they are always ready to function; with training, most reflexes can be modulated to become parts of more complicated movements. A reflex may involve neurons in a single cord segment (i.e., segmental reflexes), several or many segments (i.e., intersegmental reflexes), or structures in the brain (i.e., suprasegmental reflexes). Two important types of spinal motor reflexes are the withdrawal reflex and myotatic reflex.

The *withdrawal reflex* is stimulated by a painful (nociceptive) stimulus and quickly moves the body part away from the offending stimulus, usually by flexing a limb part. The withdrawal reflex is a powerful reflex, taking precedence over other reflexes associated with locomotion. Any of the major joints may be involved, depending on the site of afferent stimulation. All the joints of an extremity (e.g., finger, wrist, elbow, shoulder) typically are involved. This complex, polysynaptic reflex also shifts postural support to the opposite side of the body with a crossed extensor reflex and simultaneously alerts the forebrain to the offending stimulus event. The withdrawal reflex also can produce contraction of muscles other than the extremities. For example, irritation of the abdominal viscera may cause contraction of the abdominal muscles.

The *myotatic* or *stretch reflex* controls muscle tone and helps maintain posture. Specialized sensory nerve terminals in skeletal muscles and tendons relay information on muscle stretch and joint tension to the CNS (see Chapter 36). This information, which drives postural reflex mechanisms, also is relayed to the thalamus and the sensory cortex and is experienced as *proprioception*, the sense of body movement and position.

The Brain

The brain is divided into three regions, the hindbrain, the midbrain, and the forebrain (Fig. 34-15). The hindbrain includes the medulla oblongata, the pons, and its dorsal outgrowth, the cerebellum. Midbrain structures include two pairs of dorsal enlargements, the superior and inferior colliculi. The forebrain, which consists of two hemispheres and is covered by the cerebral cortex, contains central masses of gray matter, the basal ganglia (discussed in Chapter 36), and the rostral end of the neural tube, the diencephalon with its adult derivatives—the thalamus and hypothalamus. With the exception of the olfactory and optic nerves, which are considered part of the forebrain, the motor and sensory nuclei of the 3rd to the 12th cranial nerves are located in the midbrain and hindbrain.

An important concept is that the more rostral, recently developed parts of the neural tube gain dominance or control over regions and functions at lower levels. They do not replace the earlier developed circuitry but merely dominate it. After damage to the more vulnerable parts of the forebrain, as occurs with severe brain injury, a brain stem–controlled organism remains that is capable of breathing and may survive if the environmental temperature is regulated and nutrition and other aspects of care are provided. However, all aspects of intellectual function, experience, perception, and memory usually are permanently lost. The organization of content in this section moves from the less developed circuitry of the hindbrain to the more dominant and recently developed structures of the forebrain.

Hindbrain

During embryonic development, the hindbrain becomes subdivided into the three important structures, the cerebellum, the pons, and the medullar oblongata—also referred to as the medulla. The pons and cerebellum derive from the rostral half of the hindbrain (called the *metencephalon*) and the medulla from the caudal half

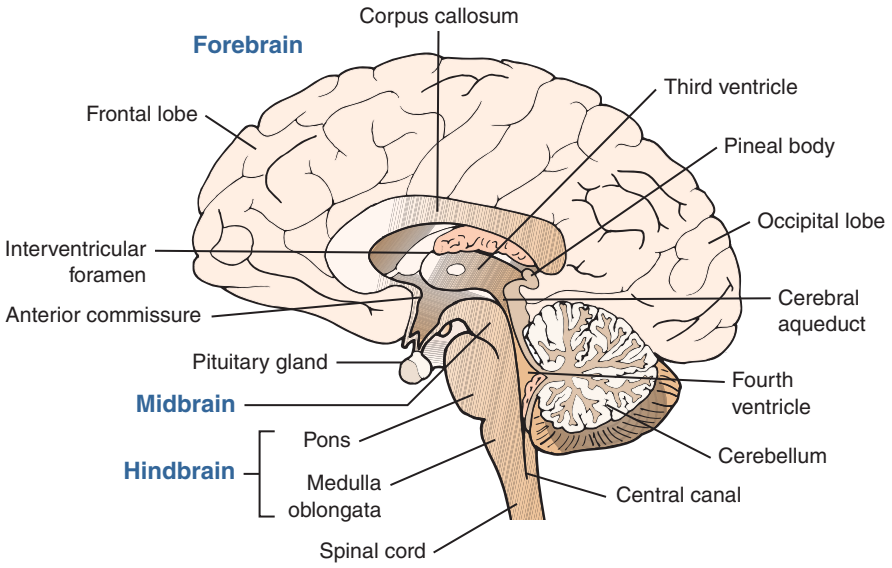


FIGURE 34-15. Midsagittal section showing structures of the hindbrain, midbrain, and forebrain.

(called the *myelencephalon*). The CSF-filled tube becomes the fourth ventricle, which is continuous with the cerebral aqueduct of the midbrain (Fig. 34-15). The cerebellum, the "little brain," is an important movement control center (see Chapter 36). It receives massive axonal inputs from the spinal cord and the pons. The spinal cord provides information about the body's position in space, and the pons relays information from the cerebral cortex specifying the goals of intended movements.

Brain Stem. The term *brain stem* often is used to include the medulla and pons. This area has the organization of spinal cord segments, except that more longitudinal cell columns are present, reflecting the increased complexity of the cranial segmental nerves. In the brain stem, the reticular formation has been greatly expanded. Certain groups of neurons termed *vital centers* are located in the reticular formation of the pons and medulla. These centers include the respiratory, cardiovascular, and vasomotor centers. Still other centers in the brain stem are concerned with swallowing, intestinal movements, control of micturition, and a variety of more specific functions such as salivation and pupillary diameter.

The *medulla* represents the caudal five segments of the brain part of the neural tube; the cranial nerve branches entering and leaving it have functions similar to the spinal segmental nerves. Although the ventral horn areas in the medulla are quite small, the dorsal horn areas are enlarged, processing the large amount of the information pouring through the cranial nerves. Cranial nerves XII (hypoglossal), X (vagus), and IX (glossopharyngeal) have their origin in the medulla (see Table 34-1).

The *pons*, which develops from the fifth neural tube segment, is located between the medulla and the midbrain. Dorsally, it forms part of the anterior wall of the fourth ventricle (see Fig. 34-15). As the name implies (*pons,* Latin for "bridge"), the pons is composed chiefly of conduction fibers. The enlarged area on the ventral surface of the pons contains the pontine nuclei, which receive information from all parts of the cerebral cortex. The axons of these neurons form a massive bundle that swings around the lateral side of the fourth ventricle to enter the cerebellum. In the pons, the reticular formation is large and contains the circuitry for masticating food and manipulating the jaws during speech. Cranial nerves VIII, VII, and VI have their origin in the pons (see Table 34-1).

Midbrain

The midbrain develops from the fourth segment of the neural tube, and its organization is similar to that of a spinal segment. Two prominent bundles of nerve fibers, the *cerebral peduncles,* pass along the ventral surface of the midbrain. These fibers include the corticospinal tracts and are the main motor pathways between the forebrain and the pons. On the dorsal surface, four "little hills," the *superior* and *inferior colliculi,* are areas of cortical formation. The inferior colliculus is involved in directional head turning and, to some extent, in experiencing the direction of sound sources. The superior colliculi are essential to the reflex mechanisms that control conjugate eye movements when the visual environment is surveyed. Two general somatic efferent cranial nerves, the oculomotor nerve, or cranial nerve III, and the trochlear nerve, or cranial nerve IV, exit the midbrain (see Table 34-1).

Forebrain

The most rostral part of the brain, the forebrain consists of the telencephalon, or "end brain," and the diencephalon, or "between brain." The diencephalon forms the core of the forebrain, and the telencephalon forms the cerebral hemispheres.

Diencephalon. Three of the most forward brain segments form an enlarged dorsal horn and ventral horn with a narrow, deep, enlarged central canal—the third ventricle—separating the two sides. This region is called the *diencephalon*. The dorsal horn part of the diencephalon is the thalamus and subthalamus, and the ventral horn part is the hypothalamus (Fig. 34-16). The optic nerve, or cranial nerve II, and retina are outgrowths of the diencephalon.

The thalamus consists of two large, egg-shaped masses, one on either side of the third ventricle. The thalamus is divided into several major parts, and each part is divided into distinct nuclei, which are the major relay stations for information going to and from the cerebral cortex. All sensory pathways have direct projections to thalamic nuclei, which convey the information to restricted areas of the sensory cortex. Coordination and integration of peripheral sensory stimuli occur in the thalamus, along with some crude interpretation of highly emotion-laden auditory experiences that not only occur but can be remembered. For example, a person can recover from a deep coma in which cerebral cortex activity was minimal and remember some of what was said at the bedside.

The thalamus also plays a role in relaying critical information regarding motor activities to and from selected areas of the motor cortex. Two neuronal circuits are significant in this regard. One is the pathway from the cerebral cortex to the pons and cerebellum and then, by way of the thalamus, back to the motor cortex. The second is the feedback circuit that travels from the cortex to the basal ganglia, then to the thalamus, and from the thalamus back to the cortex. The subthalamus also contains movement control systems related to the basal ganglia.

Through its connections with the ascending reticular activating system, the thalamus processes neural influences that are basic to cortical excitatory rhythms (i.e., those recorded on the electroencephalogram), to essential sleep–wake cycles, and to the process of attending to stimuli. Besides their cortical connections, the thalamic nuclei have connections with each other and with neighboring nonthalamic brain structures such as the limbic system. Through their connections with the limbic system, some thalamic nuclei are involved in relating stimuli with the emotional responses they evoke.

The ventral horn portion of the diencephalon is the hypothalamus, which borders the third ventricle and includes a ventral extension, the posterior pituitary gland or neurohypophysis. The hypothalamus is the area of

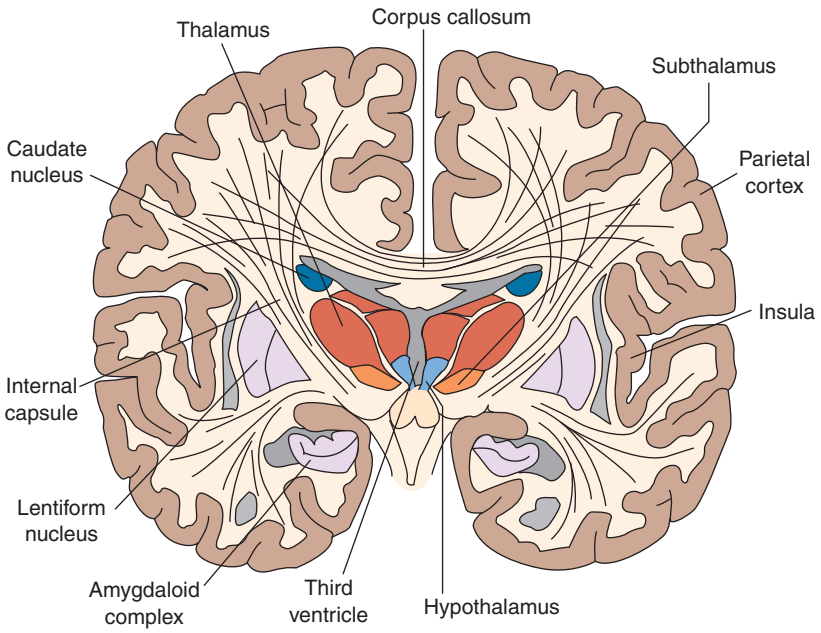


FIGURE 34-16. Frontal section of the brain passing through the third ventricle, showing the thalamus, subthalamus, hypothalamus, internal capsule, corpus callosum, basal ganglia (caudate nucleus, lentiform nucleus), amygdaloid complex, insula, and parietal cortex.

master-level integration of homeostatic control of the body's internal environment. Maintenance of blood gas concentration, water balance, food consumption, and major aspects of endocrine and ANS control require hypothalamic function.

The internal capsule is a broad band of projection fibers that lies between the thalamus medially and the basal ganglia laterally (see Fig. 34-16). It contains all of the fibers that connect the cerebral cortex with deeper structures, including the basal ganglia, thalamus, midbrain, pons, medulla, and spinal cord.

Cerebral Hemispheres. The two cerebral hemispheres are lateral outgrowths of the diencephalon. The cerebral hemispheres contain the lateral ventricles, which are connected with the third ventricle of the diencephalon by a small opening called the *interventricular foramen* (see Fig. 34-15). Axons of the olfactory nerve, or cranial nerve I, terminate in the most primitive portion of the cerebrum—the olfactory bulb, where initial processing of olfactory information occurs. Projection axons from the olfactory bulb relay information through the olfactory tracts to the thalamus and to other parts of the cerebral cortex (i.e., orbital cortex), where olfactory-related reflexes and olfactory experience occur.

The *corpus callosum* is a massive commissure, or bridge, of myelinated axons that connects the cerebral cortex of the two sides of the brain (see Fig. 34-16). Two smaller commissures, the anterior and posterior commissures, connect the two sides of the more specialized regions of the cerebrum and diencephalon.

The surface of the hemispheres, which contains the six-layered neocortex, can be described as lateral (side), medial (area between the two sides of the brain), and basal (ventral). The surface of the hemispheres contains many ridges and grooves. A *gyrus* is the ridge between two grooves, and the groove is called a *sulcus* or *fissure*. The cerebral cortex is arbitrarily divided into lobes named after the bones that cover them: the frontal, parietal, temporal, and occipital lobes (Fig. 34-17A).

Frontal Lobe. The frontal lobe extends from the frontal pole to the central sulcus and is separated from the temporal lobe by the lateral sulcus. The frontal lobe can be subdivided rostrally into the frontal pole and laterally into the superior, middle, and inferior gyri, which continue on the undersurface over the eyes as the orbital cortex. These areas are associated with the medial thalamic nuclei, which also are related to the limbic system. In terms of function, the prefrontal cortex is thought to be involved in anticipation and prediction of consequences of behavior.

The precentral gyrus (area 4), next to the central sulcus, is the *primary motor cortex* (see Fig. 34-17B). This area of the cortex provides precise movement control for distal flexor muscles of the hands and feet and of the phonation apparatus required for speech. Just rostral to the precentral gyrus is a region of the frontal cortex called the *premotor* or *motor association cortex*. This region (area 8 and rostral area 6) is involved in the planning of complex learned movement patterns. The primary motor cortex and the association motor cortex are connected with lateral thalamic nuclei, through which they receive feedback information from the basal ganglia and cerebellum. On the medial surface of the hemisphere, the premotor area includes a *supplementary motor cortex* involved in the control of bilateral movement patterns requiring great dexterity.

Parietal Lobe. The parietal lobe of the cerebrum lies behind the central sulcus and above the lateral sulcus. The strip of cortex bordering the central sulcus is called the *primary somatosensory cortex* (areas 3, 1, and 2) because it receives very discrete sensory information

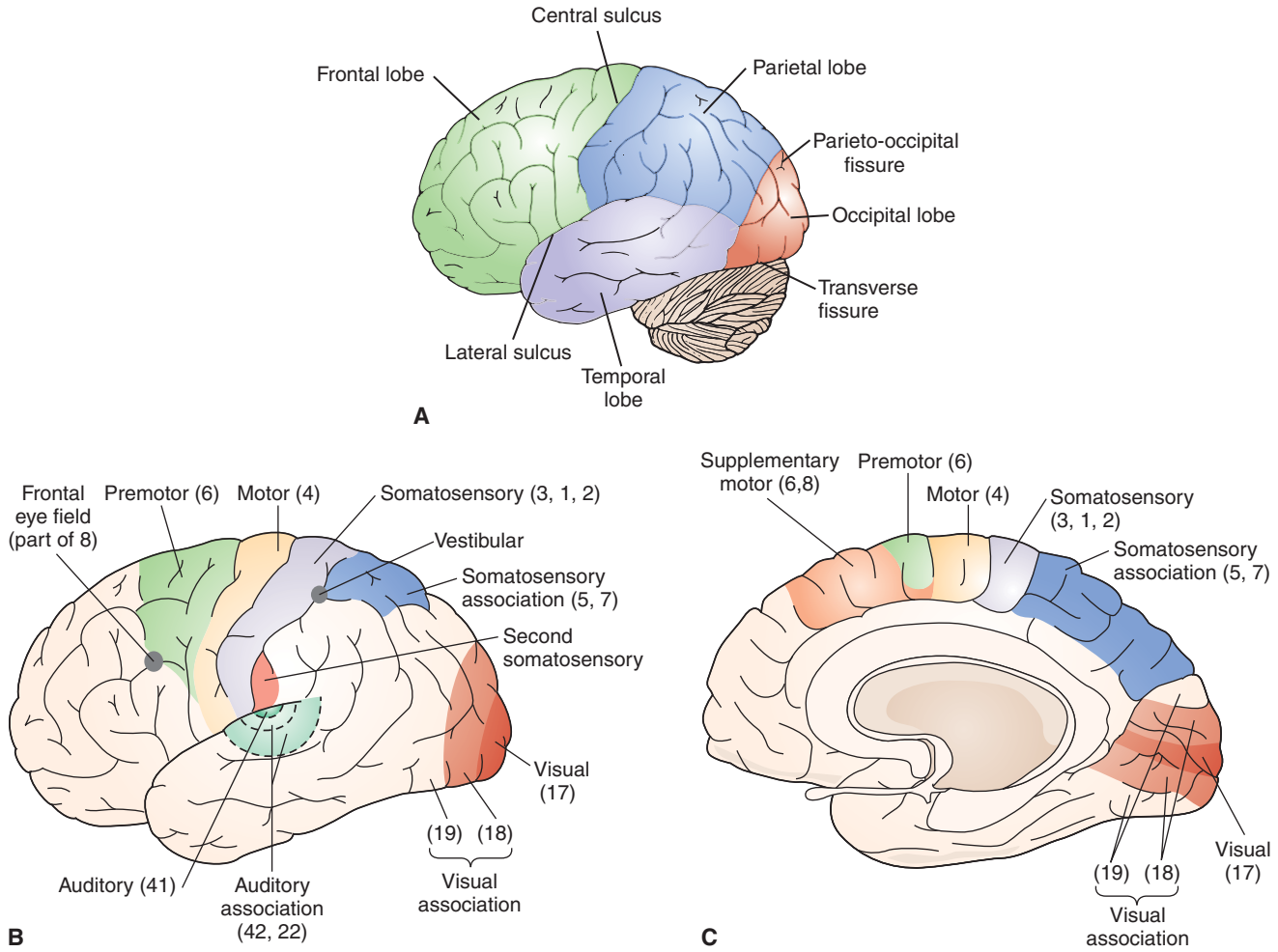


FIGURE 34-17. Cerebral hemispheres. **(A)** Lateral view of the cerebral hemispheres showing the frontal, parietal, occipital, and temporal lobes. **(B)** Left lateral view of the motor and sensory areas of the cerebral cortex. **(C)** Areas of the motor and sensory cortex in a brain that has been sectioned in the median plane.

from the lateral nuclei of the thalamus. Just behind the primary sensory cortex is the *somatosensory association cortex* (areas 5 and 7), which is connected with the thalamic nuclei and with the primary sensory cortex. This region is necessary for perceiving the meaningfulness of integrated sensory information from various sensory systems, especially the perception of "where" the stimulus is in space and in relation to body parts. Localized lesions of this region can result in the inability to recognize the meaningfulness of an object (i.e., agnosia). With the person's eyes closed, a screwdriver can be felt and described as to shape and texture. Nevertheless, the person cannot integrate the sensory information required to identify it as a screwdriver.

Temporal Lobe. The temporal lobe lies below the lateral sulcus and merges with the parietal and occipital lobes. It includes the temporal pole and three primary gyri: the superior, middle, and inferior gyri. The primary auditory cortex (area 41) involves the part of the superior temporal gyrus that extends into the lateral sulcus. This area is particularly important in discrimination of sounds entering opposite ears. It receives auditory input projections by way of the inferior colliculus of the midbrain and a ventrolateral thalamic nucleus. The more exposed part of the superior temporal gyrus involves the auditory association area (area 22). The recognition of certain sound patterns and their meaning requires the function of this area. The remaining portion of the temporal cortex is less defined functionally but apparently is important in long-term memory recall. This is particularly true with respect to perception and memory of complex sensory patterns, such as geometric figures and faces (i.e., recognition of "what" or "who" the stimulus is). Irritation or stimulation can result in vivid hallucinations of long-past events.

Occipital Lobe. The occipital lobe lies posterior to the temporal and parietal lobes and is only arbitrarily separated from them. The medial surface of the occipital lobe contains a deep sulcus extending from the limbic lobe to the occipital pole, the *calcarine sulcus,* which is surrounded

by the primary visual cortex (area 17). Stimulation of this cortex causes the experience of bright lights called *phosphenes* in the visual field. Just superior and inferior and extending onto the lateral side of the occipital pole is the *visual association cortex* (areas 18 and 19). This area is closely connected with the primary visual cortex and with complex nuclei of the thalamus. Integrity of the association cortex is required for *gnostic visual function*, by which the meaningfulness of visual experience, including experiences of color, motion, depth perception, pattern, form, and location in space, occurs.

The neocortical areas of the parietal lobe, between the somatosensory and the visual cortices, have a function in relating the texture, or "feel," and location of an object with its visual image. Between the auditory and visual association areas, the *parieto-occipital region* is necessary for relating the meaningfulness of a sound and image to an object or person.

Limbic System. The medial aspect of the cerebrum is organized into concentric bands of cortex, the *limbic system* (from the Latin *limbus,* "border"), which surrounds the connection between the lateral and third ventricles. The innermost band just above and below the cut surface of the corpus callosum is folded out of sight but is a three-layered cortex ending as the hippocampus in the temporal lobe. Just outside the folded area is a band of transitional cortex, which includes the cingulate and the parahippocampal gyri (Fig. 34-18). The limbic lobe has reciprocal connections with the medial and the intralaminar nuclei of the thalamus, with the deep nuclei of the cerebrum (e.g., amygdaloid nuclei, septal nuclei), and with the hypothalamus. Overall, this region of the brain is involved in emotional experience and in the control of emotion-related behavior. Stimulation of specific areas in this system can lead to feelings of dread, high anxiety, or exquisite pleasure. It also can result in violent behaviors, including attack, defense, or explosive and emotional speech.

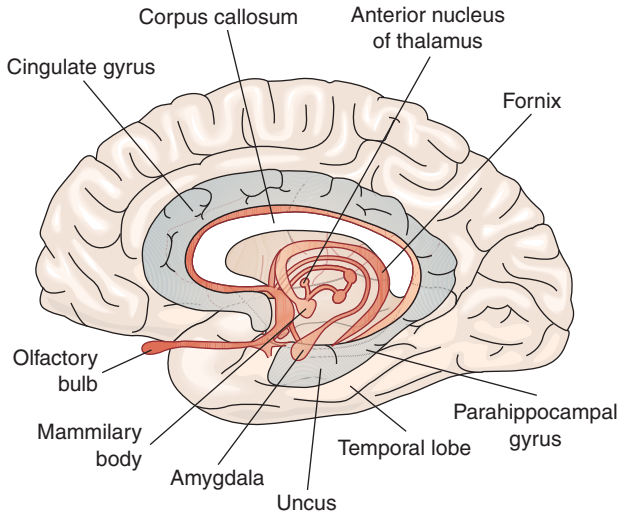


FIGURE 34-18. The limbic system includes the limbic cortex (cingulate gyrus, parahippocampal gyrus, uncus) and associated subcortical structures (mammilary body, amygdala).

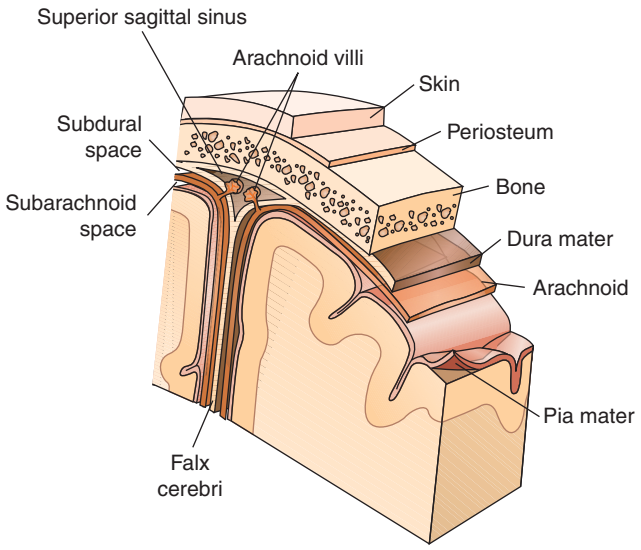


FIGURE 34-19. The cranial meninges. Arachnoid villi, shown within the superior sagittal sinus, are one site of cerebrospinal fluid absorption into the blood.

Meninges

Inside the skull and vertebral column, the brain and spinal cord are loosely suspended and protected by several connective tissue sheaths called the *meninges* (Fig. 34-19). The surfaces of the spinal cord, brain, and segmental nerves are covered with a delicate connective tissue layer called the *pia mater* (Latin for "delicate mother"). The surface blood vessels and those that penetrate the brain and spinal cord are encased in this protective tissue layer. A second, very delicate, nonvascular, and waterproof layer, called the *arachnoid,* encloses the entire CNS. The arachnoid layer is named for its spider-web appearance. The CSF is contained in the subarachnoid space. Immediately outside the arachnoid is a continuous sheath of strong connective tissue, the *dura mater* (Latin for "tough mother"), which provides the major protection for the brain and spinal cord. The cranial dura often splits into two layers, with the outer layer serving as the periosteum of the inner surface of the skull.

The inner layer of the dura forms two major folds. The first, a longitudinal fold called the *falx cerebri,* separates the cerebral hemispheres and fuses with a second transverse fold, called the *tentorium cerebelli* (Fig. 34-20). The tentorium cerebelli separates the anterior and middle depression in the skull (cranial fossae), which contains the cerebral hemispheres, from the posterior fossa, found interiorly and containing the brain stem and cerebellum. A semicircular gap, or incisura, is formed at the midline to permit the midbrain to pass forward from the posterior fossa.

Ventricular System and Cerebrospinal Fluid

The ventricular system is a series of CSF-filled cavities in the brain (Fig. 34-21). Cerebrospinal fluid is a clear, colorless ultrafiltrate of blood plasma, composed of 99% water with other constituents, making it close to the composition of the brain extracellular fluid. Humans

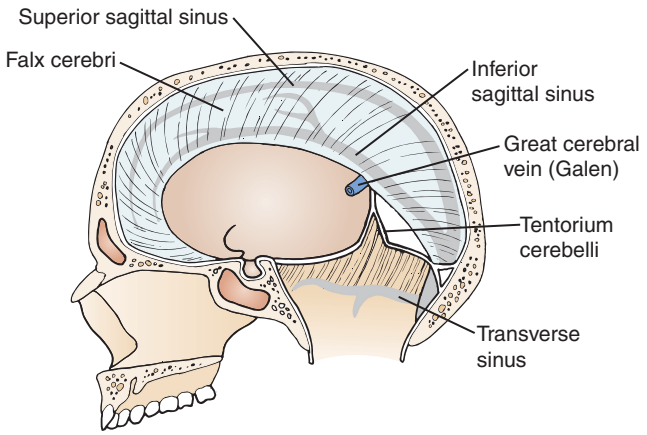


FIGURE 34-20. Cranial dura mater. The skull is open to show the falx cerebri and the right and left portions of the tentorium cerebelli, as well as some of the cranial venous sinuses.

secrete approximately 500 mL of CSF each day. However, only approximately 150 mL is in the ventricular system at any one time, meaning that the CSF is continuously being absorbed.

The CSF provides a supporting and protective fluid in which the brain and spinal cord float, and it helps to maintain a constant ionic environment that serves as a medium for diffusion of nutrients, electrolytes, and metabolic end products into the extracellular fluid surrounding CNS neurons and glia. Filling the ventricles, the CSF supports the mass of the brain. Because it fills the subarachnoid space surrounding the CNS, a physical force delivered to either the skull or spine is to some extent diffused and cushioned.

The CSF is produced by tiny reddish masses of specialized capillaries from the pia mater, called the *choroid plexus*, that project into the ventricles. Once produced,

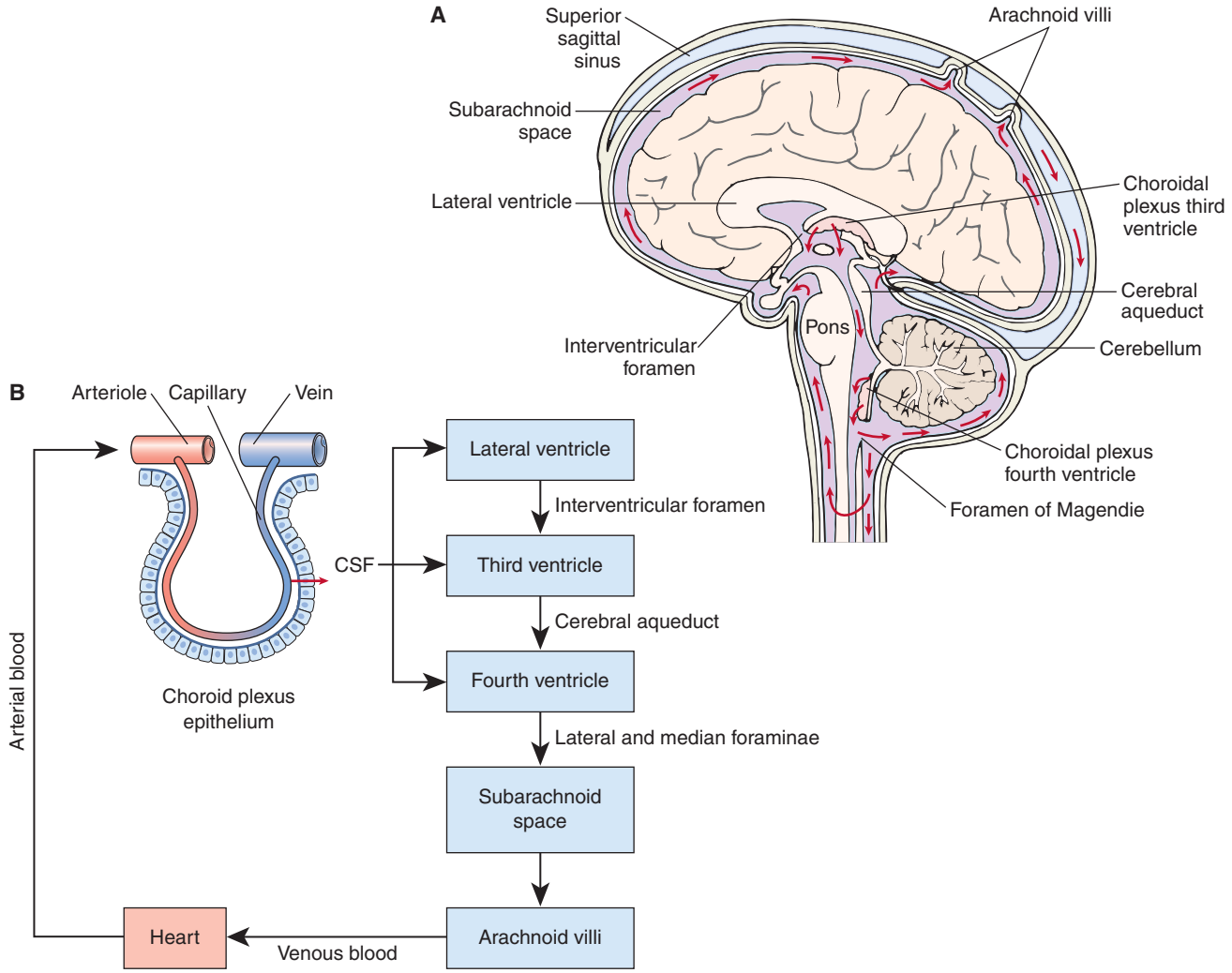


FIGURE 34-21. **(A)** The flow of cerebrospinal fluid (CSF) from the time of its formation from blood in the choroid plexuses until its return to the blood in the superior sagittal sinus. Plexuses in the lateral ventricles are not illustrated. **(B)** CSF is a blood filtrate produced by the choroid plexus epithelium that is found in each brain ventricle. The flow of CSF from the lateral ventricles flows through the interventricular foramen (Monroe) into the third ventricle. From the third ventricle, CSF is conveyed to the fourth ventricle via the cerebral aqueduct (Sylvius). Three openings, a midline foramen of Magendie and two lateral foramina (Luschka), pass the CSF into the subarachnoid space, where it is returned to the venous circulation through the arachnoid villi.

the CSF flows freely through the ventricles. Three openings, or foramina, allow the CSF to pass into the subarachnoid space. Two of these, the foramina of Luschka, are located at the lateral corners of the fourth ventricle. The third, the median foramen of Magendie, is in the midline at the caudal end of the fourth ventricle (see Fig. 34-21B). Approximately 30% of the CSF passes down into the subarachnoid space that surrounds the spinal cord, mainly on its dorsal surface, and moves back up to the cranial cavity along its ventral surface.

Reabsorption of CSF into the vascular system occurs along the sides of the superior sagittal sinus in the anterior and middle fossa. Here, the waterproof arachnoid has protuberances, the *arachnoid villi,* that penetrate the inner dura and venous walls of the superior sagittal sinus (see Fig. 34-21A). The arachnoid villi function as one-way valves, permitting CSF outflow into the blood but not allowing blood to pass into the arachnoid spaces.

Blood-Brain and Cerebrospinal Fluid–Brain Barriers

Maintenance of a chemically stable environment is essential to the function of the brain. In most regions of the body, extracellular fluid undergoes small fluctuations in pH and concentrations of hormones, amino acids, and potassium ions during routine daily activities such as eating and exercising. If the brain were to undergo such fluctuations, the result would be uncontrolled neural activity because some substances such as amino acids act as neurotransmitters, and ions such as potassium influence the threshold for neural firing. Two barriers, the blood-brain barrier and the CSF-brain barrier, provide the means for maintaining the stable chemical environment of the brain. Only water, carbon dioxide, and oxygen enter the brain with relative ease; the transport of other substances between the brain and the blood is slower and more controlled.

Blood-Brain Barrier. The blood-brain barrier depends on the unique characteristics of the brain capillaries. The endothelial cells of brain capillaries are joined by continuous tight junctions. In addition, most brain capillaries are completely surrounded by a basement membrane and by the processes of previously described supporting astrocyte cells of the brain (Fig. 34-22). The blood-brain barrier permits passage of essential substances while excluding unwanted materials. Reverse transport systems remove materials from the brain. Large molecules such as proteins and peptides are largely excluded from crossing the blood-brain barrier. Acute cerebral lesions, such as trauma and infection, increase the permeability of the blood-brain barrier and alter brain concentrations of proteins, water, and electrolytes.

The blood-brain barrier prevents many drugs from entering the brain. Most highly water-soluble compounds are excluded from the brain, especially molecules with high ionic charge, such as many of the catecholamines. In contrast, many lipid-soluble molecules cross the lipid layers of the blood-brain barrier with ease. Alcohol, nicotine, and heroin are very lipid soluble and rapidly enter the brain. Some substances that enter the capillary endothelium are converted by metabolic processes to a chemical form incapable of moving into the brain.

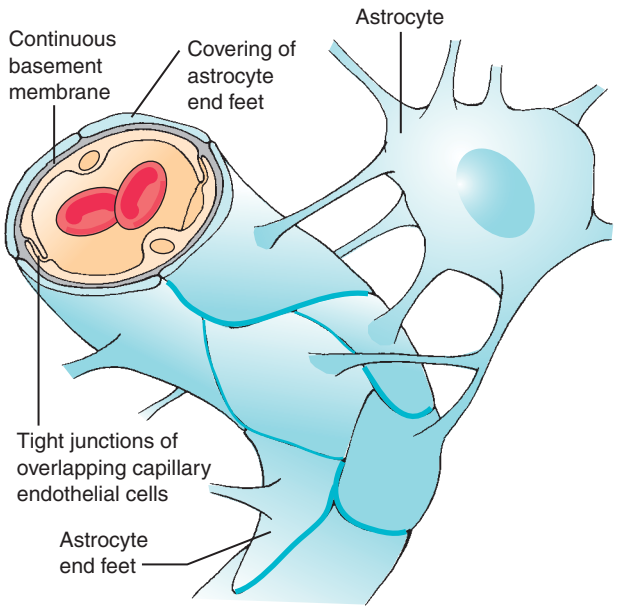


FIGURE 34-22. The three components of the blood-brain barrier: the astrocyte and astrocyte end feet that encircle the capillary, the capillary basement membrane, and the tight junctions that join the overlapping capillary endothelial cells.

The cerebral capillaries are much more permeable at birth than in adulthood, and the blood-brain barrier develops during the early years of life. In severely jaundiced infants, bilirubin can cross the immature blood-brain barrier, producing kernicterus and brain damage (see Chapter 13). In adults, the mature blood-brain barrier prevents bilirubin from entering the brain, and the nervous system is not affected.

Cerebrospinal Fluid–Brain Barrier. The ependymal cells covering the choroid plexus are linked together by tight junctions, forming a blood-CSF barrier to diffusion of many molecules from the blood plasma of choroid plexus capillaries to the CSF. Water is transported through the choroid epithelial cells by osmosis. Oxygen and carbon dioxide move into the CSF by diffusion, resulting in partial pressures roughly equal to those of plasma. The high sodium and low potassium contents of the CSF are actively regulated and kept relatively constant. Lipids and nonpeptide hormones diffuse through the barrier rather easily, but most large molecules, such as proteins, peptides, many antibiotics, and other medications, do not normally get through. Many substances such as proteins, sodium ions, and a number of micronutrients such as vitamins C, B_6 (pyridoxine), and folate are actively secreted into the CSF by the choroid epithelium. Because the brain and spinal cord have no lymphatic channels, the CSF serves this function.

There are several specific areas of the brain where the blood-CSF barrier does not exist. One area is at the

caudal end of the fourth ventricle, where specialized receptors for the carbon dioxide level of the CSF influence respiratory function. Another area consists of the walls of the third ventricle, which permit hypothalamic neurons to monitor blood glucose levels. This mechanism permits hypothalamic centers to respond to these blood glucose levels, contributing to hunger and eating behaviors.

In summary, in the adult, the spinal cord is in the upper two thirds of the spinal canal of the vertebral column. On transverse section, the spinal cord has an oval shape, and the internal gray matter has the appearance of a butterfly or letter "H." The dorsal horns contain the IA neurons and receive afferent information from dorsal root and other connecting neurons. The ventral horns contain the output association neurons and lower motor neurons that leave the cord by the ventral roots. Thirty-two pairs of spinal nerves (i.e., 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 2 or more coccygeal) are present. Each pair communicates with its corresponding body segments. The spinal nerves and the blood vessels that supply the spinal cord enter the spinal canal through an intervertebral foramen. After entering the foramen, they divide into two branches, or roots, one of which enters the dorsolateral surface of the cord (i.e., dorsal root), carrying the axons of afferent neurons into the CNS. The other root leaves the ventrolateral surface of the cord (i.e., ventral root), carrying the axons of efferent neurons into the periphery. These two roots fuse at the intervertebral foramen, forming the mixed spinal nerve.

The brain can be divided into three regions: the hindbrain, the midbrain, and the forebrain. The hindbrain, consisting of the medulla oblongata, pons, and cerebellum, contains the neuronal circuits for the eating, breathing, and locomotive functions required for survival. Cranial nerves XII, XI, X, IX, VIII, VII, VI, and V are located in the hindbrain. The midbrain contains cranial nerves IV and III.

The forebrain is the most rostral part of the brain; it consists of the diencephalon and the telencephalon. The diencephalon forms the core of the forebrain, and the telencephalon forms the cerebral hemispheres. The dorsal horn part of the diencephalon contains the thalamus and subthalamus, and the ventral horn contains the hypothalamus. All sensory pathways have direct projections to the thalamic nuclei, which convey the information to restricted parts of the sensory cortex. The hypothalamus functions in the homeostatic control of the internal environment. The cerebral hemispheres are the lateral outgrowths of the diencephalon and are arbitrarily divided into lobes—the frontal, parietal, temporal, and occipital lobes. The premotor area and primary motor cortex are located in the frontal lobe; the primary sensory cortex and somatosensory association area are in the parietal cortex; the primary auditory cortex and the auditory association area are in the temporal lobe; and the primary visual cortex and association visual cortex are in the occipital lobe. The limbic system, which is involved in emotional experience and release of emotional behaviors, is located in the medial aspect of the cerebrum.

The brain is enclosed and protected by connective tissue sheaths (i.e., the pia mater, arachnoid, and dura mater) called the *meninges*. The protective CSF in which the brain and spinal cord float isolates them from minor and moderate trauma. The CSF is secreted into the ventricles, circulates through the ventricular system, passes outside to surround the brain, and is reabsorbed into the venous system through the arachnoid villi. The blood-brain barrier and CSF-brain barrier protect the brain from substances in the blood that would disrupt brain function.

The Autonomic Nervous System

The ability to maintain homeostasis and perform the activities of daily living in an ever-changing physical environment is largely vested in the ANS. The ANS functions at the subconscious level and is involved in regulating, adjusting, and coordinating vital visceral functions such as blood pressure and flow. The ANS is strongly affected by emotional influences and is involved in many of the expressive aspects of behavior. Blushing, pallor, palpitations of the heart, clammy hands, and dry mouth are several emotional expressions that are mediated through the ANS.

As with the somatic nervous system, the ANS is represented in both the CNS and the PNS. Traditionally, the ANS has been defined as a general efferent system innervating visceral organs. The efferent outflow from the ANS has two divisions: the sympathetic nervous system and the parasympathetic nervous system. The afferent input to the ANS is provided by visceral afferent neurons, usually not considered to be part of the ANS.

The functions of the sympathetic nervous system include maintaining body temperature, respiration, digestion, and elimination and adjusting blood flow and blood pressure to meet the changing needs of the body. The sympathoadrenal system also can discharge as a unit when there is a critical threat to the integrity of the individual—the so-called fight-or-flight response. During a stress situation, the heart rate accelerates, the blood pressure rises, blood flow shifts from the skin and gastrointestinal tract to the skeletal muscles and brain, blood sugar increases, the bronchioles and pupils dilate, the sphincters of the stomach and intestine and the internal sphincter of the urethra constrict, and the rate of secretion of exocrine glands that are involved in digestion diminishes. Emergency situations often require vasoconstriction and shunting of blood away from the skin and into the muscles and brain, a mechanism that, should a wound occur, provides for a reduction in blood flow and preservation of vital functions needed for survival.

In contrast to the sympathetic nervous system, the functions of the parasympathetic nervous system are concerned with conservation of energy, resource replenishment and storage, and maintenance of organ function

The Autonomic Nervous System (ANS)

- The ANS functions at the subconscious level and is responsible for maintaining homeostatic functions of the body.
- The ANS has two divisions: the sympathetic and parasympathetic systems. Although the two divisions function in concert, they are generally viewed as having opposite and antagonistic actions.
- The sympathetic division functions in maintaining vital functions and responding when there is a critical threat to the integrity of the individual—the "fight-or-flight" response.
- The parasympathetic nervous system is concerned with conservation of energy, resource replenishment, and maintenance of organ function during periods of minimal activity.
- The outflow of both divisions of the ANS consists of a two-neuron pathway: a preganglionic and a postganglionic neuron. Acetylcholine is the neurotransmitter for the preganglionic neurons for both ANS divisions, as well as the postganglionic neurons of the parasympathetic nervous system. Norepinephrine and epinephrine are the neurotransmitters for most sympathetic postganglionic neurons.

during periods of minimal activity. The parasympathetic nervous system slows heart rate, stimulates gastrointestinal function and related glandular secretion, promotes bowel and bladder elimination, and contracts the pupil, protecting the retina from excessive light during periods when visual function is not vital to survival.

The two divisions of the ANS usually are viewed as having opposite and antagonistic actions (i.e., if one activates, the other inhibits a function). Exceptions are functions, such as sweating and regulation of arteriolar blood vessel diameter, that are controlled by a single division of the ANS, in this case the sympathetic nervous system.

The sympathetic and parasympathetic nervous systems are continually active. The effect of this continual or basal (baseline) activity is referred to as *tone*. The tone of an effector organ or system can be increased or decreased and usually is regulated by a single division of the ANS. For example, vascular smooth muscle tone is controlled by the sympathetic nervous system. Increased sympathetic activity produces local vasoconstriction from increased vascular smooth muscle tone, and decreased activity results in vasodilatation caused by decreased tone. In structures such as the sinoatrial node and atrioventricular node of the heart, which are innervated by both divisions of the ANS, one division predominates in controlling tone. In this case, the tonically active parasympathetic nervous system exerts a constraining or braking effect on heart rate, and when parasympathetic outflow is withdrawn, similar to releasing a brake, the heart rate increases. The increase in heart rate that occurs with vagal withdrawal can be further augmented by sympathetic stimulation.

Autonomic Efferent Pathways

The outflow of both divisions of the ANS follows a two-neuron pathway. The first motor neuron, called the *preganglionic neuron,* lies in the intermediolateral cell column in the ventral horn of the spinal cord or its equivalent location in the brain stem. The second motor neuron, called the *postganglionic neuron,* synapses with a preganglionic neuron in an autonomic ganglion located in the PNS. The two divisions of the ANS differ in terms of location of preganglionic cell bodies, relative length of preganglionic fibers, general function, nature of peripheral responses, and preganglionic and postganglionic neuromediators (Table 34-3). This two-neuron outflow pathway and the interneurons in the autonomic ganglia that add further modulation to ANS function are features distinctly different from the arrangement in somatic motor innervation.

Most visceral organs are innervated by both sympathetic and parasympathetic fibers. Exceptions include structures such as blood vessels and sweat glands that have input from only one division of the ANS. The fibers of the sympathetic nervous system are distributed to effectors throughout the body, and as a result, sympathetic actions tend to be more diffuse than those of the parasympathetic nervous system, in which there is a more localized distribution of fibers. The preganglionic fibers of the sympathetic nervous system may traverse a considerable distance and pass through several ganglia before synapsing with postganglionic neurons, and their terminals make contact with a large number of postganglionic fibers. In some ganglia, the ratio of preganglionic to postganglionic cells may be 1:20; because of this, the effects of sympathetic stimulation are diffuse. There is considerable overlap, and one ganglion cell may be supplied by several preganglionic fibers. In contrast to the sympathetic nervous system, the parasympathetic nervous system has its postganglionic neurons located very near or in the organ of innervation. Because the ratio of preganglionic to postganglionic communication often is 1:1, the effects of the parasympathetic nervous system are much more circumscribed.

Sympathetic Nervous System

The preganglionic neurons of the sympathetic nervous system are located primarily in the thoracic and upper lumbar segments (T1 to L2) of the spinal cord; thus, the sympathetic nervous system often is referred to as the *thoracolumbar division* of the ANS. These preganglionic neurons, which are located primarily in the ventral horn intermediolateral cell column, have axons that are largely myelinated and relatively short. The postganglionic

TABLE 34-3 Characteristics of the Sympathetic and Parasympathetic Nervous Systems

Characteristic	Sympathetic Outflow	Parasympathetic Outflow
Location of preganglionic cell bodies	T1–T12, L1 and L2	Cranial nerves: III, VII (intermedius), IX, and X; sacral segments 2, 3, and 4
Relative length of preganglionic fibers	Short—to paravertebral chain of ganglia or to aortic prevertebral of ganglia	Long—to ganglion cells near or in the innervated organ
General function	Catabolic—mobilizes resources in anticipation of challenge for survival (preparation for "fight-or-flight" response)	Anabolic—concerned with conservation, renewal, and storage of resources
Nature of peripheral response	Generalized	Localized
Transmitter between preganglionic terminals and postganglionic neurons	ACh	ACh
Transmitter of postganglionic neuron	ACh (sweat glands and skeletal muscle vasodilator fibers); norepinephrine (most synapses); norepinephrine and epinephrine (secreted by adrenal gland)	Ach

ACh, acetylcholine.

neurons of the sympathetic nervous system are located in the paravertebral ganglia of the sympathetic chain that lie on either side of the vertebral column, or in prevertebral sympathetic ganglia such as the celiac ganglia (Fig. 34-23). Besides postganglionic efferent neurons, the sympathetic ganglia contain neurons of the internuncial, short-axon type, similar to those associated with complex circuitry in the brain and spinal cord. Many of these inhibit and others modulate preganglionic-to-postganglionic transmission.

The axons of the preganglionic neurons leave the spinal cord through the ventral root of the spinal nerves (T1 to L2), enter the ventral primary rami, and leave the spinal nerve through white rami of the rami communicantes to reach the paravertebral ganglionic chain (Fig. 34-24). In the sympathetic chain of ganglia, preganglionic fibers may synapse with neurons of the ganglion they enter, pass up or down the chain and synapse with one or more ganglia, or pass through the chain and move outward through a splanchnic nerve to terminate in one of the prevertebral ganglia (i.e., celiac, superior mesenteric, or inferior mesenteric) that are scattered along the dorsal aorta and its branches. The adrenal medulla, which is part of the sympathetic nervous system, contains postganglionic sympathetic neurons that secrete sympathetic neurotransmitters directly into the bloodstream.

Parasympathetic Nervous System

The preganglionic fibers of the parasympathetic nervous system, also referred to as the *craniosacral division* of the ANS, originate in some segments of the brain stem and sacral segments of the spinal cord (see Fig. 34-23). The central regions of origin are the midbrain, pons, medulla oblongata, and sacral part of the spinal cord. The outflow from the midbrain passes through the oculomotor nerve (cranial nerve III) to supply the pupillary sphincter muscle of each eye and the ciliary muscles that control lens thickness for accommodation. Caudal pontine outflow comes from branches of the facial nerve (cranial nerve VII) that supply the lacrimal and nasal glands. The medullary outflow develops from cranial nerves VII, IX, and X. Fibers in the glossopharyngeal nerve (cranial nerve IX) supply the parotid salivary glands. Approximately 75% of parasympathetic efferent fibers are carried in the vagus nerve (cranial nerve X). The vagus nerve provides parasympathetic innervation for the heart, trachea, lungs, esophagus, stomach, small intestine, proximal half of the colon, liver, gallbladder, pancreas, kidneys, and upper portions of the ureters.

Sacral preganglionic axons leave the S2 to S4 segmental nerves by gathering into the pelvic nerves. The pelvic nerves leave the sacral plexus on each side of the cord and distribute their peripheral fibers to the bladder, uterus, urethra, prostate, distal portion of the transverse colon, descending colon, and rectum. The sacral parasympathetic fibers also supply the venous outflow from the external genitalia to facilitate erectile function.

With the exception of cranial nerves III, VII, and IX, which synapse in discrete ganglia, the long parasympathetic preganglionic fibers pass uninterrupted to short postganglionic fibers located in the organ wall. In the walls of these organs, postganglionic neurons send axons to smooth muscle and glandular cells that modulate their functions.

Central Integrative Pathways

General visceral afferent fibers accompany the sympathetic and parasympathetic outflow into the spinal and cranial nerves, bringing chemoreceptor, pressure, and nociceptive information from organs of the viscera to the brain stem, thoracolumbar cord, and sacral cord. Local reflex circuits relating visceral afferent and autonomic efferent activity are integrated into a hierarchic control system in the spinal cord and brain stem. Progressively greater complexity in the responses and greater precision in their control occur at each higher level of the nervous system. Most visceral reflexes contain contributions from

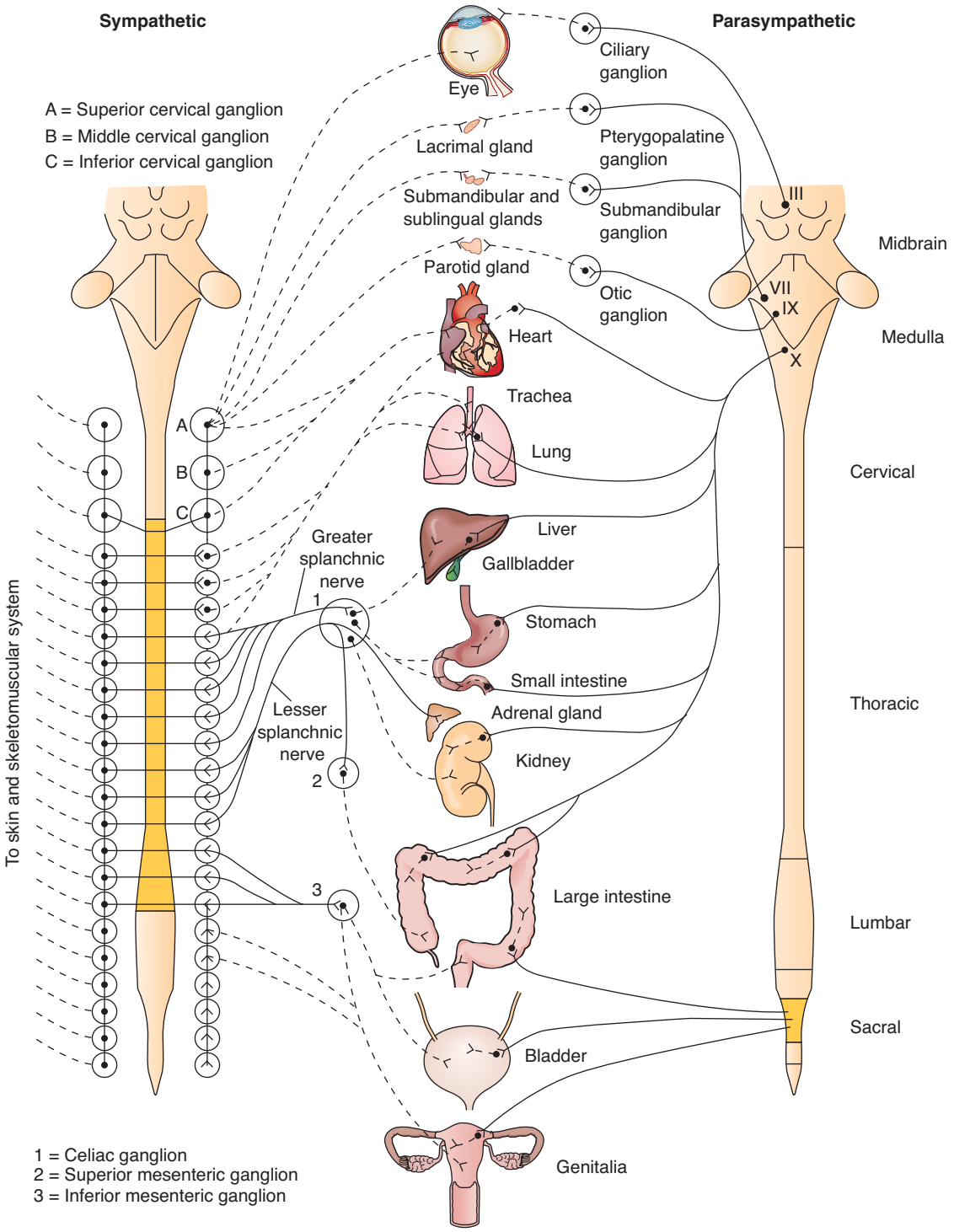


FIGURE 34-23. The autonomic nervous system. The involuntary organs are depicted with their parasympathetic innervation (craniosacral) indicated on the right and sympathetic innervation (thoracolumbar) on the left. Preganglionic fibers are *solid lines;* postganglionic fibers are *dashed lines.* For purposes of illustration, the sympathetic outflow to the skin and skeletomuscular system is shown separately (to the far left); effectors include sweat glands, pilomotor muscles and blood vessels of the skin, and blood vessels of the skeletal muscles and bones. (Modified from Hemer L. [1983]. *The human brain and spinal cord: Functional neuroanatomy and dissection guide.* New York: Springer-Verlag.)

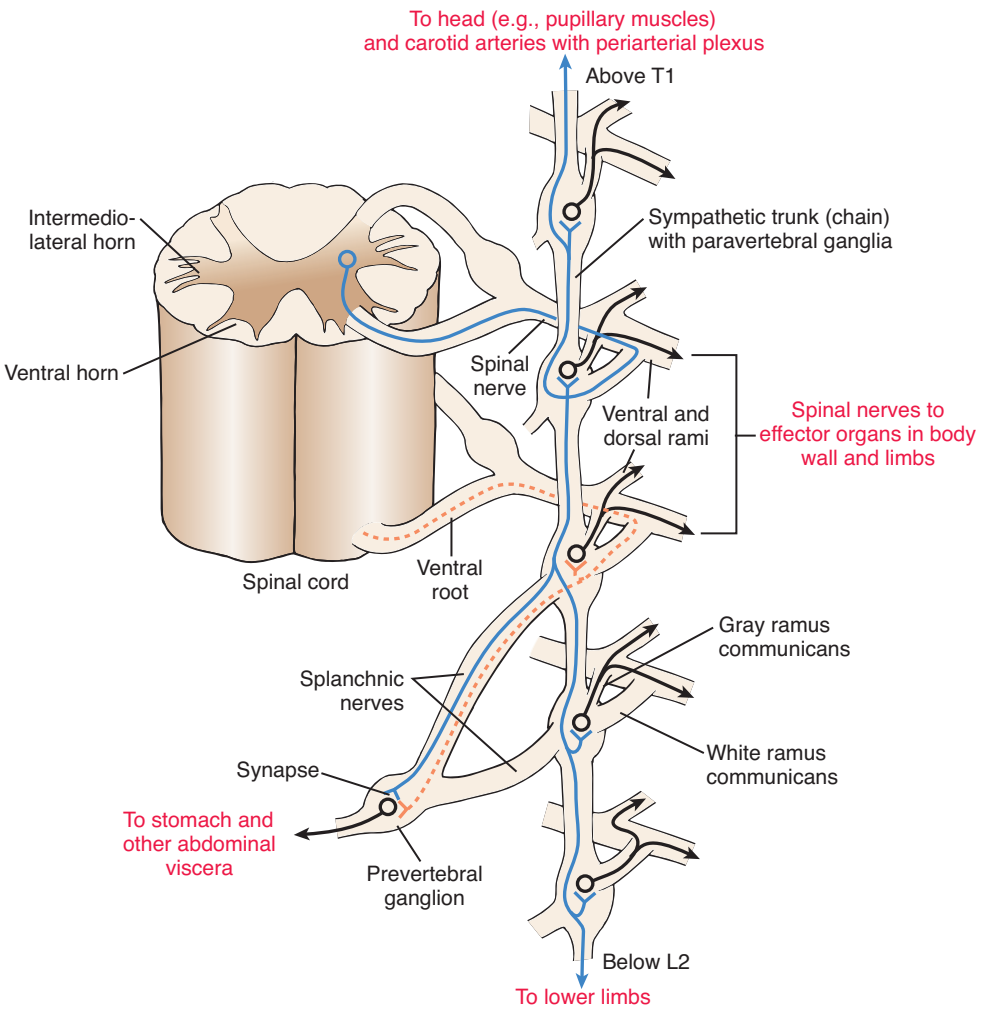


FIGURE 34-24. Sympathetic pathways. Sympathetic preganglionic fibers (*blue*) leave the spinal cord by way of the ventral root of the spinal nerves, enter the ventral primary rami, and pass through the white rami to the prevertebral or paravertebral ganglia of the sympathetic chain, where they synapse with postganglionic neurons (*black*). Other preganglionic neurons (*red dotted lines*) travel directly to their destination in the various effector organs.

the LMNs that innervate skeletal muscles as part of their response patterns.

For most autonomic-mediated functions, the hypothalamus serves as the major control center. The hypothalamus, which has connections with the cerebral cortex, the limbic system, and the pituitary gland, is in a prime position to receive, integrate, and transmit information to other areas of the nervous system. The neurons concerned with thermoregulation, thirst, and feeding behaviors are found in the hypothalamus. The hypothalamus also is the site for integrating neuroendocrine function. Hypothalamic releasing and inhibiting hormones control the secretion of anterior pituitary hormones (see Chapter 31).

The organization of many life-support reflexes occurs in the reticular formation of the medulla and pons. These areas of reflex circuitry, often called *centers*, produce complex combinations of autonomic and somatic efferent functions required for the cough, sneeze, swallow, and vomit reflexes, as well as for the more purely autonomic control of the cardiovascular system. One of the striking features of ANS function is the rapidity and intensity with which it can change visceral function. Within 3 to 5 seconds, it can increase heart rate to approximately twice its resting level. Bronchial smooth muscle tone is largely controlled by parasympathetic fibers carried in the vagus nerve. These nerves produce mild to moderate constriction of the bronchioles.

Other important ANS reflexes are located at the level of the spinal cord. As with other spinal reflexes, these reflexes are modulated by input from higher centers. When there is loss of communication between the higher centers and the spinal reflexes, as occurs in spinal cord injury, these reflexes function in an unregulated manner (see Chapter 36).

Autonomic Neurotransmission

The generation and transmission of impulses in the ANS occur in the same manner as in the CNS. There are self-propagating action potentials with transmission of impulses across synapses and other tissue junctions by way of neurohumoral transmitters. The postganglionic fibers of the ANS form a diffuse neural plexus at the site of innervation. The membranes of the cells of many smooth muscle fibers are connected by conductive protoplasmic bridges, called *gap junctions*, that permit rapid conduction of impulses through whole sheets of smooth

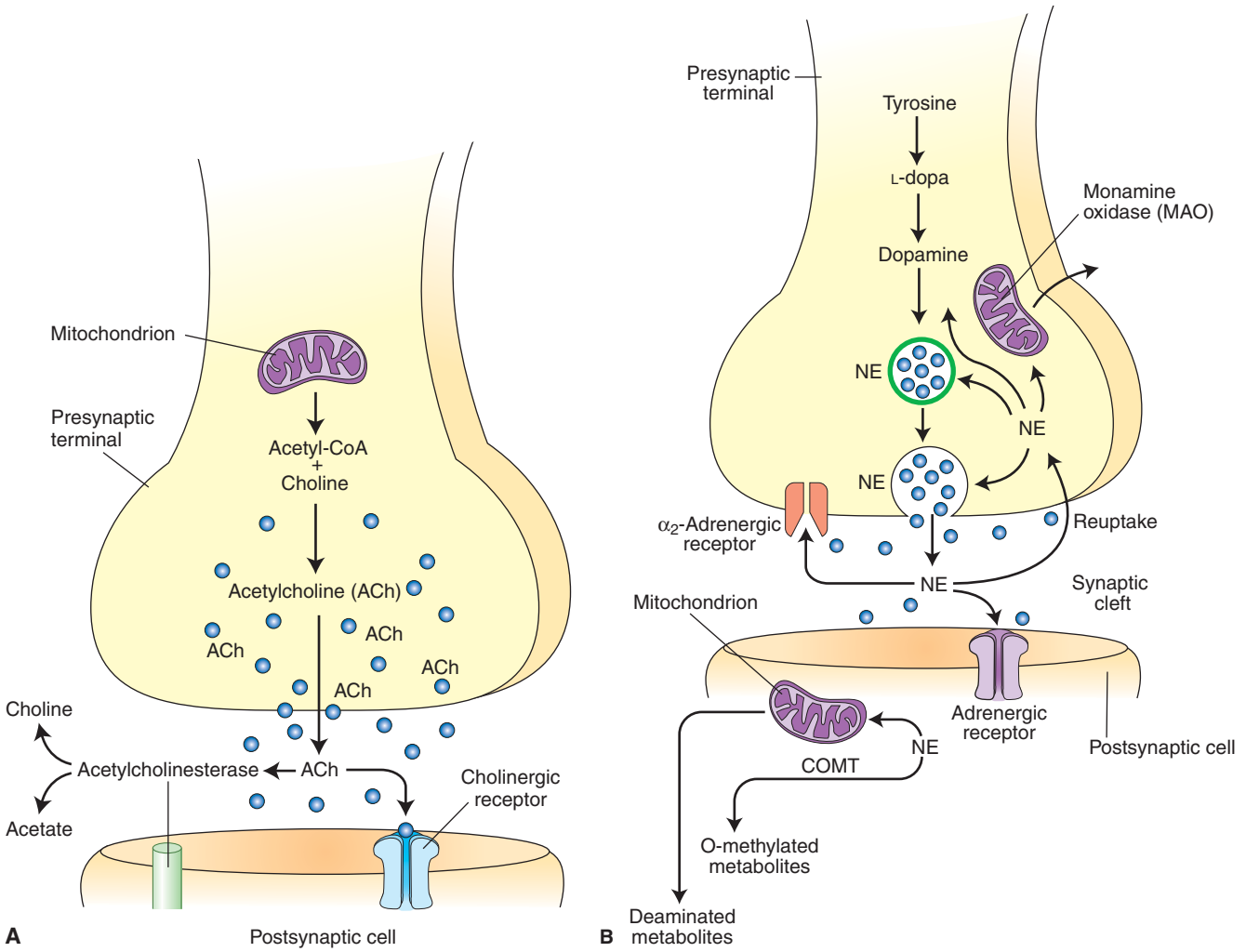


FIGURE 34-25. Schematic illustration of **(A)** parasympathetic cholinergic and **(B)** sympathetic noradrenergic neurotransmitter synthesis, release, receptor binding, neurotransmitter degradation, and metabolite transport back into the presynaptic neuron (acetylcholine) and reuptake (norepinephrine). COMT, catechol-*O*-methyltransferase; NE, norepinephrine.

muscle, often in repeating waves of contraction. Autonomic neurotransmitters released near a limited portion of these fibers provide a modulating function extending to a large number of effector cells. The muscle layers of the gut and of the bladder wall are examples.

The main neurotransmitters of the ANS are acetylcholine and the catecholamines epinephrine and norepinephrine. Acetylcholine is released at all of the sites of preganglionic transmission in the autonomic ganglia of sympathetic and parasympathetic nerve fibers and at the sites of postganglionic transmission in parasympathetic nerve endings. It also is released at sympathetic nerve endings that innervate the sweat glands and cholinergic vasodilator fibers found in skeletal muscle. Norepinephrine is released at most sympathetic nerve endings. The adrenal medulla, which is a modified neural crest tissue, produces epinephrine along with small amounts of norepinephrine. Dopamine, which is an intermediate compound in the synthesis of norepinephrine, also acts as a neurotransmitter. It is the principal inhibitory transmitter of internuncial neurons in the sympathetic ganglia. It also has vasodilator effects on renal, splanchnic, and coronary blood vessels when given intravenously and is sometimes used in the treatment of shock (see Chapter 20).

Acetylcholine and Cholinergic Receptors

Acetylcholine is synthesized in the cholinergic neurons from choline and acetyl coenzyme A (acetyl CoA). After acetylcholine is secreted by the cholinergic nerve endings, it is rapidly broken down by the enzyme acetylcholinesterase (Fig. 34-25A). The choline molecule is transported back into the nerve ending, where it is used again in the synthesis of acetylcholine.

Cell membrane receptors that respond to acetylcholine are called *cholinergic receptors*. There are two types of cholinergic receptors: muscarinic and nicotinic. Muscarinic receptors are present on the innervational

targets of postganglionic fibers of the parasympathetic nervous system and the sweat glands, which are innervated by the sympathetic nervous system. Nicotinic receptors are found in autonomic ganglia and the endplates of skeletal muscle. Acetylcholine has an excitatory effect on muscarinic and nicotinic receptors, except for those in the heart and lower esophagus, where it has an inhibitory effect. The drug atropine is an antimuscarinic or muscarinic cholinergic-blocking drug that prevents the action of acetylcholine at excitatory and inhibitory muscarinic receptor sites. Because it is a muscarinic-blocking drug, it exerts little effect at nicotinic receptor sites.

Catecholamines and Adrenergic Receptors

The catecholamines, which include norepinephrine, epinephrine, and dopamine, are synthesized in the sympathetic nervous system. Synthesis of dopamine and norepinephrine begins in the axoplasm of sympathetic nerve terminals with the conversion of the amino acid tyrosine to dopa, dopa to dopamine, and dopamine to norepinephrine (Fig. 34-25B). In the adrenal gland an additional step takes place during which approximately 80% of the norepinephrine is transformed into epinephrine.

Each of the steps in sympathetic neurotransmitter synthesis requires a different enzyme, and the type of neurotransmitter that is produced depends on the types of enzymes that are available in a nerve terminal. For example, the postganglionic sympathetic neurons that supply blood vessels have the needed enzymes for the synthesis of norepinephrine, whereas those in the adrenal medulla have the enzymes needed to convert norepinephrine into epinephrine. As the catecholamines are synthesized, they are stored in vesicles. The final step of norepinephrine synthesis occurs in these vesicles. When an action potential reaches an axon terminal, the neurotransmitter molecules are released from the storage vesicles. The storage vesicles provide a means for concentrated storage of the catecholamines and protect them from the cytoplasmic enzymes that degrade the neurotransmitters.

In addition to neuronal synthesis, there is a second major mechanism for replenishment of norepinephrine in sympathetic nerve terminals. This mechanism consists of the active reuptake of the released neurotransmitter into the nerve terminal. Between 50% and 80% of the norepinephrine that is released during an action potential is removed from the synaptic area by an active reuptake process. This process terminates the action of the neurotransmitter and allows it to be reused by the neuron. The remainder of the released catecholamines diffuse into the surrounding tissue fluids or are degraded by two special enzymes: catechol-*O*-methyltransferase, which is diffusely present in all tissues, and monoamine oxidase (MAO), which is found in the nerve endings themselves.

Catecholamines can cause excitation or inhibition of smooth muscle contraction, depending on the site, dose, and type of receptor present. The excitatory or inhibitory responses of organs to sympathetic neurotransmitters are mediated by interaction with cell membrane receptors. There are two types of sympathetic receptors: α and β receptors. In vascular smooth muscle, excitation of α-adrenergic receptors causes vasoconstriction, and excitation of β-adrenergic receptors causes vasodilatation. Constriction of blood vessels in the skin, kidneys, and splanchnic circulation is mediated by α-adrenergic receptors. The β-adrenergic receptors are most prevalent in the heart, the blood vessels of skeletal muscle, and the bronchioles.

β-Adrenergic receptors have been further subdivided into α_1 and α_2 receptors, and β-adrenergic receptors into β_1 and β_2 receptors. β_1-Adrenergic receptors are found primarily in the heart and can be selectively blocked by β_1-receptor–blocking drugs. β_2-Adrenergic receptors are found in the bronchioles and in other sites that have β-mediated functions. The α_1 receptors are found primarily in postsynaptic effector sites; they mediate responses in vascular smooth muscle. The α_2 receptors are mainly located presynaptically and can inhibit the release of norepinephrine from sympathetic nerve terminals. The α_2 receptors are abundant in the CNS and are thought to influence the central control of blood pressure.

In summary, the autonomic nervous system (ANS) regulates, adjusts, and coordinates the visceral functions of the body. The ANS, which is divided into the sympathetic and parasympathetic systems, is an efferent system. It receives its afferent input from visceral afferent neurons. The ANS has central nervous system and peripheral nervous system components. The outflow of the sympathetic and parasympathetic nervous system follows a two-neuron pathway, which consists of a preganglionic neuron located in the central nervous system (CNS) and a postganglionic neuron located outside the CNS. Sympathetic fibers leave the CNS at the thoracolumbar level, and the parasympathetic fibers leave at the craniosacral level.

In general, the sympathetic and parasympathetic nervous systems have opposing effects on visceral function—if one excites, the other inhibits. The hypothalamus serves as the major control center for most ANS functions; local reflex circuits relating visceral afferent and autonomic efferent activity are integrated in a hierarchic control system in the spinal cord and brain stem.

The main neurotransmitters for the ANS are acetylcholine and the catecholamines epinephrine and norepinephrine. Acetylcholine is the transmitter for all preganglionic neurons, for postganglionic parasympathetic neurons, and for selected postganglionic sympathetic neurons. The catecholamines are the neurotransmitters for most postganglionic sympathetic neurons. The ANS neurotransmitters exert their action through specialized cell surface receptors—cholinergic receptors that bind acetylcholine and adrenergic receptors that bind the catecholamines. The cholinergic receptors are divided into nicotinic and muscarinic receptors, and adrenergic receptors are divided into α and β receptors.

REVIEW EXERCISES

1. An event such as cardiac arrest, which produces global ischemia of the brain, can produce a selective loss of recent memory and cognitive skills, while the more vegetative and life-sustaining functions such as breathing are preserved.

A. Use principles related to the development of the nervous system and hierarchy of control to explain why.

2. Usually spinal cord injury or disease produces both sensory and motor deficits. An exception is infection by the poliomyelitis virus, which produces muscle weakness and paralysis without loss of sensation in the affected extremities.

A. Explain, using information on the cell column organization of the spinal cord.

3. The functions of the sympathetic nervous system are often described in relation to the "fight-or-flight" response. Using this description, explain the physiologic advantage for the following distribution of sympathetic nervous system receptors:

A. The presence of β_2 receptors on the blood vessels that provide blood flow to the skeletal muscles during "fight or flight," and the presence of α_1 receptors on the resistance vessels that control blood pressure.

4. The presence of acetylcholine receptors on the sweat glands that allow for evaporative loss of body heat during "fight or flight," and the presence of α_1 receptors that constrict the skin vessels that control blood flow to the skin.

A. The presence of β_2 receptors that produce relaxation in the detrusor muscle of the bladder during "fight or flight," and the presence of α_1 receptors that produce contraction of the smooth muscle in the internal sphincter of the bladder.

BIBLIOGRAPHY

Alberts B., Johnson A., Lewis J., et al. (2008). *Molecular biology of the cell* (5th ed., pp. 675–694, 1048–1050). New York: Garland Science.

Bear M.F., Connors B.W., Paradiso M.A. (2001). *Neuroscience: Exploring the brain* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins.

Brodal P. (1998). *The central nervous system: Structure and function* (2nd ed.). New York: Oxford University Press.

Carlson B.M. (2004). *Human embryology and developmental biology* (3rd ed., pp. 65–81, 103–127, 233–275, 277–290). St. Louis: C.V. Mosby.

Gartner L.P., Hiatt J.L. (2007). *Color textbook of histology* (3rd ed., pp. 185–218, 511–536). Philadelphia: Elsevier Saunders.

Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 555–619). Philadelphia: Elsevier Saunders.

Haines D.E. (Ed.). (1997). *Fundamental neuroscience* (pp. 115–121, 126–127, 146–148, 443–454). New York: Churchill Livingstone.

Jung C., Chylinski T.M., Pimenta A., et al. (2004). Neurofilament transport is dependent on actin and myosin. *Journal of Neuroscience* 24, 9486–9496.

Kandel E.R., Schwartz J.H., Jessell T.M. (2000). *Principles of neural science* (4th ed.). New York: McGraw-Hill.

Kierszenbaum A.L. (2007). *Histology and cell biology: An introduction to pathology* (2nd ed., pp. 221–250, 251–290). St. Louis: Mosby.

Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 885–955). Philadelphia: Lippincott Williams & Wilkins.

Moore K.L., Persaud T.V.N. (2003). *The developing human: Clinically oriented embryology* (7th ed., pp. 59–76, 427–463). Philadelphia: W.B. Saunders.

Parent A. (1996). *Carpenter's human neuroanatomy* (9th ed., pp. 186–192, 268–292, 748–756). Baltimore: Williams & Wilkins.

Ross M.H., Pawlina W. (2006). *Histology: A text and Atlas* (5th ed., pp. 318–363). Philadelphia: Lippincott Williams & Wilkins.

Sadler T.W. (2006). *Langman's medical embryology* (10th ed., pp. 5–10, 67–72, 285–316). Philadelphia: Lippincott Williams & Wilkins.

Squire L.R., Bloom F.E., McConnell S.K., et al. (2003). *Fundamental neuroscience* (2nd ed., pp. 188–189, 391–416). New York: Academic Press.

Takano T., Tian G., Peng W., et al. (2006). Astrocyte-mediated control of cerebral blood flow. *Nature Neuroscience* 9, 260–267.

Tortora G.J., Derrickson B. (2009). *Principles of anatomy and physiology* (12th ed.). Hoboken, NJ: John Wiley & Sons.

Organization and Control of Somatosensory Function
Somatosensory Systems
The Sensory Unit
Dermatomal Pattern of Innervation
Spinal Circuitry and Ascending Neural Pathways
Central Processing of Somatosensory Information
Somatosensory Modalities
Tactile Sensation
Thermal Sensation
Position Sense
Pain Sensation
Pain Theories
Pain Mechanisms and Pathways
Pain Receptors and Primary Afferent Pathways
Spinal Cord Circuitry and Ascending Pathways
Brain Centers and Pain Perception
Central Pathways for Pain Modulation
Endogenous Analgesic Mechanisms
Types of Pain
Cutaneous and Deep Somatic Pain
Visceral Pain
Referred Pain
Acute and Chronic Pain
Pain Management
Assessment
Nonpharmacologic Interventions
Pharmacologic Treatment
Surgical Interventions
Alterations in Pain Sensitivity and Special Types of Pain
Alterations in Pain Sensitivity
Special Types of Pain
Neuropathic Pain
Neuralgia
Complex Regional Pain Syndrome
Phantom Limb Pain
Headache and Associated Pain
Headache
Migraine Headache
Cluster Headache
Tension-Type Headache
Chronic Daily Headache
Temporomandibular Joint Pain
Pain in Children and Older Adults
Pain in Children
Pain in Older Adults

Chapter 35

Somatosensory Function, Pain, and Headache

Sensory mechanisms provide individuals with a continuous stream of information about their bodies, the outside world, and the interactions between the two. The somatosensory component of the nervous system provides an awareness of the body's deep and superficial parts as compared to the specialized senses of sight and hearing (discussed in Chapter 38), which provide awareness of external world. Between 2 and 3 million nerve endings in the skin and deep body tissues provide a steady stream of encoded somatosensory information to the central nervous system. Only a small portion of this information reaches awareness; most provides input essential for the myriad of reflexes and automatic mechanisms that keep us alive and manage our functioning.

This chapter is organized into two distinct parts. The first part describes the organization and control of somatosensory function, and the second focuses on pain as a somatosensory modality.

Organization and Control of Somatosensory Function

The somatosensory sensory system is designed to provide the central nervous system (CNS) with information related to deep and superficial body structures. There are three types of sensory neurons that vary in terms of distribution and type of sensation that is detected—general somatic, special somatic, and general visceral. *General somatic afferent neurons* have branches with widespread distribution throughout the body and with many distinct types of receptors that result in sensations such as pain, touch, and temperature. *Special somatic afferent neurons* have receptors located primarily in muscles, tendons, and joints. These receptors sense position and movement of the body. *General visceral afferent neurons* have receptors on various visceral structures that sense fullness and discomfort.

Somatosensory Systems

Sensory systems can be conceptualized as a series of neurons consisting of first-order, second-order, and third-order neurons. *First-order neurons* transmit sensory information from the periphery to the CNS. *Second-order neurons* communicate with various reflex networks and sensory pathways in the spinal cord and travel directly to the thalamus. *Third-order neurons* relay information from the thalamus to the cerebral cortex (Fig. 35-1).

This organizing framework corresponds with the three primary levels of neural integration in the somatosensory system: the sensory units, which contain the sensory receptors; the ascending pathways; and the central processing centers in the thalamus and cerebral cortex. Sensory information usually is relayed and processed in a cephalad (toward the head) direction by the three orders of neurons. Many interneurons process and modify the sensory information at the level of the second- and third-order neurons, and many more participate before coordinated and appropriate learned-movement responses occur. The number of participating neurons increases exponentially from the primary through the secondary and the secondary through the tertiary levels.

The Somatosensory System

- The somatosensory system relays information about four major modalities: touch, temperature, pain, and body position.
- The system is organized segmentally into dermatomes, with each segment supplied by a single dorsal root ganglion that contains the neuronal cell bodies for the sensory units of the segment.
- Somatosensory information is sequentially transmitted over three types of neurons: first-order neurons, which transmit information from sensory receptors to dorsal horn neurons; second-order CNS association neurons, which communicate with various reflex circuits and transmit information to the thalamus; and third-order neurons, which forward the information from the thalamus to the sensory cortex.

The Sensory Unit

The somatosensory experience arises from information provided by a variety of receptors distributed throughout the body. These receptors monitor four major types or modalities of sensation: discriminative touch, which is required to identify the size and shape of objects and their movement across the skin; temperature sensation; sense of movement of the limbs and joints of the body; and nociception, or pain.

Each of the somatosensory modalities is mediated by a distinct system of receptors and pathways to the brain; however, all somatosensory information from the limbs and trunk shares a common class of sensory neurons called *dorsal root ganglion neurons*. Somatosensory information from the face and cranial structures is transmitted by the trigeminal sensory neurons, which function in the same manner as the dorsal root ganglion neurons. The cell body of the dorsal root ganglion neuron, its peripheral branch (which innervates a small area of periphery), and its central axon (which projects to the CNS) form what is called a *sensory unit*.

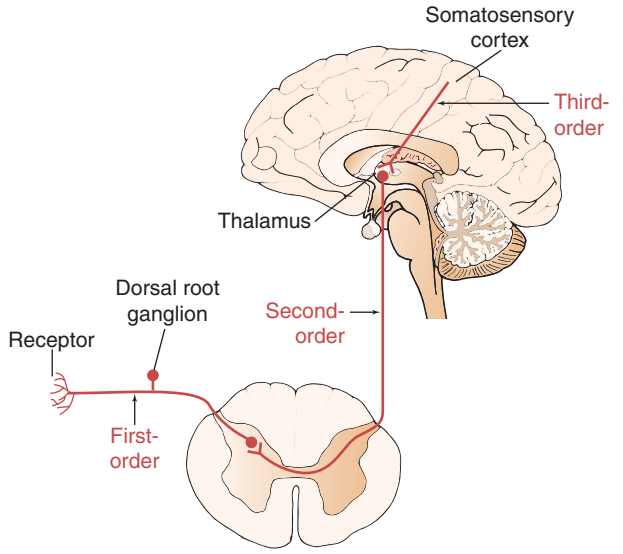


FIGURE 35-1. Arrangement of first-order, second-order, and third-order neurons of the somatosensory system.

The fibers of different dorsal root ganglion neurons conduct impulses at varying rates, ranging from 0.5 to 120 m/second. This rate depends on the diameter of the nerve fiber. There are three types of nerve fibers that transmit somatosensory information: types A, B, and C. Type A fibers, which are myelinated, have the fastest rate of conduction.[1,2] Type A fibers convey cutaneous pressure and touch sensation, cold sensation, mechanical pain, and heat pain. Type B fibers, which also are myelinated, transmit information from cutaneous and subcutaneous mechanoreceptors. The unmyelinated type C fibers have the smallest diameter and the slowest rate of conduction. They convey warm–hot sensation and mechanical and chemical as well as heat- and cold-induced pain sensation.

Dermatomal Pattern of Innervation

The somatosensory innervation of the body, including the head, retains a basic segmental pattern that was established during embryonic development. Thirty-three paired spinal (i.e., segmental) nerves provide sensory and motor innervation of the body wall, the limbs, and the viscera (see Chapter 34, Fig. 34-12). Sensory input to each spinal cord segment is provided by sensory neurons with cell bodies in the dorsal root ganglia. The head and face are innervated by the three branches of the trigeminal cranial nerve (CN V).

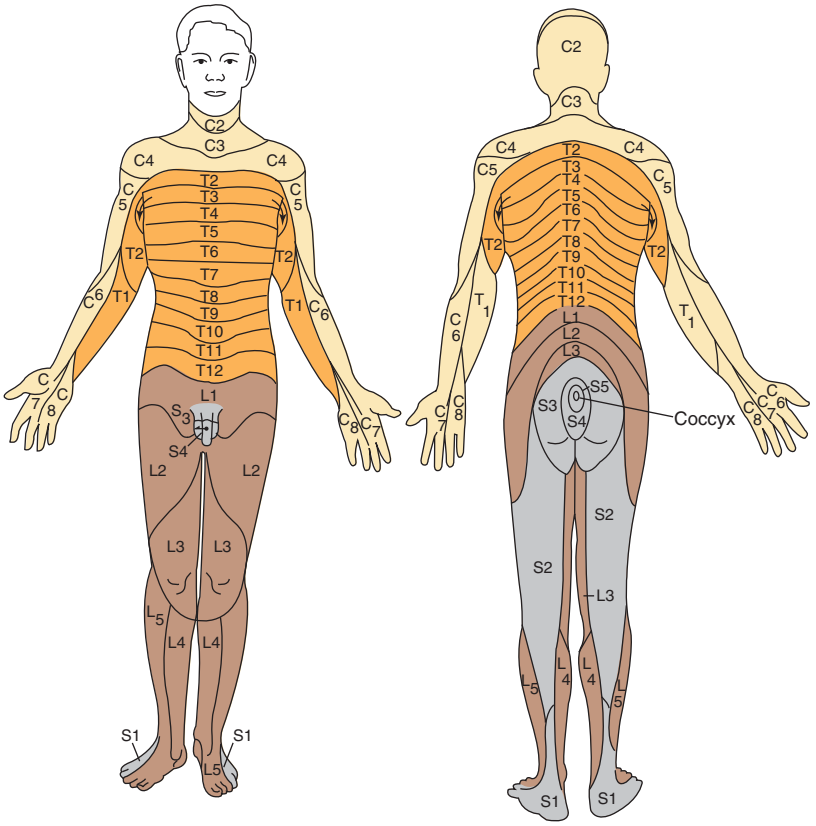


FIGURE 35-2. Cutaneous distribution of spinal nerves (dermatomes). (From Barr M. [1993]. *The human nervous system.* New York: Harper & Row.)

The region of the body wall that is supplied by a single pair of dorsal root ganglia is called a *dermatome*. These dorsal root ganglion–innervated strips occur in a regular sequence moving upward from the second coccygeal segment through the cervical segments, reflecting the basic segmental organization of the body and the nervous system (Fig. 35-2). The trigeminal nerve branches that innervate the head send their axons to equivalent nuclei in the brain stem. Neighboring dermatomes overlap one another sufficiently so that a loss of one dorsal root or root ganglion results in reduced but not total loss of sensory innervation of a dermatome (Fig. 35-3). Dermatome maps are helpful in interpreting the level and extent of sensory deficits that are the result of segmental nerve and spinal cord damage. For example, on the basis of the dermatomal map we can predict that sensory changes limited to the distal forearm and fourth and fifth fingers are the result of injury to the cervical (C) 8 and thoracic (T) 1 dorsal roots.

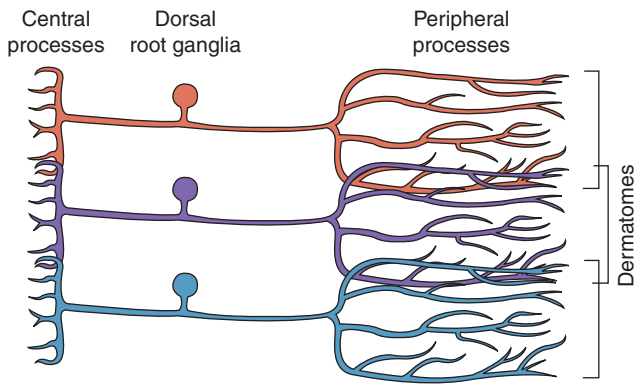


FIGURE 35-3. The dermatomes formed by the peripheral processes of adjacent spinal nerves overlap on the body surface. The central processes of these fibers also overlap in their spinal distribution.

Spinal Circuitry and Ascending Neural Pathways

On entry into the spinal cord, the central axons of the somatosensory neurons branch extensively and project to neurons in the spinal cord gray matter. Some branches become involved in local spinal cord reflexes and directly initiate motor reflexes (e.g., flexor-withdrawal reflex). Two parallel pathways, the *discriminative pathway* and the *anterolateral pathway,* carry the information from the spinal cord to the thalamic level of sensation, each taking a different route through the CNS.[1,2] Having a two-pathway system has several advantages. It adds richness to the sensory input by allowing sensory information to be handled in two different ways, and it ensures that if one pathway is damaged, the other still can provide input.

Dorsal Column–Medial Lemniscal Pathway. The dorsal column–medial lemniscal pathway, also known as the *discriminative pathway*, is used for the rapid transmission of sensory information such as discriminative touch. It contains branches of primary afferent axons that travel

up the ipsilateral (i.e., same side) dorsal columns of the spinal cord white matter and synapse with highly evolved somatosensory input association neurons in the medulla. The discriminative pathway uses only three neurons to transmit information from a sensory receptor to the somatosensory strip of parietal cerebral cortex of the opposite side of the brain: (1) the dorsal root ganglion neurons, which project their central axons to the dorsal horn in the spinal cord; (2) the dorsal column nuclei, which send their axons upward and across the midline of the medulla where they form a band of white matter called the *medial lemniscus* that passes upward to the thalamus; and (3) the thalamic neurons, which project through the somatosensory radiation to the primary sensory cortex (Fig. 35-4A). As the fibers in the medial lemniscus ascend through the brain stem, they are joined by sensory fibers from the trigeminal nerve that supplies the head and face. Sensory information arriving at the sensory cortex by this route can be discretely localized and discriminated in terms of intensity.

One of the distinct features of the discriminative pathway is that it relays precise information regarding spatial orientation. This is the only pathway taken by the sensations of muscle and joint movement, vibration, and delicate discriminative touch, as is required to differentiate correctly the location of touch on the skin at two neighboring points (i.e., two-point discrimination). One of the important functions of the discriminative pathway is to integrate the input from multiple receptors. The sense of shape and size of an object in the absence of visualization, called *stereognosis,* is based on precise afferent information from muscle, tendon, and joint receptors. For example, a screwdriver is perceived as being different from a knife in terms of its texture (tactile sensibility) and shape based on the relative position of the fingers as they move over the object. This complex interpretive perception requires that both the discriminative system and the higher-order parietal association cortex are functioning properly. If the discriminative somatosensory pathway is functional but the parietal association cortex has become discretely damaged, the person can correctly describe the object but does not recognize that it is a screwdriver. This deficit is called *astereognosis*.

Anterolateral Pathway. The anterolateral pathway (anterior and lateral spinothalamic tracts) consists of bilateral, multisynaptic, slow-conducting tracts (see Chapter 34, Fig. 34-11). These tracts provide for transmission of

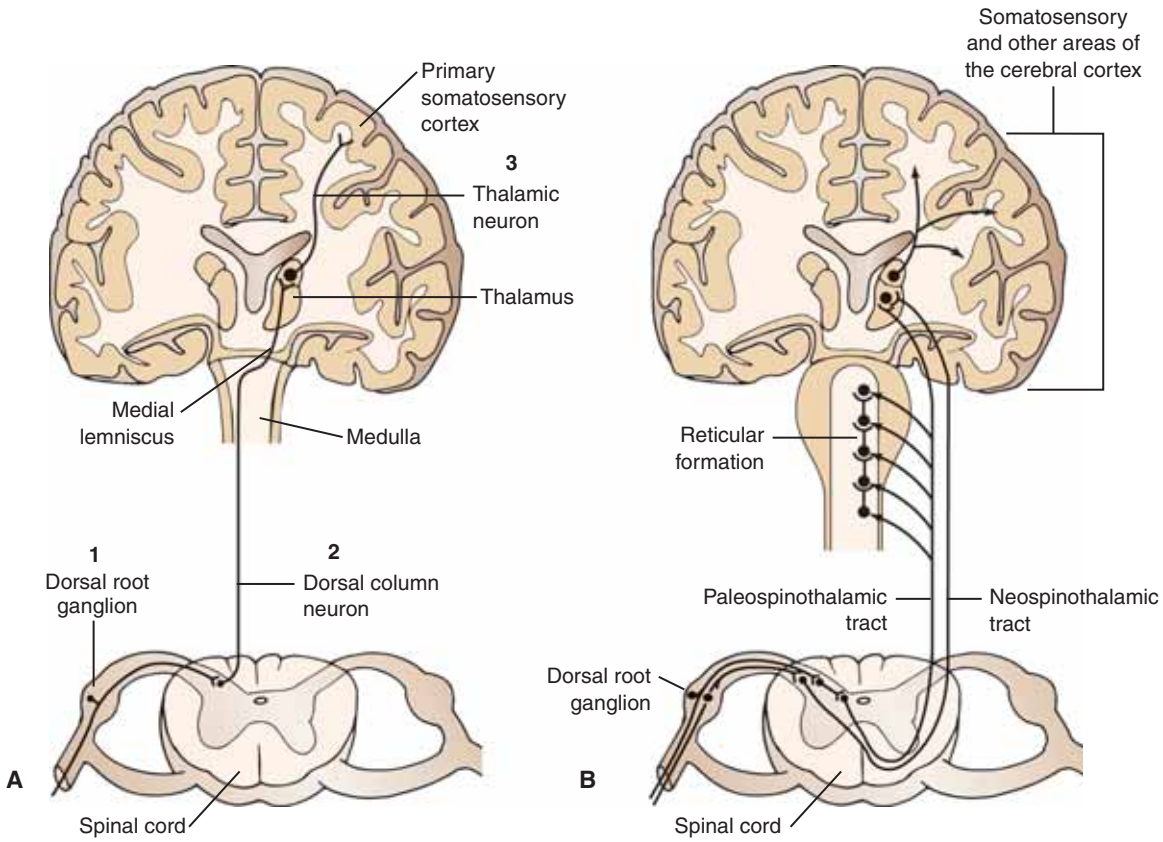


FIGURE 35-4. **(A)** Rapid-transmitting discriminative (dorsal column–medial lemniscal) pathway carrying axons mediating tactile sensation and proprioception. **(B)** Neospinothalamic and paleospinothalamic subdivisions of the anterolateral sensory pathway. The neurons of anterolateral pathways cross within the same segment as the cell body and ascend in the contralateral side of the spinal cord. The neospinothalamic tract travels mainly to thalamic nuclei that have third-order fibers projecting to the somatosensory cortex. The paleospinothalamic tract sends collaterals to the reticular formation and other structures, from which further fibers project to the thalamus.

sensory information such as pain, thermal sensations, crude touch, and pressure that does not require discrete localization of signal source or fine discrimination of intensity. The fibers of the anterolateral pathway originate in the dorsal horns at the level of the segmental nerve, where the dorsal root ganglion neurons enter the spinal cord. These spinal neurons cross in the anterior commissure, within a few segments of origin, to the anterolateral column on the opposite side of the cord, where they ascend upward toward the brain. The anterolateral tract fibers synapse with several nuclei in the thalamus, but en route they give off numerous branches that travel to the reticular activating system of the brain stem. These projections provide the basis for increased wakefulness or awareness after strong somatosensory stimulation and for the generalized startle reaction that occurs with sudden and intense stimuli. They also stimulate autonomic nervous system responses, such as a rise in heart rate and blood pressure, dilation of the pupils, and the pale, moist skin that results from constriction of the cutaneous blood vessels and activation of the sweat glands.

There are two subdivisions in the anterolateral pathway: the neospinothalamic and the paleospinothalamic tracts[1] (see Fig. 35-4B). The *neospinothalamic tract* consists of a sequence of at least three neurons with long axons. It provides for relatively rapid transmission of sensory information to the thalamus. The *paleospinothalamic tract*, which is phylogenically older than the neospinothalamic system, consists of bilateral, multisynaptic, slow-conducting tracts that transmit sensory signals that do not require discrete localization or discrimination of fine gradations in intensity. This slower-conducting pathway also projects into the intralaminar nuclei of the thalamus, which have close connections with the limbic cortical systems. This circuitry gives touch its affective or emotional aspects, such as the particular unpleasantness of heavy pressure and the peculiar pleasantness of the tickling and gentle rubbing of the skin.

Central Processing of Somatosensory Information

Perception, or the final processing of somatosensory information, involves awareness of the stimuli, localization and discrimination of their characteristics, and interpretation of their meaning.[1,2] As sensory information reaches the thalamus, it begins to enter the level of consciousness. In the thalamus, the sensory information is roughly localized and perceived as a crude sense. The full localization, discrimination of the intensity, and interpretation of the meaning of the stimuli require processing by the somatosensory cortex.

The somatosensory cortex is located in the parietal lobe, which lies behind the central sulcus and above the lateral sulcus (Fig. 35-5). The strip of parietal cortex that borders the central sulcus is called the *primary somatosensory cortex* because it receives primary sensory information by direct projections from the thalamus. A distorted map of the body and head surface, called the *sensory homunculus,* reflects the density of cortical neurons devoted to sensory input from afferents in

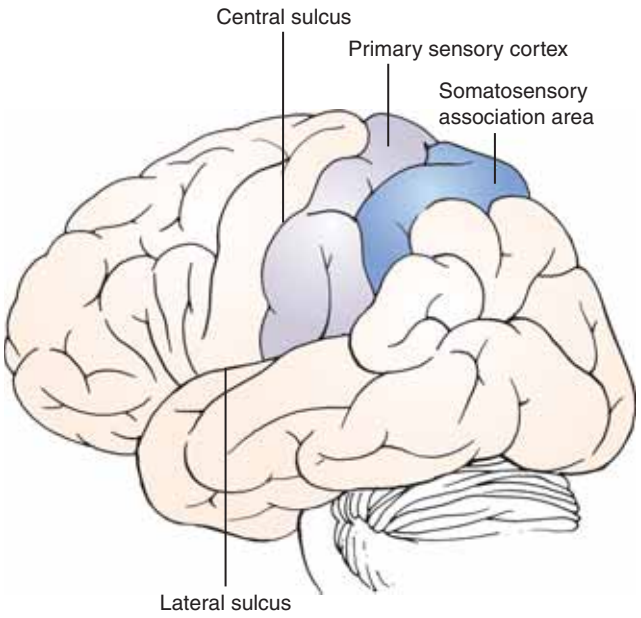


FIGURE 35-5. Primary somatosensory cortex and somatosensory association area.

corresponding peripheral areas. As depicted in Figure 35-6, most of the cortical surface is devoted to areas of the body such as the thumb, forefinger, lips, and tongue, where fine touch and pressure discrimination are essential for normal function.

Parallel to and just behind the primary somatosensory cortex (i.e., toward the occipital cortex) lie the somatosensory association areas, which are required to transform

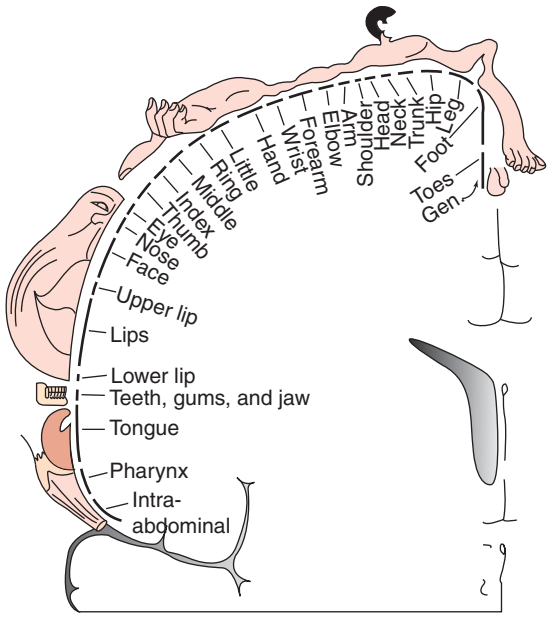


FIGURE 35-6. Homunculus, as determined by stimulation studies on the human cortex during surgery. (From Penfield E., Rasmussen T. [1955]. *The cerebral cortex of man.* New York: Macmillan. Copyright © by Macmillan Publishing Co., Inc., renewed 1978 by Theodore Rasmussen.)

the raw material of sensation into meaningful learned perception. Most of the perceptive aspects of body sensation, or somesthesia, require the function of this parietal association cortex. The perceptive aspect, or meaningfulness, of a stimulus pattern involves the integration of present sensation with past learning. For instance, a person's past learning plus present tactile sensation provides the perception of sitting on a soft chair rather than on a hard bicycle seat.

Somatosensory Modalities

Somatosensory experience can be divided into *modalities*, a term used for qualitative, subjective distinctions between sensations such as touch, temperature, and pain.[1,2] Such experiences require the function of sensory receptors and forebrain structures in the thalamus and cerebral cortex. Sensory experience also involves quantitative sensory discrimination or the ability to distinguish between different levels of sensory stimulation.

The receptive endings of different afferent neurons are particularly sensitive to specific forms of physical and chemical energy. They can initiate action potentials to many forms of energy at high energy levels, but they usually are highly tuned to be differentially sensitive to low levels of a particular energy type. For instance, a receptive ending may be particularly sensitive to a small increase in local skin temperature. Stimulating the ending with electric current or strong pressure also can result in action potentials. The amount of energy required, however, is much greater than it is for a change in temperature. Other afferent sensory terminals are most sensitive to slight indentations of the skin, and their signals are subjectively interpreted as touch. Cool versus warm, sharp versus dull pain, and delicate touch versus deep pressure are all based on different populations of afferent neurons or on central integration of simultaneous input from several differently tuned afferents.

Tactile Sensation

The tactile system, which relays sensory information regarding touch, pressure, and vibration, is considered the basic somatosensory system. Loss of temperature or pain sensitivity leaves the person with no awareness of deficiency. If the tactile system is lost, however, total anesthesia (i.e., numbness) of the involved body part results.

Touch sensation results from stimulation of tactile receptors in the skin and in tissues immediately beneath the skin, pressure from deformation of deeper tissues, and vibration from rapidly repetitive sensory signals. There are at least six types of specialized tactile receptors in the skin and deeper structures: free nerve endings, Meissner corpuscles, Merkel disks, pacinian corpuscles, hair follicle end-organs, and Ruffini end-organs[1,2] (Fig. 35-7).

Free nerve endings are found in skin and many other tissues, including the cornea. They detect touch and pressure. *Meissner corpuscles* are elongated, encapsulated nerve endings present in nonhairy parts of the skin. They are particularly abundant in the fingertips, lips, and other areas where the sense of touch is highly developed. *Merkel disks* are dome-shaped receptors found in nonhairy areas and in hairy parts of the skin. In contrast to Meissner corpuscles, which adapt within a fraction of a second, Merkel disks transmit an initial strong signal that diminishes in strength but is slow in adapting. For this reason, Meissner corpuscles are particularly sensitive to the movement of very light objects over the surface of the skin and to low-frequency vibration. Merkel disks are responsible for giving steady-state signals that allow for continuous determination of touch against the skin.

The *pacinian corpuscle* is located immediately beneath the skin and deep in the fascial tissues of the body. This type of receptor, which is stimulated by rapid movements of the tissues and adapts within a few hundredths of a second, is important in detecting tissue vibration. The *hair follicle end-organ* consists of afferent unmyelinated fibers entwined around most of the length of the hair follicle. These receptors, which are rapidly adapting, detect movement on the surface of the body. *Ruffini end-organs* are found in the skin and deeper structures, including the joint capsules. These receptors, which have multibranched encapsulated endings, have very little adaptive capacity and are important for signaling continuous states of deformation, such as heavy and continuous touch and pressure.

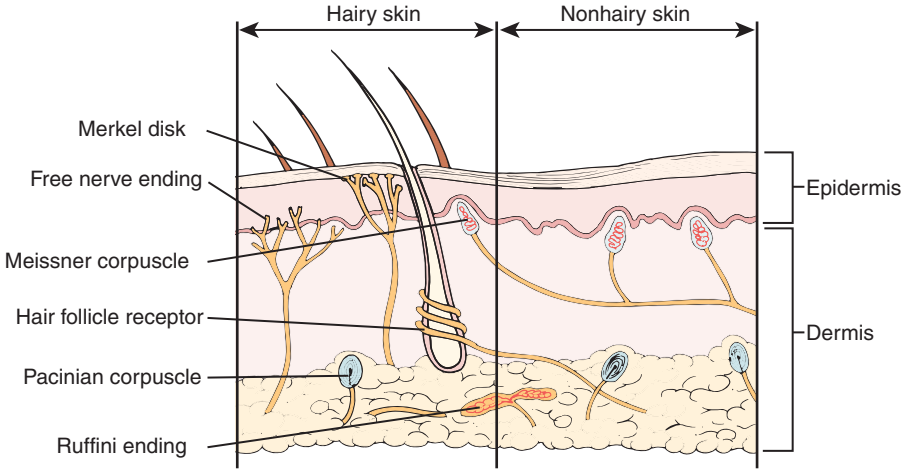


FIGURE 35-7. Somatic sensory receptors in the skin. Hairy skin and nonhairy skin have a variety of sensory receptors. (Adapted from Bear M.F., Connors B.W., Paradiso M.A. [1996]. *Neuroscience: Exploring the brain* [p. 311]. Baltimore: Williams & Wilkins.)

Almost all the specialized touch receptors, with the exception of free nerve endings, transmit their signals through large myelinated nerve fibers (i.e., types Aα, Aβ) that have transmission velocities ranging from 25 to 70 m/second. Most free nerve endings transmit signals by way of small myelinated fibers (i.e., type Aδ) with conduction velocities of 10 to 30 m/second.

The sensory information for tactile sensation enters the spinal cord through the dorsal roots of the spinal nerves. All tactile sensation that requires rapid transmission is transmitted through the discriminative pathway to the thalamus by way of the medial lemniscus. This includes touch sensation requiring a high degree of localization or fine gradations of intensity, vibratory sensation, and sensation that signals movement against the skin. In addition to the ascending discriminative pathway, tactile sensation uses the more primitive and crude anterolateral pathway. The afferent axons that carry tactile information up the dorsal columns have many branches or collaterals, some of which synapse in the dorsal horn near the level of dorsal root entry. After several synapses, axons are projected up both sides of the anterolateral aspect of the spinal cord to the thalamus. Few fibers travel all the way to the thalamus. Most synapse on reticular formation neurons that then send their axons on toward the thalamus. The thalamus is capable of contributing a crude, poorly localized sensation from the opposite side of the body. From the thalamus, some projections travel to the somatosensory cortex, especially to the side opposite the stimulus.

Because of these multiple routes, total destruction of the anterolateral pathway seldom occurs. The only time this crude alternative system becomes essential is when the discriminative pathway is damaged. Then, despite projection of the anterolateral system information to the somatosensory cortex, only a poorly localized, high-threshold sense of touch remains. Such persons lose all sense of joint and muscle movement, body position, and two-point discrimination.

Thermal Sensation

Thermal sensation is discriminated by three types of receptors: cold, warmth, and pain. The cold and warmth receptors are located immediately under the skin at discrete but separate points, each serving an area of approximately 1 mm^2. In some areas, there are more cold receptors than warmth receptors. For example, the lips have 15 to 25 cold receptors per square centimeter, compared with 3 to 5 in the same-sized area of the finger.[1] Different gradations of heat and cold reception result from the relative degrees of stimulation of the different types of nerve endings. Warmth receptors respond proportionately to increases in skin temperature above resting values of 34°C and cold receptors to temperatures below 34°C.[2] The thermal pain receptors are stimulated only by extremes of temperature such as "freezing cold" (temperatures below 5°C) and "burning hot" (temperatures above 45°C) sensations.[2] Thermal receptors respond rapidly to sudden changes in temperature and then adapt over the next few minutes. They do not adapt completely, however, but continue to respond to steady states of temperature. For example, the sensation of heat one feels on entering a tub of hot water or the extreme degree of cold experienced when going outside on a cold day is the initial response to a change in temperature, followed by an adaptation in which one gets accustomed to the temperature change but still feels the heat or cold because the receptors have not adapted completely.

Thermal afferents, with receptive thermal endings in the skin, send their central axons into the segmental dorsal horn of the spinal cord. On entering the dorsal horn, thermal signals are processed by second-order input association neurons. These association neurons activate projection neurons whose axons then cross to the opposite side of the cord and ascend in the multisynaptic, slow-conducting anterolateral system to the opposite side of the brain. Thalamic and cortical somatosensory regions for temperature are mixed with those for tactile sensibility.

Conduction of thermal information through peripheral nerves is quite slow compared with the rapid tactile afferents that travel through the discriminative system. If a person places a foot in a tub of hot water, the tactile sensation occurs well in advance of the burning sensation. The foot has been removed from the hot water by the local withdrawal reflex well before the excessive heat is perceived by the forebrain. Local anesthetic agents block the small-diameter afferents that carry thermal sensory information before they block the large-diameter axons that carry discriminative touch information.

Position Sense

Position sense refers to the sense of limb and body movement and position without using vision. It is mediated by input from proprioceptive receptors (muscle spindle receptors and Golgi tendon organs) found primarily in muscles, tendons, and joint capsules (see Chapter 36). There are two submodalities of proprioception: the stationary or static component (limb position sense) and the dynamic aspects of position sense (kinesthesia). Both of these depend on constant transmission of information to the CNS regarding the degree of angulation of all joints and the rate of change in angulation. In addition, stretch-sensitive receptors in the skin (Ruffini end-organs, pacinian corpuscles, and Merkel cells) also signal postural information. Signals from these receptors are processed through the dorsal column–medial lemniscus pathway. In addition to the transmission of signals from the periphery to the cerebral cortex, the signals are processed in the thalamus before reaching the cerebral cortex. Lesions affecting the posterior column of the spinal cord impair position sense. The vestibular system (see Chapter 38) also plays an essential role in position sense.

In summary, the somatosensory component of the nervous system provides an awareness of body sensations such as touch, temperature, position sense, and pain. There are three primary levels of neural integration

in the somatosensory system: the sensory units containing the sensory receptors, the ascending pathways, and the central processing centers in the thalamus and cerebral cortex. A sensory unit consists of a single dorsal root ganglion neuron, its receptors, and its central axon that terminates in the dorsal horn of the spinal cord or medulla. The part of the body innervated by the somatosensory afferent neurons of one set of dorsal root ganglia is called a *dermatome.* Ascending pathways include the discriminative pathway, which crosses at the base of the medulla, and the anterolateral pathway, which crosses within the first few segments of entering the spinal cord. Perception, or the final processing of somatosensory information, involves centers in the thalamus and somatosensory cortex. In the thalamus, the sensory information is crudely localized and perceived. The full localization, discrimination of the intensity, and interpretation of the meaning of the stimuli require processing by the somatosensory cortex. A distorted map of the body and head surface, called the *sensory homunculus,* reflects the density of cortical neurons devoted to sensory input from afferents in corresponding peripheral areas.

The tactile system relays the sensations of touch, pressure, and vibration. It uses two anatomically separate pathways to relay touch information to the opposite side of the forebrain: the dorsal column discriminative pathway and the anterolateral pathway. Delicate touch, vibration, position, and movement sensations use the discriminative pathway to reach the thalamus, where third-order relay occurs to the primary somatosensory strip of the parietal cortex. Crude tactile sensation is carried by the bilateral slow-conducting anterolateral pathway. Temperature sensations of warm–hot and cool–cold are the result of stimulation of thermal receptors of sensory units projecting to the thalamus and cortex through the anterolateral system on the opposite side of the body. Position sense or proprioception is processed through the rapid-transmitting dorsal column–medial lemniscus pathway.

Pain Sensation

Pain is an unpleasant sensory and emotional sensation associated with actual and potential tissue damage.[1–4] Unlike other somatic modalities, pain has an urgent and primitive quality, a quality responsible for the psychological, social, cultural, and cognitive aspects of the pain experience. Despite its unpleasantness, pain can serve a useful purpose in that it warns of impending tissue injury, motivating the person to seek relief. For example, an inflamed appendix could progress in severity, rupture, and even cause death were it not for the warning afforded by pain.

Pain is a common symptom that varies widely in intensity and spares no age group. It can be equally devastating for infants and children, young and middle-aged adults, and the young-old and the old-old. Both acute pain and chronic pain can be major health problems. It is the most common reason for visits to health care facilities. Acute pain often results from injury, surgery, or invasive medical procedures. It also can be a presenting symptom of infections, such as otitis media. Chronic pain can be symptomatic of a wide range of health problems including arthritis, back injury, and cancer.

Pain Theories

Traditionally, two theories have been offered to explain the physiologic basis for the pain experience. The first, *specificity theory,* regards pain as a separate sensory modality evoked by the activity of specific receptors that transmit information by special nerve endings to pain centers or regions in the forebrain where pain is experienced.[5] The second theory includes a group of theories collectively referred to as *pattern theory.* It proposes that pain receptors share endings or pathways with other sensory modalities, but that different patterns of activity (i.e., spatial or temporal) of the same neurons can be used to signal painful and nonpainful stimuli.[5] For example, light touch applied to the skin would produce the sensation of touch through low-frequency firing of the receptor; intense pressure would produce pain through high-frequency firing of the same receptor. Both theories focus on the neurophysiologic basis of pain, and both probably apply. Specific nociceptive afferents have been identified; however, almost all afferent stimuli, if driven at a very high frequency, can be experienced as painful.

Gate control theory, a modification of specificity theory, was proposed by Melzack and Wall in 1965 to meet the challenges presented by the pattern theories. This theory postulated the presence of neural gating mechanisms at the segmental spinal cord level to account for interactions between pain and other sensory modalities.[6] The original gate control theory proposed a spinal cord–level network of transmission or projection cells and internuncial neurons that inhibits the transmission cells, forming a segmental-level gating mechanism that could block projection of pain information to the brain.

According to the gate control theory, the internuncial neurons involved in the gating mechanism are activated by large-diameter, faster-propagating fibers that carry tactile information. The simultaneous firing of the large-diameter touch fibers has the potential for blocking the transmission of impulses from the small-diameter myelinated and unmyelinated pain fibers. Pain therapists have long known that pain intensity can be temporarily modified by the stimulation of other sensory fibers. For example, repeated sweeping of a soft-bristled brush on the skin (i.e., brushing) over or near a painful area may result in pain reduction for several minutes to several hours.

Pain modulation is now known to be a much more complex phenomenon than that proposed by the original gate control theory. Tactile information is transmitted by small- and large-diameter fibers. Major interactions between sensory modalities, including the so-called gating phenomenon, occur at several levels of the CNS rostral to the input segment. Perhaps the most puzzling

aspect of locally applied stimuli, such as brushing, that can block the experience of pain is the relatively long-lasting effect (minutes to hours) of such treatments. This prolonged effect has been difficult to explain on the basis of specificity theories, including the gate control theory. Other important factors include the effect of endogenous opioids and their receptors at the segmental and brain stem level, descending feedback modulation, altered sensitivity, learning, and culture. Despite this complexity, the Melzack and Wall theory has served a useful purpose. It sparked interest in pain and stimulated research and clinical activity related to the pain-modulating systems.

More recently, Melzack has developed the *neuromatrix theory* to address further the brain's role in pain as well as the psychological and emotional sequelae that contribute to the multiple dimensions and determinants of pain.[7] This theory is particularly useful in understanding chronic pain and phantom limb pain, in which there is not a simple one-to-one relationship between tissue injury and pain experience. The neuromatrix theory proposes that the brain contains a widely distributed neural network, called the *body–self neuromatrix,* that has multiple somatosensory, limbic, and thalamocortical components. Genetic and sensory influences determine the synaptic architecture of an individual's neuromatrix that integrates multiple sources of input and yields the neurosignature pattern that evokes the sensory, affective, and cognitive dimensions of pain experience and behavior. These multiple sources include somatosensory inputs; other sensory inputs affecting interpretation of the situation; phasic and tonic inputs from the brain addressing such things as attention, expectation, culture, and personality; intrinsic neural inhibitory modulation; and various components of stress regulation systems. The neuromatrix theory of pain, which places genetic and neuroendocrine mechanisms of stress on a level equal to that of the neural mechanisms of sensory transmission, has important implications for research and therapy.[7]

Pain Sensation

- Pain is both a protective and an unpleasant physical and emotionally disturbing sensation originating in pain receptors that respond to a number of stimuli that threaten tissue integrity.
- There are two pathways for pain transmission:
  - The pathway for fast, sharply discriminated pain that moves directly from the receptor to the spinal cord using myelinated Aδ fibers and from the spinal cord to the thalamus using the neospino-thalamic tract
  - The pathway for slow, continuously conducted pain that is transmitted to the spinal cord using unmyelinated C fibers and from the spinal cord to the thalamus using the more circuitous and slower-conducting paleospinothalamic tract
- The central processing of pain information includes transmission to the somatosensory cortex, where pain information is perceived and interpreted; the limbic system, where the emotional components of pain are experienced; and to brain stem centers, where autonomic nervous system responses are recruited.
- Modulation of the pain experience occurs by way of the endogenous analgesic center in the midbrain, the pontine noradrenergic neurons, and the nucleus raphe magnus in the medulla, which sends inhibitory signals to dorsal horn neurons in the spinal cord or trigeminal nerve.

Pain Mechanisms and Pathways

Pain can be either nociceptive or neuropathic in origin. The term *nociception,* which means "pain sense," comes from the Latin word *nocere,* "to injure." *Nociceptive pain* is initiated by nociceptors that are activated by noxious insults to peripheral tissues. *Neuropathic pain,* on the other hand, arises from direct injury or dysfunction of the sensory axons of peripheral or central nerves.

Two aspects of pain affect an individual's response to a painful stimulus—pain threshold and tolerance. Although the terms often are used interchangeably, pain threshold and pain tolerance have distinct meanings. *Pain threshold* is closely associated with the point at which a nociceptive stimulus is perceived as painful. *Pain tolerance* relates more to the total pain experience; it is defined as the maximum intensity or duration of pain that a person is willing to endure before the person wants something done about the pain. Psychological, familial, cultural, and environmental factors significantly influence the amount of pain a person is willing to tolerate. The threshold for pain is fairly uniform from one person to another, whereas pain tolerance is extremely variable.

The mechanisms of pain are many and complex. As with other forms of somatosensation, the pathways are composed of first-, second-, and third-order neurons[1,2] (Fig. 35-8). The first-order neurons and their receptive endings detect stimuli that threaten the integrity of innervated tissues. Second-order neurons are located in the spinal cord and process nociceptive information. Third-order neurons project pain information to the brain. The thalamus and somatosensory cortex integrate and modulate pain as well as the person's subjective reaction to the pain experience.

Pain Receptors and Primary Afferent Pathways

Nociceptors, or pain receptors, are sensory receptors that are activated by noxious insults to peripheral tissues. Structurally, the receptive endings of the peripheral pain fibers are free nerve endings. These receptive endings,

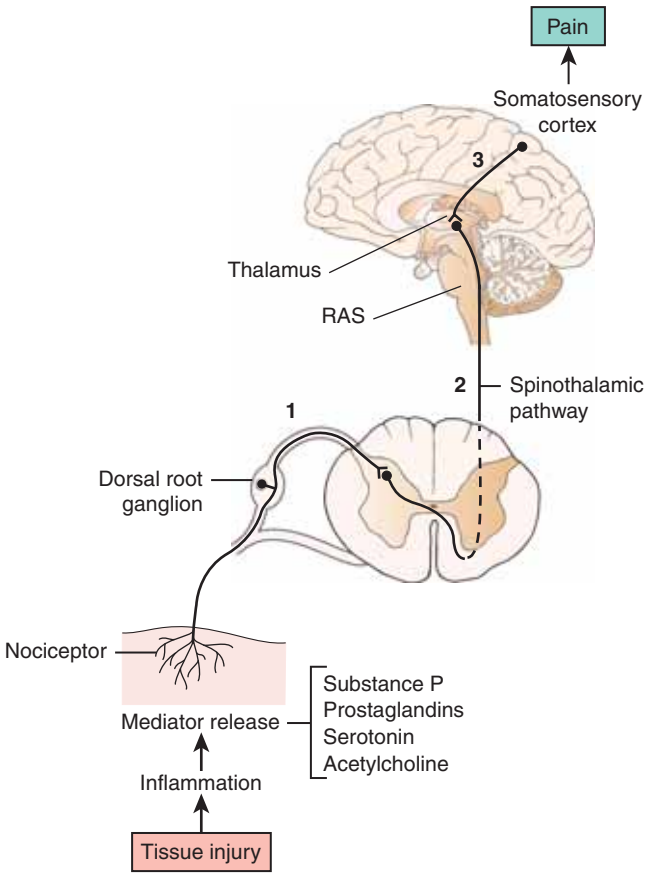


FIGURE 35-8. Mechanism of acute pain. Tissue injury leads to release of inflammatory mediators with subsequent nociceptor stimulation. Pain impulses are then transmitted to the dorsal horn of the spinal cord, where they make contact with second-order neurons that cross to the opposite side of the cord and ascend by the spinothalamic tract to the reticular activating system (RAS) and thalamus. The localization and meaning of pain occur at the level of the somatosensory cortex. 1, first-order sensory neurons; 2, second-order sensory neurons; 3, third-order sensory neurons.

which are widely distributed in the skin, dental pulp, periosteum, meninges, and some internal organs, translate the noxious stimuli into action potentials that are transmitted by a dorsal root ganglion to the dorsal horn of the spinal cord.

Nociceptive Simulation. Unlike other sensory receptors, nociceptors respond to several forms of stimulation, including mechanical, thermal, and chemical. Some receptors respond to a single type of stimuli (mechanical or thermal) and others, called *polymodal receptors*, respond to all three types of stimuli (mechanical, thermal, and chemical). Mechanical stimuli can arise from intense pressure applied to skin or from the violent contraction or extreme stretch of a muscle. Both extremes of heat and cold can stimulate nociceptors. Chemical stimuli arise from a number of sources, including tissue trauma, ischemia, and inflammation. A wide range of chemical mediators are released from injured and inflamed tissues, including hydrogen and potassium ions, prostaglandins, leukotrienes, histamine, bradykinin, acetylcholine, and serotonin. These chemical mediators produce their effects by directly stimulating nociceptors or sensitizing them to the effects of nociceptive stimuli; perpetuating the inflammatory responses that lead to the release of chemical agents that act as nociceptive stimuli; or inciting neurogenic reflexes that increase the response to nociceptive stimuli. For example, bradykinin, histamine, serotonin, and potassium activate and also sensitize nociceptors.[8] Other chemical mediators act alone or in concert to sensitize nociceptors through other chemical agents such as prostaglandins. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in controlling pain because they block the enzyme needed for prostaglandin synthesis.

Peripheral Pain Fibers. There are two types of afferent fibers that transmit pain signals from the free nerve endings into the CNS: myelinated Aδ fibers and unmyelinated C fibers.[1,2] The larger Aδ fibers have considerably greater conduction velocities, transmitting impulses at a rate of 10 to 30 m/second. The C fibers are the smallest of all peripheral nerve fibers; they transmit impulses at the rate of 0.5 to 2.5 m/second. Pain conducted by Aδ fibers traditionally is called *fast pain* or first pain and typically is elicited by mechanical or thermal stimuli. C-fiber pain often is described as *slow-wave pain* or second pain because it is slower in onset and longer in duration, continuing to elicit pain for up to 80 hours.[9] It typically is incited by chemical stimuli or by persistent mechanical or thermal stimuli. The slow postexcitatory potentials generated in C fibers are now believed to be responsible for central sensitization to chronic pain.

Nociceptive stimulation that activates C fibers can cause a response known as *neurogenic inflammation* that produces vasodilation and an increased release of chemical mediators to which nociceptors respond.[8] This mechanism is thought to be mediated by a dorsal root neuron reflex that produces retrograde transport and release of chemical mediators, which in turn causes increasing inflammation of peripheral tissues. This reflex can set up a vicious cycle, which has implications for persistent pain and hyperalgesia.

The transmission of impulses between the peripheral nociceptive neurons and dorsal horn neurons in the spinal cord is mediated by neurotransmitters released from nerve endings of the nociceptive neurons.[10] Some of these neurotransmitters are amino acids (e.g., glutamate), others are amino acid derivatives (e.g., norepinephrine), and still others are low–molecular-weight peptides composed of two or more amino acids. The amino acid glutamate is a major excitatory neurotransmitter released from the central nerve endings of the nociceptive neurons. Substance P, a neuropeptide, also is released in the dorsal horn by C fibers in response to nociceptive stimulation. Substance P elicits slow excitatory potentials in dorsal horn neurons. Unlike glutamate, which confines its action to the immediate area of the synaptic terminal, some neuropeptides released in the dorsal horn can diffuse some distance because they are not inactivated by reuptake mechanisms. In persistent pain, this may help to explain the excitability and unlocalized

nature of many painful conditions. Neuropeptides such as substance P also appear to prolong and enhance the action of glutamate. If these neurotransmitters are released in large quantities or over extended periods, they can lead to secondary hyperalgesia, a condition in which the second-order neurons are overly sensitive to low levels of noxious stimulation.

Spinal Cord Circuitry and Ascending Pathways

On entering the spinal cord through the dorsal roots, the pain fibers bifurcate and ascend or descend one or two segments before synapsing with association neurons in the dorsal horn. From the dorsal horn, the axons of association projection neurons cross through the anterior commissure to the opposite side and then ascend upward in the previously described neospinothalamic and anterolateral pathways (Fig. 35-9).

The faster-conducting fibers in the neospinothalamic tract are associated mainly with the transmission of sharp–fast pain information to the thalamus. In the thalamus, synapses are made and the pathway continues to the contralateral parietal somatosensory area to provide the precise location of the pain. Typically, the pain is experienced as bright, sharp, or stabbing in nature.

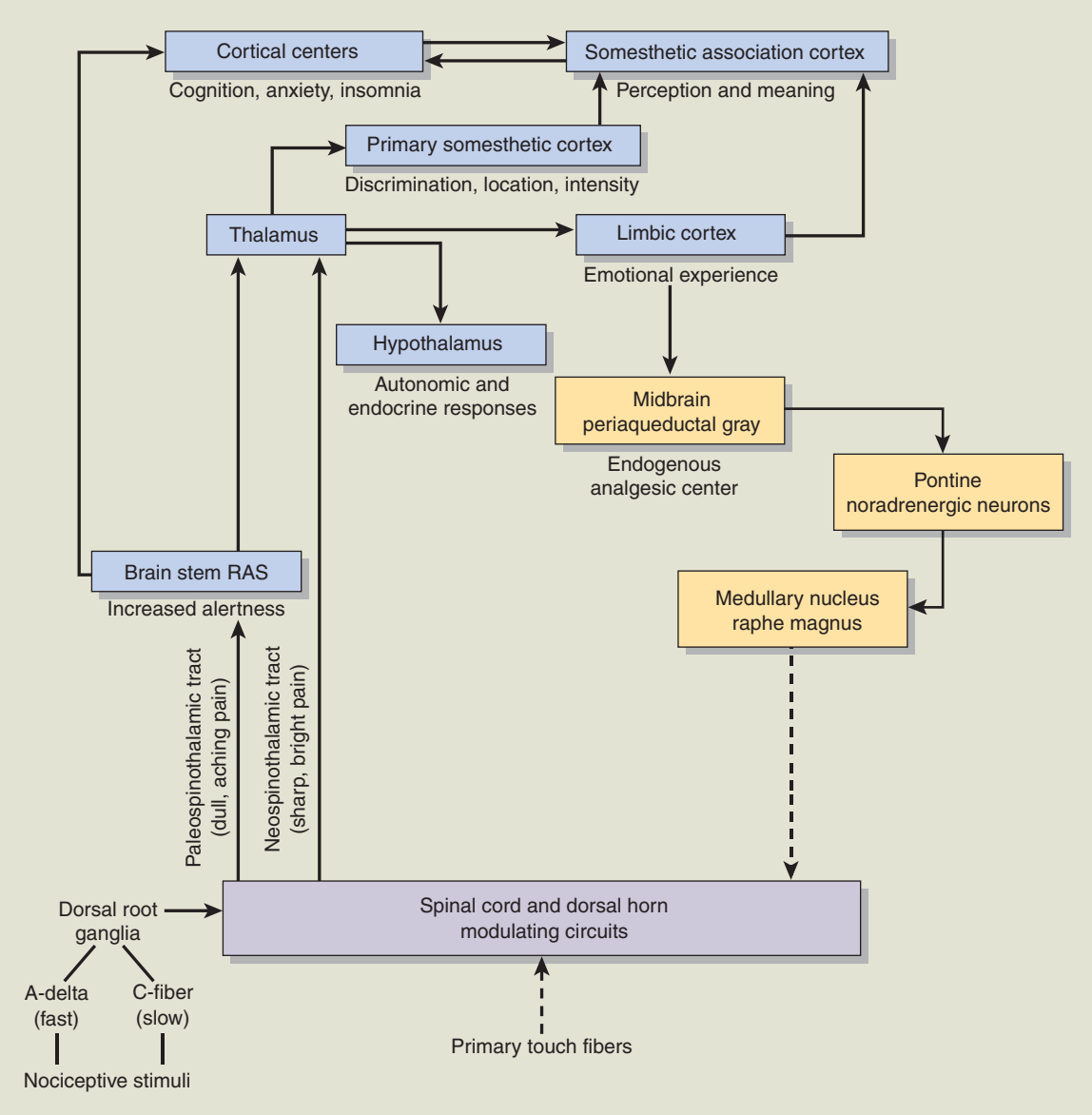


FIGURE 35-9. Primary pain pathways. The transmission of incoming nociceptive impulses is modulated by dorsal horn circuitry that receives input from primary touch receptors and from descending pathways that involve the limbic cortical systems (orbital frontal cortex, amygdala, and hypothalamus), the periaqueductal endogenous analgesic center in the midbrain, pontine noradrenergic neurons, and the nucleus raphe magnus (NRM) in the medulla. *Dashed lines* indicate inhibition or modulation of pain transmission by dorsal horn projection neurons. RAS, reticular activating system.

The paleospinothalamic tract is a slower-conducting, multisynaptic tract concerned with the diffuse, dull, aching, and unpleasant sensations that commonly are associated with chronic and visceral pain. Fibers of this system also travel up the contralateral (i.e., opposite) anterolateral pathway to terminate in several thalamic regions, including the intralateral nuclei, which project to the limbic system. These projections are associated with the emotional or affective–motivational aspects of pain. Spinoreticular fibers from this pathway project bilaterally to the reticular formation of the brain stem. This component of the paleospinothalamic system facilitates avoidance reflexes at all levels. It also contributes to elevated levels of alertness and increased heart rate and blood pressure that can occur with pain.

Brain Centers and Pain Perception

Information from tissue injury is carried from the spinal cord to brain centers in the thalamus where the basic sensation of hurtfulness, or pain, occurs (see Fig. 35-9). In the neospinothalamic system, interconnections between the lateral thalamus and the somatosensory cortex are necessary to add precision, discrimination, and meaning to the pain sensation. The paleospinothalamic system projects diffusely from the intralaminar nuclei of the thalamus to large areas of the limbic cortex. These connections probably are associated with the hurtfulness and the mood-altering and attention-narrowing effect of pain.

Recent research has demonstrated cortical representation of fast–sharp and slow–chronic types of pain sensation. In healthy adults, nociceptive Aδ afferent stimulation is related to activation in the contralateral primary somatosensory cortex in the parietal lobe, whereas C afferent stimulation is related to activation of the secondary somatosensory cortices and the anterior cingulated cortex, which is part of the limbic system. With both afferents there is activation of the bilateral secondary somatosensory cortices in the posterior parietal lobes.[11]

Central Pathways for Pain Modulation

A major advance in understanding pain was the discovery of neuroanatomic pathways that arise in the midbrain and brain stem, descend to the spinal cord, and modulate ascending pain impulses. One such pathway begins in an area of the midbrain called the *periaqueductal gray* (PAG) region. Through research it was found that electrical stimulation of the midbrain PAG regions produced a state of analgesia that lasted for many hours. This stimulation-induced analgesia was found to be remarkably specific and was not associated with changes in either the levels of consciousness or the reactions to auditory and visual stimuli.[2] Subsequently, opioid receptors were found to be highly concentrated in this and other regions of the CNS where electrical stimulation produced analgesia through the release of endorphins, enkephalins and dynorphines, endogenous opioids. Because of these findings, the PAG area of the midbrain often is referred to as the *endogenous analgesia center.*[1]

The PAG area receives input from widespread areas of the CNS, including the cerebral cortex, hypothalamus, brain stem reticular formation, and spinal cord, by way of the paleospinothalamic and neospinothalamic tracts. This region is intimately connected to the limbic system, which is associated with emotional experience. The neurons of the PAG have axons that descend into an area in the rostral medulla called the *nucleus raphe magnus* (NRM). The axons of these NRM neurons project to the dorsal horn of the spinal cord, where they terminate in the same layers as the entering primary pain fibers (see Fig. 35-9). In the spinal cord these descending pathways inhibit pain transmission by dorsal horn projection neurons.[2] Serotonin has been identified as a neurotransmitter in the NRM medullary nuclei. Tricyclic antidepressant drugs, such as amitriptyline, which enhance the effects of serotonin by blocking its presynaptic uptake, have been found to be effective in the management of certain types of chronic pain.[12] Additional inhibitory spinal projections arise from noradrenergic neurons in the pons and medulla, which also receive input from the PAG.[2] The discovery that norepinephrine can block pain transmission led to studies directed at the combined administration of opioids and clonidine, a central-acting α-adrenergic agonist, for pain relief.

Endogenous Analgesic Mechanisms

There is evidence that opioid receptors and endogenously synthesized opioid peptides are found on the peripheral processes of primary afferent neurons, in human synovia, and in many regions of the CNS.[13] Three families of opioid peptides have been identified—the enkephalins, endorphins, and dynorphins. Although the endogenous opioid peptides appear to function as neurotransmitters, their full significance in pain control and other physiologic functions is not completely understood. Probably of greater importance in understanding the mechanisms of pain control has been the characterization of receptors that bind the endogenous opioid peptides. The identification of these receptors has facilitated a more thorough understanding of the actions of available opioid drugs, such as morphine, and it also has facilitated ongoing research into the development of new preparations that are more effective in relieving pain, but with fewer side effects than existing preparations.[13]

Types of Pain

The most widely accepted classifications of pain are according to source or location (somatic or visceral), referral, and duration (acute or chronic). Classification based on associated medical diagnosis (e.g., surgery, trauma, cancer, sickle cell disease, fibromyalgia) is useful in planning appropriate interventions.

Cutaneous and Deep Somatic Pain

Cutaneous pain arises from superficial structures, such as the skin and subcutaneous tissues. A paper cut on the finger is an example of easily localized superficial, or cutaneous, pain. It is a sharp pain with a burning quality and may be abrupt or slow in onset. It can be localized

Types of Pain

- Pain can be classified according to location (cutaneous or deep and visceral), duration (acute or chronic), and site of referral.
- Cutaneous pain is a sharp, burning pain that has its origin in the skin or subcutaneous tissues.
- Deep pain is a more diffuse and throbbing pain that originates in structures such as the muscles, bones, and tendons and radiates to the surrounding tissues.
- Visceral pain is a diffuse and poorly defined pain that results from stretching, distention, or ischemia of tissues in a body organ.
- Acute pain is a self-limiting pain that remits when the underlying cause is removed.
- Chronic pain is persistent pain that lasts longer than expected, lacks the autonomic and somatic responses associated with acute pain, and is accompanied by loss of appetite, sleep disturbances, depression, and other debilitating responses.
- Referred pain is pain that originates at a visceral site but is perceived as originating in the part of the body wall that is innervated by neurons entering the same segment of the nervous system.

accurately and may be distributed along the dermatomes. Because there is an overlap of nerve fiber distribution between the dermatomes, the boundaries of pain frequently are not as clear-cut as dermatome diagrams indicate.

Deep somatic pain originates in deep body structures, such as the periosteum, muscles, tendons, joints, and blood vessels. This pain is more diffuse than cutaneous pain. Various stimuli, such as strong pressure exerted on bone, ischemia to a muscle, and tissue damage, can produce deep somatic pain. This is the type of pain a person experiences from a sprained ankle. Radiation of pain from the original site of injury can occur. For example, damage to a nerve root can cause a person to experience pain radiating along its fiber distribution.

Visceral Pain

Visceral, or splanchnic, pain has its origin in the visceral organs and is one of the most common pains produced by disease. While similar to somatic pain in many ways, both the neurologic mechanisms and the perception of visceral pain differ from somatic pain. One of the most important differences between somatic and visceral pain is the type of damage that causes pain. For example, "a surgeon can cut the bowel entirely in two in a patient who is awake without causing significant pain."[1] In contrast, strong contractions, distention, or ischemia affecting the walls of the viscera can induce severe pain. Also, visceral pain is not evoked from all viscera (e.g., the liver, lung parenchyma).[14] Another difference is the diffuse and poorly localized nature of visceral pain—its tendency to be referred to other locations and to be accompanied by symptoms associated with autonomic reflexes (e.g., nausea).[15] There are several explanations for this. There is a low density of nociceptors in the viscera compared with the skin. There is functional divergence of visceral input within the CNS, which occurs when many second-order neurons respond to a stimulus from a single visceral afferent. There is also convergence between somatic and visceral afferents in the spinal cord and in the supraspinal centers and possibly also between visceral afferents (e.g., bladder, uterus, cervix, and vagina).

Visceral afferents are predominantly small, unmyelinated pain fibers that terminate in the dorsal horn of the spinal cord and express peptide neurotransmitters such as substance P.[14] There are thought to be two classes of nociceptive receptors that innervate the viscera: high-threshold and intensity-coding receptors.[14,15] High-threshold receptors have a high threshold for stimulation and respond only to stimuli within the nociceptive range. Intensity-coding receptors have a lower threshold for stimulation and an encoding function that incorporates the intensity of the stimulus into the magnitude of their discharge. Acute visceral pain, such as pain produced by intense contraction of a hollow organ, is thought to be triggered initially by high-threshold receptors. More extended forms of visceral stimulation, such as that caused by hypoxia and inflammation, often result in sensitization of the receptors. Once sensitized, these receptors begin to respond to otherwise innocuous stimuli (e.g., motility and secretory activity) that normally occur in the viscera. This sensitization may resolve more slowly than the initial injury and thus visceral pain may persist longer than expected based on the initial injury.[14]

Referred Pain

Referred pain is pain that is perceived at a site different from its point of origin but innervated by the same spinal segment. It is hypothesized that visceral and somatic afferent neurons converge on the same dorsal horn projection neurons (Fig. 35-10). For this reason, it can be difficult for the brain to correctly identify the original source of pain. Pain that originates in the abdominal or thoracic viscera is diffuse and poorly localized and often perceived at a site far removed from the affected area. For example, the pain associated with myocardial infarction commonly is referred to the left arm, neck, and chest, which may delay diagnosis and treatment of a potentially life-threatening condition.

Referred pain may arise alone or concurrent with pain located at the origin of the noxious stimuli. This lack of correspondence between the location of the pain and the location of the painful stimuli can make diagnosis difficult. Although the term *referred* usually is applied to pain that originates in the viscera and is experienced as if originating

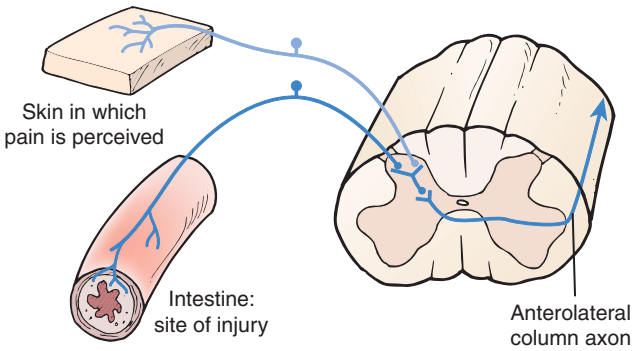


FIGURE 35-10. Convergence of cutaneous and visceral inputs onto the same second-order projection neuron in the dorsal horn of the spinal cord. Although virtually all visceral inputs converge with cutaneous inputs, most cutaneous inputs do not converge with other sensory inputs.

from the body wall, it also may be applied to pain that arises from somatic structures. For example, pain referred to the chest wall could be caused by nociceptive stimulation of the peripheral portion of the diaphragm, which receives somatosensory innervation from the intercostal nerves. An understanding of pain referral is of great value in diagnosing illness. The typical pattern of pain referral can be derived from understanding that the afferent neurons from visceral or deep somatic tissue enter the spinal cord at the same level as the afferent neurons from the cutaneous areas to which the pain is referred (Fig. 35-11).

The sites of referred pain are determined embryologically with the development of visceral and somatic structures that share the same site for entry of sensory information into the CNS and then move to more distant locations. For example, a person with peritonitis may complain of pain in the shoulder. Internally, there is inflammation of the peritoneum that lines the central part of the diaphragm. In the embryo, the diaphragm originates in the neck, and its central portion is innervated by the phrenic nerve, which enters the cord at the level of the third to fifth segments (C3 to C5). As the fetus develops, the diaphragm descends to its adult position between the thoracic and abdominal cavities while maintaining its embryonic pattern of innervation. Thus, fibers that enter the spinal cord at the C3 to C5 levels carry information from both the neck area and the diaphragm, and the diaphragmatic pain is interpreted by the forebrain as originating in the shoulder or neck area.

Although the visceral pleura, pericardium, and peritoneum are said to be relatively free of pain fibers, the parietal pleura, pericardium, and peritoneum do react to nociceptive stimuli. Visceral inflammation can involve parietal and somatic structures, and this may give rise to diffuse local or referred pain. For example, irritation of the parietal peritoneum resulting from appendicitis typically gives rise to pain directly over the inflamed area in the lower right quadrant, while producing referred pain in the umbilical area.

Muscle spasm, or *guarding,* occurs when somatic structures are involved. Guarding is a protective reflex rigidity; its purpose is to protect the affected body parts

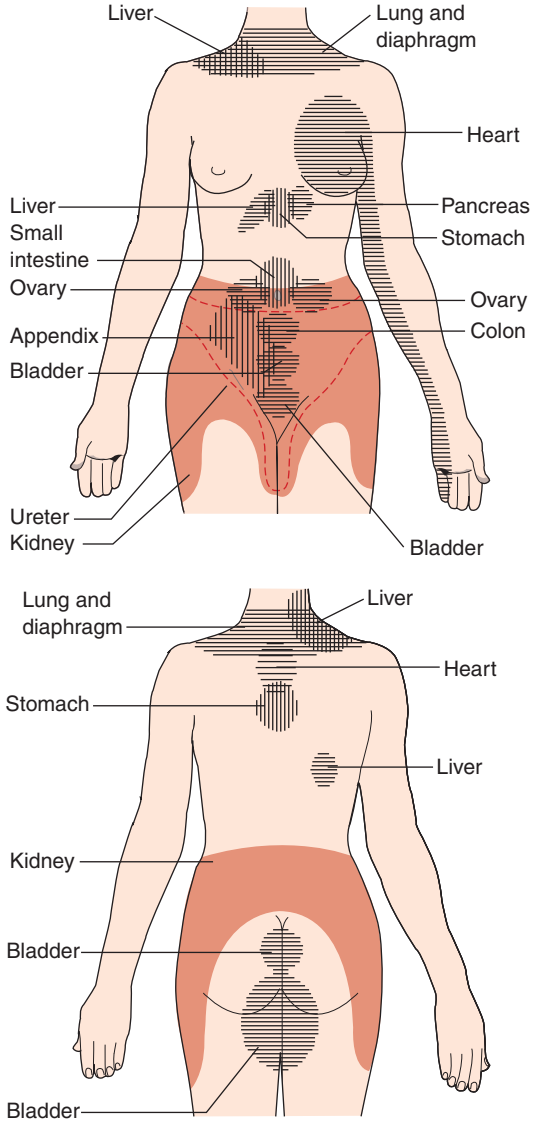


FIGURE 35-11. Areas of referred pain. (*Top*) Anterior view. (*Bottom*) Posterior view.

(e.g., an abscessed appendix or a sprained muscle). This protective guarding may cause blood vessel compression and give rise to the pain of muscle ischemia, causing local and referred pain.

Acute and Chronic Pain

It is common to classify pain according to its duration. Pain research of the last several decades has emphasized the importance of differentiating acute pain from chronic pain. The diagnosis and therapy for each is distinctive because they differ in cause, function, mechanisms, and psychological sequelae (Table 35-1).

Traditionally, the distinction between acute and chronic pain has relied on a single continuum of time with some interval (e.g., 6 months) since the onset of pain used to designate the onset of acute pain or the transition when acute pain became chronic.[16] A more recent conceptualization includes both time and pathophysiologic dimensions.

TABLE 35-1 Characteristics of Acute and Chronic Pain

Characteristic	Acute Pain	Chronic Pain
Onset	Recent	Continuous or intermittent
Duration	Short (<6 months)	6 months or more
Autonomic responses	Consistent with sympathetic fight-or-flight response* Increased heart rate Increased stroke volume Increased blood pressure Increased pupillary dilation Increased muscle tension Decreased gut motility Decreased salivary flow (dry mouth)	Absence of autonomic responses
Psychological component	Associated anxiety	Increased irritability Associated depression Somatic preoccupation Withdrawal from outside interests Decreased strength of relationships
Other types of response		Decreased sleep Decreased libido Appetite changes

Some conditions such as osteoarthritis exhibit dimensions of both acute and chronic pain.

Acute Pain. Acute pain is generally of short duration and remits when the underlying pathologic process has resolved.[16] The purpose of acute pain is to serve as a warning system. Besides alerting the person to the existence of actual or impending tissue damage, it prompts a search for professional help. The pain's location, radiation, intensity, and duration, as well as those factors that aggravate or relieve it, provide essential diagnostic clues.

Acute pain is pain that is elicited by surgery or trauma to body tissues and activation of nociceptive stimuli at the site of tissue damage.[17,18] This may induce an early wave of hyperexcitability of neurons within the CNS. The development of an inflammatory reaction to the tissue injury, with sensitization of peripheral receptors, often results in a second wave of longer-acting afferent input and a new increase in central hyperexcitability.[18,19] The resulting hyperalgesia can lead to an increased postoperative and posttraumatic pain, usually about the second or third day, and in some cases an increased likelihood of developing chronic pain. A number of chronic pain syndromes, including whiplash injury and phantom pain, develop after trauma and surgery.[18]

Because acute pain is self-limited, in that it resolves as the injured tissues heal, long-term therapy usually is not needed. Acute pain (i.e., pain from acute illness, trauma, surgery, or medical procedures) should be aggressively managed and preemptive analgesia provided before the pain becomes severe. The use of preemptive and multimodal therapy (two or more analgesics with differing analgesic mechanisms) not only allows the person to be more comfortable and active, but also helps to prevent peripheral sensitization of pain receptors and hyperexcitability of central pain centers.[19] Usually, less medication is needed when the drug is given before the pain becomes severe and the pain pathways become sensitized. Interventions that alleviate acute pain also relieve the anxiety and musculoskeletal spasms, as well increasing mobility and respiratory movements such as deep breathing and coughing.

Chronic Pain. Chronic pain is pain that persists longer than might be reasonably expected after an inciting event and is sustained by factors that are both pathologically and physically remote from the originating cause.[16,20,21] Chronic pain is highly variable. It may be unrelenting and extremely severe, as in metastatic bone pain. It can be relatively continuous with or without periods of escalation, as with some forms of back pain. Some conditions with recurring episodes of acute pain are particularly problematic because they have characteristics of both acute and chronic pain, as in sickle cell crisis or migraine headaches.

The biologic factors that contribute to chronic pain include peripheral mechanisms, peripheral–central mechanisms, and central mechanisms.[20] Peripheral mechanisms result from persistent stimulation of nociceptors, termed *peripheral sensitization*. Inflammatory mediators released from injured tissues increase the sensitivity of the C fibers and lead to increased duration of pain associated with chronic musculoskeletal, visceral, and vascular disorders. Peripheral–central mechanisms involve abnormal function of the peripheral and central portions of the somatosensory system.[21] These disorders include conditions such as those resulting from partial or complete loss of descending inhibitory pathways or spontaneous firing of regenerated nerve fibers. They include conditions such as causalgia, phantom limb pain, and postherpetic neuralgia. Central pain

mechanisms are associated with disease or injury of the CNS. Central pain is characterized by burning, aching, hyperalgesia, dysesthesia, and other abnormal sensations and is experienced as superficial (skin) or deep (bone or muscle) pain.[22] Central pain is associated with conditions such as thalamic lesions (thalamic pain), spinal cord injury, surgical interruption of pain pathways, and multiple sclerosis.

Unlike acute pain, chronic pain serves no useful purpose. To the contrary, it imposes physiologic, psychological, familial, and economic stresses and may exhaust a person's resources. Persons with chronic pain may not exhibit the somatic, autonomic, or affective behaviors often associated with acute pain. In addition, chronic pain often is associated with loss of appetite, sleep disturbances, and depression. Amazingly, depression commonly is relieved once the pain is removed.

Chronic pain management is complex and treatment depends on the cause of the pain, the natural history of the underlying health problem, and the life expectancy of the individual.[20,21] If the organic illness causing the pain cannot be cured, then noncurative methods of pain control become the cornerstone of treatment. Chronic pain is best handled by a multidisciplinary team that includes specialists in areas such as anesthesiology, nursing, physical therapy, social services, and surgery.

Cancer is a common cause of chronic pain.[23–25] The goal of chronic cancer pain management should be pain alleviation and prevention. Preemptive therapy tends to reduce sensitization of pain pathways and provides for more effective pain control. Pharmacologic and nonpharmacologic interventions are the same as those used for other types of chronic pain. Depending on the form and stage of the cancer, other treatments such as palliative radiation, antineoplastic therapies, and palliative surgery may help to control the pain. In 1986, the World Health Organization (WHO) developed a three-step ladder that assists clinicians in choosing the appropriate analgesic medications.[26] Step 1 involves the use of nonopioid analgesics, and steps 2 and 3 involve the use of opioid analgesics.

Pain Management

Assessment

Careful assessment of pain assists clinicians in diagnosing, managing, and relieving the patient's pain. Reports of pain are almost entirely subjective. Assessment includes such things as the nature, severity, location, and radiation of the pain. As with other disease states, eliminating the cause of the pain is preferable to simply treating the symptom. A careful history often provides information about the triggering factors (i.e., injury, infection, or disease) and the site of nociceptive stimuli (i.e., peripheral receptor or visceral organ).[21] A comprehensive pain history should include pain onset; description, localization, radiation, intensity, quality, and pattern of the pain; anything that relieves or exacerbates it; and the individual's personal reaction to the pain. Probably, the single most reliable indicator of the existence and intensity of acute pain is the person's self-report.

Unlike many other bodily responses, such as temperature and blood pressure, the nature, severity, and distress of pain cannot be measured objectively. To overcome this problem, various methods have been developed for quantifying pain based on the person's report. They include numeric pain intensity, visual analog, and verbal descriptor scales. Most pain questionnaires assess a single aspect of pain such as pain intensity. For example, a *numeric pain intensity* scale would have patients select which number best represents the intensity of their pain, where 0 represents no pain and 10 represents the most intense pain imaginable. A *visual analog* scale also can be used; it is a straight line, often 10 cm in length, with a word description (e.g., "no pain" and "the most intense pain imaginable") at each of the ends of the line representing the continuum of pain intensity.

Nonpharmacologic Interventions

A number of nonpharmacologic methods of pain control are used in pain management. These include cognitive behavioral interventions (e.g., relaxation, distraction, imagery, and biofeedback), physical agents (e.g., heat and cold), electroanalgesia (transcutaneous electrical nerve stimulation [TENS]), and acupuncture. Often these methods are used in addition to analgesics rather than as the sole form of pain management.

Pharmacologic Treatment

Pharmacologic treatment involves the use of drugs in the management of pain. It includes the use of nonnarcotic and narcotic analgesics, as well as adjuvant medications, such as depressants, anticonvulsants, and muscle relaxants. Topical medications (e.g., fentanyl patch) are a new aspect of pain management, whose full potential has yet to be determined.

An analgesic drug is a medication that acts on the nervous system to decrease or eliminate pain without inducing unconsciousness. Analgesic drugs do not cure the underlying cause of the pain, but their appropriate use makes the pain more tolerable and, in the case of acute pain, may prevent it from progressing to chronic pain. The ideal analgesic would be effective and nonaddictive and produce minimal adverse effects. Although long-term treatment with opioids can result in opioid tolerance (i.e., increasingly greater drug dosages being needed to achieve the same effect) and physical dependence, this should not be confused with addiction. Long-term drug-seeking behavior is rare in persons who are treated with opioids only during the time that they require pain relief. The unique needs and circumstances presented by each person in pain must be addressed to achieve satisfactory pain management.

Nonnarcotic Analgesics. Nonnarcotic oral analgesic medications include aspirin, other NSAIDs, and acetaminophen. Aspirin, or acetylsalicylic acid, acts peripherally

and centrally to block the transmission of pain impulses. It also has antipyretic and anti-inflammatory properties. The action of aspirin and other NSAIDs is through the inhibition of the cyclooxygenase (COX) enzymes, which mediate the biosynthesis of prostaglandins. Prostaglandins (particularly prostaglandin E_2) exert their effect through peripheral sensitization of nociceptors to chemical mediators such as bradykinin and histamine.[27] The NSAIDs also decrease the sensitivity of blood vessels to bradykinin and histamine, affect cytokine production by T lymphocytes, inhibit vasodilation, and decrease the release of inflammatory mediators from granulocytes and mast cells. Acetaminophen is an alternative to the NSAIDs. Although usually considered equivalent to aspirin as an analgesic and antipyretic agent, it lacks anti-inflammatory properties.

Opioid Analgesics. The term *opioid* or *narcotic* is used to refer to a group of medications, natural or synthetic, with morphinelike actions. The opioids (e.g., morphine, codeine, and many other semisynthetic congeners of morphine) exert their action through opioid receptors. There are three major categories of opioid receptors in the CNS, designated as mu (μ, for "morphine"), delta (δ), and kappa (κ).[27] Analgesia, as well as respiratory depression, miosis, reduced gastrointestinal motility (causing constipation), feelings of well-being or euphoria, and physical dependence, results principally from morphine and morphinelike opioid analgesics that act at the mu receptors. Part of the pain-relieving properties of exogenous opioids such as morphine involve the release of endogenous opioids.[27]

Opioids are used in the management of acute and chronic pain. When given for temporary relief of severe pain, such as that occurring after surgery, there is much evidence that opioids given routinely before the pain starts or becomes extreme are far more effective than those administered in a sporadic manner. Persons who are treated in this manner usually require fewer doses and are able to resume regular activities sooner. Opioids also are used for persons with chronic pain such as that caused by cancer. Morphine remains the most useful strong opioid, and the WHO has recommended that oral morphine be part of the essential medication list and be made available throughout the world as the medication of choice for cancer pain.[24,27]

Adjuvant Analgesics. Adjuvant analgesics include medications such as tricyclic antidepressants, antiseizure medications, and neuroleptic anxiolytic agents.[28] The fact that the pain suppression system has nonendorphin synapses raises the possibility that potent, centrally acting, nonopiate medications may be useful in relieving pain. Serotonin has been shown to play an important role in producing analgesia. The tricyclic antidepressant medications that block the removal of serotonin from the synaptic cleft have been shown to produce pain relief in some persons. These medications are particularly useful in some chronic painful conditions, such as postherpetic neuralgia. Certain antiseizure medications, which suppress spontaneous neuronal firing, are particularly useful in the management of pain that occurs after nerve injury (neuropathic pain), including diabetic neuropathy and chronic regional pain syndrome. Other agents, such as the corticosteroids, may be used to decrease inflammation and the nociceptive stimuli responsible for pain.

Surgical Interventions

If surgery removes the problem causing the pain, such as a tumor pressing on a nerve or an inflamed appendix, it can be curative. In other situations, surgery is used for symptom management rather than for cure. However, with rare exceptions, noninvasive analgesic approaches for pain relief should precede invasive surgical approaches.[17] Surgery for severe, intractable pain of peripheral or central origin has met with some success. It can be used to remove the cause or block the transmission of intractable pain from phantom limb pain, severe neuralgia, inoperable cancer of certain types, and causalgia.

In summary, pain is an elusive and complex phenomenon; it is a symptom common to many illnesses. It is a highly individualized experience that is shaped by a person's culture and previous life experiences, and it is difficult to measure. Traditionally, there have been two principal theories of pain, specificity and pattern theories. Scientifically, pain is viewed within the context of nociception. Nociceptors are receptive nerve endings that respond to noxious stimuli. Pain receptors respond to mechanical, thermal, and chemical stimuli. Nociceptive neurons transmit impulses to the dorsal horn neurons using chemical neurotransmitters. The neospinothalamic and the paleospinothalamic pathways are used to transmit pain information to the brain. Several neuroanatomic pathways as well as endogenous opioid peptides modulate pain in the CNS.

Pain can be classified according to location, referral, and duration as well as associated medical diagnoses. Pain can arise from cutaneous, deep somatic, or visceral locations. Referred pain is pain perceived at a site different from its origin. Acute pain is self-limiting pain that ends when the injured tissue heals, whereas chronic pain is pain that lasts much longer than the anticipated healing time for the underlying cause of the pain. Pain threshold, pain tolerance, age, sex, and other factors affect an individual's reaction to pain.

Treatment modalities for pain include the use of nonpharmacologic and pharmacologic agents either singly or in combination. In acute pain, therapy is directed at providing preemptive pain relief by interrupting the nociceptive stimulus. Chronic pain management is much more complex and is based on multiple considerations, including life expectancy. It is becoming apparent that with both acute and chronic pain, the most effective approach is early interventions.

Alterations in Pain Sensitivity and Special Types of Pain

Alterations in Pain Sensitivity

Sensitivity to and perception of pain varies among persons and in the same person under different conditions and in different parts of the body. Irritation, mild hypoxia, and mild compression of a peripheral nerve often result in hyperexcitability of the sensory nerve fibers or cell bodies. This is experienced as unpleasant hypersensitivity (i.e., *hyperesthesia*) or increased painfulness (i.e., *hyperalgesia*). Primary hyperalgesia describes pain sensitivity that occurs directly in damaged tissues. Secondary hyperalgesia occurs in the surrounding uninjured tissue. An example of primary hyperalgesia is the extreme sensitivity of sunburned skin, which results from sensitization of the skin pain endings by local products from the burn. Secondary hyperalgesia frequently results from lesions of the spinal cord or thalamus.

More severe pathologic processes can result in reduced or lost tactile (e.g., *hypoesthesia, anesthesia*), temperature (e.g., *hypothermia, athermia*), and pain sensation (i.e., *hypoalgesia*). *Analgesia* is the absence of pain on noxious stimulation or the relief of pain without loss of consciousness. The inability to sense pain may result in trauma, infection, and even loss of a body part or parts. Inherited insensitivity to pain may take the form of congenital indifference or congenital insensitivity to pain. In the former, transmission of nerve impulses appears normal but appreciation of painful stimuli at higher levels appears to be absent. In the latter, a peripheral nerve defect apparently exists such that transmission of painful nerve impulses does not result in perception of pain. Whatever the cause, persons who lack the ability to perceive pain are at constant risk of tissue damage because pain is not serving its protective function.

Allodynia (Greek *allo,* "other," and *odynia,* "painful") is the term used for the puzzling phenomenon of pain that follows a nonnoxious stimulus to apparently normal skin.[2] Nonnoxious stimuli may include wind, touching sheets, and showering. This term is intended to refer to instances in which otherwise normal tissues may be abnormally innervated or may be referral sites for other loci that give rise to pain with nonnoxious stimuli. It can result from increased responsiveness within the spinal cord (central sensitization) or a reduction in the threshold for nociceptor activation (peripheral sensitization). One type of allodynia involves *trigger points,* which are highly localized points on the skin or mucous membrane that can produce immediate intense pain at that site or elsewhere when stimulated by light tactile stimulation. Myofascial trigger points are foci of exquisite tenderness found in many muscles and can be responsible for pain projected to sites remote from the points of tenderness.

Special Types of Pain

Neuropathic Pain

"Neuropathic pain refers to pain that originates from pathology of the nervous system."[29] When peripheral nerves are affected by injury or disease, it can lead to unusual and sometimes intractable sensory disturbances. The notable features that point to neuropathic processes as a cause of pain include widespread pain that is not otherwise explainable, evidence of sensory deficit (e.g., numbness, paresthesias), burning pain, pain that occurs with light stroking of the skin, and attacks of pain that occur without seeming provocation.[29] Depending on the cause, few or many axons could be damaged and the condition could be unilateral or bilateral. Neuropathic pain is distinguished from other pain conditions where the pain stimulus begins in nonneuronal tissues.

Causes of neuropathic pain can be categorized according to the extent of peripheral nerve involvement. Conditions that can lead to pain by causing damage to peripheral nerves in a single area include nerve entrapment, nerve compression from a tumor mass, and various neuralgias (e.g., trigeminal, postherpetic, and posttraumatic). Conditions that can lead to pain by causing damage to peripheral nerves in a wide area include diabetes mellitus, long-term alcohol use, hypothyroidism, renal insufficiency, and drug treatment with neurotoxic agents.[30] Diabetes often causes a length-dependent neuropathy (meaning that the longest axons in a peripheral nerve are most vulnerable). Injury to a nerve also can lead to a multisymptom, multisystem syndrome, called *complex regional pain syndrome.* Nerve damage associated with amputation is believed to be a cause of phantom limb pain.

Neuropathic pain can vary with the extent and location of disease or injury. There may be allodynia or pain that is stabbing, jabbing, burning, or shooting. The pain may be persistent or intermittent. The diagnosis depends on the mode of onset, the distribution of abnormal sensations, the quality of the pain, and other relevant medical conditions (e.g., diabetes, hypothyroidism, alcohol use, rash, or trauma). Injury to peripheral nerves sometimes results in pain that persists beyond the time required for the tissues to heal. Peripheral pathologic processes (e.g., neural degeneration, neuroma formation, and generation of abnormal spontaneous neural discharges from the injured sensory neuron) and neural plasticity (i.e., changes in CNS function) are the primary working hypotheses to explain persistent neuropathic pain.

Treatment methods include measures aimed at restoring or preventing further nerve damage (e.g., surgical resection of a tumor causing nerve compression, improving glycemic control for diabetic patients with painful neuropathies) and interventions for the palliation of pain. Although many adjuvant analgesics are used for neuropathic pain, pain control often is difficult. The initial approach in seeking adequate pain control is to try these drugs in sequence and then in combination. The adjuvant analgesics can be divided into three general classes according to the pain they are used to treat: burning, tingling, or aching pain; stabbing or shooting pain; and neurogenic pain. For pain that is burning, tingling, or aching, tricyclic antidepressants and the α_2-adrenergic agonist clonidine frequently are used. For the stabbing or shooting pain of neuralgias, antiseizure medications or baclofen, a drug used in the treatment of spasticity,

may be used.[30] Nonpharmacologic therapies such as electrical stimulation of the peripheral or spinal nerves can be used for radiculopathies and neuralgias. As a last resort, neurolysis or neurosurgical blockade sometimes is used.

Neuralgia

Neuralgia is characterized by severe, brief, often repetitive attacks of lightninglike or throbbing pain. It occurs along the distribution of a spinal or cranial nerve and usually is precipitated by stimulation of the cutaneous region supplied by that nerve.

Trigeminal Neuralgia. Trigeminal neuralgia, or *tic douloureux*, is one of the most common and severe neuralgias. It is manifested by facial tics or spasms and characterized by paroxysmal attacks of stabbing pain that usually are limited to the unilateral sensory distribution of one or more branches of the trigeminal cranial nerve (CN V), most often the maxillary or mandibular divisions.[30,31] Although intermittent, the pain often is excruciating and may be triggered by light touch, movement, drafts, and eating. Considerable controversy remains regarding the pathophysiology of trigeminal neuralgia. One theory suggests that peripheral injury or disease of the trigeminal nerve increases afferent firing in the nerve. Failure of central inhibitory mechanisms may be involved as well.[31]

Treatment of trigeminal neuralgia includes pharmacologic and surgical modalities. Other interventions include avoidance of precipitating factors (e.g., stimulation of trigger spots) and eye injury due to irritation; provision for adequate nutrition; and avoidance of social isolation. Carbamazepine, an antiseizure drug, is recognized as a first-line agent for treatment of trigeminal neuralgia. Surgical release of vessels, dural structures, or scar tissue surrounding the semilunar ganglion or root in the middle cranial fossa often eliminates the symptoms. If not, percutaneous blocking or partial destruction of peripheral branches of the trigeminal nerve with heat, glycerol, or balloon compression may be used.[31] Gamma knife radiosurgery, a form of stereotactic radiosurgery, is one of the newest techniques for trigeminal neuralgia. The procedure uses a stereotactic head frame, stereotactic imaging of the trigeminal nerve root entry zone, and radiation of the trigeminal nerve. There has also been recent interest in the use of botulinum toxin as a treatment modality.[31]

Postherpetic Neuralgia. Herpes zoster (also called *shingles*) is caused by the same herpes virus (varicella-zoster virus) that causes chickenpox and is thought to represent a localized recurrent infection by the varicella-zoster virus that has remained latent in the dorsal root ganglia since the initial attack of chickenpox[32] (see Chapter 46). Reactivation of viral replication is associated with a decline in cellular immunity, such as occurs with aging. Thus, the probability of developing herpes zoster increases strikingly with aging, and most cases occur in the elderly. Impaired cellular immunity also increases the risk of herpes zoster.

During the acute attack of herpes zoster, the reactivated virus travels from the affected sensory ganglia and peripheral nerve to the skin of the corresponding dermatomes, causing a unilateral localized vesicular eruption and hyperpathia (i.e., abnormally exaggerated subjective response to pain). In the acute infection, proportionately more of the large nerve fibers are destroyed. Regenerated fibers appear to have smaller diameters. Because there is a relative loss of large fibers with age, elderly persons are particularly prone to suffering because of the shift in the proportion of large- to small-diameter nerve fibers.

Persons with postherpetic neuralgia may suffer from constant pain ("burning, aching, throbbing"), intermittent pain ("stabbing, shooting"), and stimulus-evoked pain (allodynia). Persons with allodynia often suffer from excruciating pain after the slightest touch to affected skin by such things as cold wind or clothing. These subtypes of pain may interfere with sleep and basic activities of living, causing chronic fatigue, depression, anorexia, weight loss, and social isolation.

Early treatment of shingles with antiviral drugs such as acyclovir or valacyclovir that inhibit herpes virus deoxyribonucleic acid (DNA) replication may reduce the severity of herpes zoster. Initially, postherpetic neuralgia can be treated with a topical anesthetic agent, lidocaine–prilocaine cream or 5% lidocaine gel. A tricyclic antidepressant medication, such as amitriptyline or desipramine, may be used for pain relief. Regional nerve blockade (i.e., stellate ganglion, epidural, local infiltration, or peripheral nerve block) has been used with limited success.

A live attenuated vaccine is now available for prevention of herpes zoster among adults 60 years of age and older. The vaccine is not indicated for treatment of herpes zoster or postherpetic neuralgia.[33]

Complex Regional Pain Syndrome

The complex regional pain syndrome (CRPS), formerly known as *reflex sympathetic dystrophy* (RSD), is a rare disorder of the extremities characterized by autonomic and vasomotor instability.[34–36] There are two forms of the CRPS: CRPS I (equivalent of RSD) and CRPS II, also known as *causalgia*. The International Association for the Study of Pain (IASP) lists the diagnostic criteria for CRPS I as the presence of an initiating traumatic event, continuing pain, allodynia (perception of pain from a nonpainful stimulus), or hyperalgesia disproportionate to the inciting event with evidence at some time of edema, changes in skin blood flow, or abnormal sensorimotor activity in the area of pain. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction.[37]

According to the IASP, CRPS II (i.e., causalgia) is diagnosed as the presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve, with evidence at some time of edema, changes in skin blood flow, or abnormal sensorimotor activity in the region of pain. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and

dysfunction. The primary difference between type I and type II is the identification of a definable nerve injury.

The hallmark of both types of CRPS is pain and mobility problems more severe than the injury warrants. Characteristically, the pain is severe and burning with or without deep aching. Usually, the pain can be elicited with the slightest movement or touch to the affected area, it increases with repetitive stimulation, and it lasts even after the stimulation has stopped. The pain can be exacerbated by emotional upsets or any increased peripheral sympathetic nerve stimulation. All the variations of CRPS include sympathetic components. These are characterized by vascular and trophic (e.g., dystrophic or atrophic) changes to the skin, soft tissue, and bone, and can include rubor or pallor, sweating or dryness, edema (often sharply demarcated), and, with time, patchy osteoporosis.

The pathophysiologic process of CRPS remains uncertain. Although abnormalities in sympathetic activity are observed, recent experimental data suggest that sensitization of small-diameter, polymodal C and Aδ fibers to noxious stimuli may be the basis for hyperalgia to heat and nociceptive stimuli.[36] There is also evidence that central mechanisms may play a role in sensitization of central neurons that occurs after intense peripheral mechanical stimuli or continuous activity in nociceptors. The sympathetic nervous system, either directly or indirectly through prostaglandin or α_1-adrenergic receptor activity, is considered to contribute to the excitation and sensitization of the nociceptive afferents. Other proposed mechanisms include neurogenic inflammation caused by the activation of neuromediators, such as substance P, calcitonin gene–related peptide, and histamine, which also mediates inflammation and vasodilation of microvessels.[34] Recent research demonstrated the presence of autoantibodies against autonomic nervous system structures in patients with CRPS, especially CRPS II, suggesting that the disorder may result from dysfunction of the autonomic nervous system caused by an autoimmune attack.[37]

Early mobilization after injury or surgery reduces the likelihood of developing the syndrome.[36] In addition to addressing the underlying disorder, treatment is directed at restoration of function. Physical therapy is a cornerstone of therapy. Pain management involves the use of standard pharmacologic agents used in the management of neuropathic pain, namely, antidepressants (e.g., amitriptyline) and antiseizure drugs (e.g., gabapentin). Short-term corticosteroid (prednisone) treatment may be used in resistant cases. If this does not lead to improvement, treatment by sympathetic blockade may be used to provide pain relief and determine the extent to which the pain is sympathetically maintained. The latter mechanism, when present, might respond to the use of an α_1-adrenergic receptor antagonist (e.g., terazosin, phenoxybenzamine). Electrical neurostimulation of the spinal cord may also be considered. Neurostimulation not only may provide analgesia, but also may reduce the burning dysesthesia of which many patients complain. It may also improve circulation in the affected extremity by blocking the sympathetic efferent pathways.[36]

Phantom Limb Pain

Phantom limb pain, a type of neurologic pain, follows amputation of a limb or part of a limb. As many as 70% of amputees experience phantom limb pain.[38] The pain often begins as sensations of tingling, heat and cold, or heaviness, followed by burning, cramping, or shooting pain. It may disappear spontaneously or persist for many years. One of the more troublesome aspects of phantom pain is that the person may experience painful sensations that were present before the amputation, such as that of a painful ulcer or bunion.

Several theories have been proposed as to the causes of phantom limb pain.[38] One theory is that the end of a regenerating nerve becomes trapped in the scar tissue of the amputation site. It is known that when a peripheral nerve is cut, the scar tissue that forms becomes a barrier to regenerating outgrowth of the axon. The growing axon often becomes trapped in the scar tissue, forming a tangled growth (i.e., neuroma) of small-diameter axons, including primary nociceptive afferents and sympathetic efferent neurons. It has been proposed that these afferents show increased sensitivity to innocuous mechanical stimuli and to sympathetic activity and circulating catecholamines. A related theory proposes that the source of phantom limb pain is in the spinal cord, suggesting that the pain is due to the spontaneous firing of spinal cord neurons that have lost their normal sensory input from the body. In this case, a closed self-exciting neuronal loop in the posterior horn of the spinal cord is postulated to send impulses to the brain, resulting in pain. Even the slightest irritation to the amputated limb area can initiate this cycle. Other theories propose that the phantom limb pain may arise in the brain itself. In one hypothesis, the pain is caused by changes in the flow of signals through somatosensory areas of the brain. In other words, there appears to be plasticity even in the adult CNS. Treatment of phantom limb pain has been accomplished by the use of sympathetic blocks, TENS of the large myelinated afferents innervating the area, hypnosis, and relaxation training.

In summary, pain may occur with or without an adequate stimulus, or it may be absent in the presence of an adequate stimulus—either of which describes a pain disorder. There may be analgesia (absence of pain), hyperalgesia (increased sensitivity to pain), hypoalgesia (a decreased sensitivity to painful stimuli), hyperpathia (an unpleasant and prolonged response to pain), hyperesthesia (an abnormal increase in sensitivity to sensation), hypoesthesia (an abnormal decrease in sensitivity to sensations), paresthesia (abnormal touch sensation such as tingling or "pins and needles" in the absence of external stimuli), or allodynia (pain produced by stimuli that do not normally cause pain).

Neuropathic pain may be due to trauma or disease of neurons in a focal area or in a more global distribution (e.g., from endocrine disease or neurotoxic medications).

Neuralgia is characterized by severe, brief, often repetitive attacks of lightninglike or throbbing pain that occurs along the distribution of a spinal or cranial nerve and usually is precipitated by stimulation of the cutaneous region supplied by that nerve. Trigeminal neuralgia is one of the most common and severe neuralgias. It is manifested by facial tics or spasms. Postherpetic neuralgia is a chronic pain that can occur after shingles, an infection of the dorsal root ganglia and corresponding areas of innervation by the varicella-zoster virus. CRPS types I and II are pain syndromes characterized by severe pain or hyperalgesia, edema, changes in skin blood flow, and abnormal sensorimotor activity that typically follow an initiating traumatic event. The primary difference between CRPS I and II is the identification of a definable nerve injury. Phantom limb pain, a neurologic pain, can occur after amputation of a limb or part of a limb.

Headache and Associated Pain

Headache is a common health problem, with approximately 25% of adults reporting recurrent headaches and 4% reporting daily or nearly daily headaches.[39] Although head and facial pain have characteristics that distinguish them from other pain disorders, they also share many of the same features.

Headache

Headache is caused by a number of conditions. Some headaches represent primary disorders and others occur secondary to other disease conditions in which head pain is a symptom. In 2004, the International Headache Society (IHS) published the second edition of *The International Classification of Headache Disorders* (ICHD-2). The classification system is divided into three sections: (1) primary headaches, (2) headaches secondary to other medical conditions, and (3) cranial neuralgias and facial pain.[40,41] The most common types of primary or chronic headaches are migraine headache, tension-type headache, cluster headache, and chronic daily headache.

Although most causes of secondary headache are benign, some are indications of serious disorders such as meningitis, brain tumor, or cerebral aneurysm. The sudden onset of a severe, intractable headache in an otherwise healthy person is more likely related to a serious intracranial disorder, such as subarachnoid hemorrhage or meningitis, than to a chronic headache disorder. Headaches that disturb sleep, exertional headaches (e.g., triggered by physical or sexual activity or a Valsalva maneuver), and headaches accompanied by neurologic symptoms such as drowsiness, visual or limb disturbances, or altered mental status also are suggestive of underlying intracranial lesions or other pathologic processes. Other red flags for secondary headache disorder include a fundamental change or progression in headache pattern or a new headache in individuals younger than 5 or older than 50 years of age, or in individuals with cancer, immunosuppression, or pregnancy.[39]

The diagnosis and classification of headaches often is difficult. It requires a comprehensive history and physical examination to exclude secondary causes. The history should include factors that precipitate headache, such as foods and food additives, missed meals, and association with the menstrual period. A careful medication history is essential because many medications can provoke or aggravate headaches. Alcohol also can cause or aggravate headache. A headache diary in which the person records his or her headaches and concurrent or antecedent events may be helpful in identifying factors that contribute to headache onset. Appropriate laboratory and imaging studies of the brain may be done to rule out secondary headaches.

Migraine Headache

Migraine headaches affect approximately 20 million persons in the United States. They occur in about 18% of women and 6% of men and result in considerable time lost from work and other activities.[42] Migraine headaches tend to run in families and are thought to be inherited as an autosomal dominant trait with incomplete penetrance.

There are two major types of migraine headache—migraine without aura and migraine with aura. *Migraine without aura*, which accounts for approximately 85% of migraines, is a pulsatile, throbbing, unilateral headache that typically lasts 1 to 2 days and is aggravated by routine physical activity. The headache is accompanied by nausea and vomiting, which often is disabling, and sensitivity to light and sound. Visual disturbances occur quite commonly and consist of visual hallucinations such as stars, sparks, and flashes of light.[41] *Migraine with aura* has similar symptoms, but with the addition of reversible visual symptoms, including positive features (e.g., flickering lights, spots, or lines) or negative features (loss of vision); fully reversible sensory symptoms, including positive features (feeling of pins or needles) or negative features (numbness); and fully reversible speech disturbances or neurologic symptoms that precede the headache. The aura usually develops over a period of 5 to 20 minutes and lasts from 5 minutes to 1 hour.[41] Although only a small percentage of persons with migraine experience an aura before an attack, many persons without aura have prodromal symptoms, such as fatigue and irritability, that precede the attack by hours or even days.

Other migraine headache categories are retinal migraine, complications of migraine (e.g., chronic migraine, migrainous infarction, and migraine-triggered seizures), and childhood periodic syndromes that are commonly precursors of migraine. Retinal migraines are a rare form of migraine characterized by recurrent attacks of fully reversible scintillations (visual sensation of sparks or flashes of light), scotomata (visual blind spots), or blindness affecting one eye, followed within an hour by migrainous headache. Chronic migraine headaches represent a condition in which the headaches are present on 15 or more days per month for 3 months or more, in the

absence of medication overuse. Migrainous infarction is an uncommon occurrence in which one or more otherwise typical aura symptoms persist beyond 1 hour and neuroimaging confirms ischemic infarction. Strictly applied, these criteria distinguish this disorder from stroke, which must be excluded.[41] Migraine headache also can present as a mixed headache, including symptoms typically associated with tension-type headache, sinus headache, or chronic daily headache. These are called *transformed migraine* and are difficult to classify. Although nasal symptoms are not one of the diagnostic criteria for migraine, they frequently accompany migraine and are probably due to cranial parasympathetic activation. Sinus pain may indicate either a headache due to sinus inflammation or migraine.[43]

Migraine headaches occur in children as well as adults.[44,45] Before puberty, migraine headaches are equally distributed between the sexes. The essential diagnostic criterion for migraine in children is the presence of recurrent headaches separated by pain-free periods. Diagnosis is based on at least three of the following symptoms or associated findings: abdominal pain, nausea or vomiting, throbbing headache, unilateral location, associated aura (visual, sensory, motor), relief during sleep, and a positive family history.[45] Symptoms vary widely among children, from those that interrupt activities and cause the child to seek relief in a dark environment to those detectable only by direct questioning. A common feature of migraine in children is intense nausea and vomiting. The vomiting may be associated with abdominal pain and fever; thus, migraine may be confused with other conditions such as appendicitis. More than half of children with migraine undergo spontaneous prolonged remission after their 10th birthday. Because headaches in children can be a symptom of other, more serious disorders, including intracranial lesions, it is important that other causes of headache that require immediate treatment be ruled out.

The pathophysiologic mechanisms of the pain associated with migraine headaches remain poorly understood. Although many alternative theories exist, it is well established that during a migraine the trigeminal cranial nerve (CN V) becomes activated.[46] Activation of the trigeminal sensory fibers may lead to the release of neuropeptides, causing painful neurogenic inflammation within the meningeal vasculature characterized by plasma protein extravasation, vasodilation, and mast cell degranulation. Another possible mechanism implicates neurogenic vasodilation of meningeal blood vessels as a key component of the inflammatory processes that occur during migraine. Supporting the neurogenic basis for migraine is the frequent presence of premonitory symptoms before the headache begins; the presence of focal neurologic disturbances, which cannot be explained in terms of cerebral blood flow; and the numerous accompanying symptoms, including those related to autonomic and somatic nervous system dysfunction.

Fluctuations in hormone levels, particularly in estrogen levels, are thought to play a role in the pattern of migraine attacks. For many women, migraine headaches coincide with their menstrual periods. The greater predominance of migraine headaches in women is thought to be related to the aggravating effect of estrogen on the migraine mechanism. Dietary substances, such as monosodium glutamate, aged cheese, and chocolate, also may precipitate migraine headaches. The actual triggers for migraine are the chemicals in the food, not allergens.

The treatment of migraine headaches includes preventive and abortive nonpharmacologic and pharmacologic treatment.[47] Nonpharmacologic treatment includes the avoidance of migraine triggers, such as foods, that precipitate an attack. Many persons with migraines benefit from maintaining regular eating and sleeping habits. Measures to control stress, which also can precipitate an attack, also are important. During an attack, many persons find it helpful to retire to a quiet, darkened room until symptoms subside.

Pharmacologic treatment involves both abortive therapy for acute attacks and preventive therapy. A wide range of medications is used to treat the acute symptoms of migraine headache. Based on clinical trials, first-line agents include acetylsalicylic acid; combinations of acetaminophen, acetylsalicylic acid, and caffeine; NSAIDs (e.g., naproxen sodium, ibuprofen); serotonin (5-HT_1) receptor agonists (e.g., sumatriptan); ergotamine derivatives (e.g., dihydroergotamine); and antiemetic medications (e.g., ondansetron, metoclopramide). Nonoral routes of administration may be preferred in individuals who develop severe pain rapidly or on awakening, or in those with severe nausea and vomiting. Both sumatriptan and dihydroergotamine have been approved for intranasal administration. For intractable migraine headache, dihydroergotamine may be administered parenterally with an antiemetic or opioid analgesic.[48] Frequent use of abortive headache medications may cause rebound headache. Because of the risk of coronary vasospasm, the 5-HT_1 receptor agonists should not be given to persons with coronary artery disease. Ergotamine preparations can cause uterine contractions and should not be given to pregnant women. They also can cause vasospasm and should be used with caution in persons with peripheral arterial disease.

Preventive pharmacologic treatment may be necessary if migraine headaches become disabling, if they occur more than two or three times a month, if abortive treatment is being used more than two times a week, or if the individual has hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.[47] In most cases, preventative treatment must be taken daily for months to years. First-line agents include β-adrenergic blocking medications (e.g., propranolol, atenolol), antidepressants (amitriptyline), and antiseizure medications (e.g., divalproex, valproic acid). When a decision to discontinue preventive therapy is made, the medications should be gradually withdrawn.

Cluster Headache

Cluster headaches are relatively uncommon headaches that occur in about 1 in 1000 individuals, affecting men (80% to 85%) more frequently than women. They typically begin in the third decade of life and seldom

extend beyond age 70 years.[49] These headaches tend to occur in clusters over weeks or months, followed by a long, headache-free remission period. Cluster headache is a type of primary neurovascular headache that typically includes severe, unrelenting, unilateral pain located, in order of decreasing frequency, in the orbital, retro-orbital, temporal, supraorbital, and infraorbital regions.[49–51] The pain is of rapid onset and builds to a peak in approximately 10 to 15 minutes, and lasts for 15 to 180 minutes. The pain behind the eye radiates to the ipsilateral trigeminal nerve (e.g., temple, cheek, gum). The headache frequently is associated with one or more symptoms such as restlessness or agitation, conjunctival redness, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and eyelid edema. Because of their location and associated symptoms, cluster headaches are often mistaken for sinus infections or dental problems.

The underlying pathophysiologic mechanisms of cluster headaches are not completely known. It is thought that heredity, through an autosomal dominant gene, plays some role in the pathogenesis of the headaches. The most likely pathophysiologic mechanisms include the interplay of vascular, neurogenic, metabolic, and humoral factors. Activation of the trigeminovascular system and the cranial autonomic parasympathetic reflexes is thought to explain the pain and autonomic symptoms. The hypothalamus is believed to play a key role. The possible role of the regulating centers in the anterior hypothalamus is implicated from observations of circadian biologic changes and neuroendocrine disturbances (e.g., changes in cortisol, prolactin, and testosterone) that occur in both active periods and during clinical remission.

Because of the relatively short duration and self-limited nature of cluster headache, oral preparations typically take too long to reach therapeutic levels. The most effective treatments are those that act quickly (e.g., oxygen inhalation and subcutaneous sumatriptan). Intranasal lidocaine also may be effective.[50,51] Oxygen inhalation may be indicated for home use. Prophylactic medications for cluster headaches include ergotamine derivatives, verapamil (a calcium channel blocker), corticosteroids, and valproic acid. Deep-brain surgical neurostimulation is an experimental approach beginning to show promise in the elimination of cluster headaches.[50]

Tension-Type Headache

The most common type of headache is tension-type headache. Unlike migraine and cluster headaches, tension-type headache usually is not sufficiently severe that it interferes with daily activities. Tension-type headaches frequently are described as dull, aching, diffuse, nondescript headaches, occurring in a hatband distribution around the head, and not associated with nausea or vomiting or worsened by activity. They can be infrequent, episodic, or chronic.

The exact mechanisms of tension-type headache are not known and the hypotheses of causation are contradictory. One popular theory is that tension-type headache results from sustained tension of the muscles of the scalp and neck; however, some research has found no correlation between muscle contraction and tension-type headache. Many authorities now believe that tension-type headaches are forms of migraine headache.[52] It is thought that migraine headache may be transformed gradually into chronic tension-type headache. Tension-type headaches also may be caused by oromandibular dysfunction, psychogenic stress, anxiety, depression, and muscular stress. They also may result from overuse of analgesics or caffeine. Daily use of caffeine, whether in beverages or medications, can produce addiction, and a headache can develop in such persons who go without caffeine for several hours.[53]

Tension-type headaches often are more responsive to nonpharmacologic techniques, such as biofeedback, massage, acupuncture, relaxation, imagery, and physical therapy, than other types of headache. For persons with poor posture, a combination of range-of-motion exercises, relaxation, and posture improvement may be helpful.

The medications of choice for acute treatment of tension-type headaches are analgesics, including acetylsalicylic acid, acetaminophen, and NSAIDs.[53] Persons with infrequent tension-type headache usually self-medicate using over-the-counter analgesics to treat the acute pain, and do not require prophylactic medication. These agents should be used cautiously because rebound headaches can develop when the medications are taken regularly.

Because the "dividing lines" between tension-type headache, migraine, and chronic daily headache often are vague, addition of medications as well as the entire range of migraine medications may be tried in refractory cases. Other medications used concomitantly with analgesics include sedating antihistamines (e.g., promethazine and diphenhydramine), antiemetics (e.g., metoclopramide and prochlorperazine), or sedatives (e.g., butalbital). Prophylactic treatment for chronic tension-type headaches can include antidepressants (e.g., amitriptyline) and selective serotonin reuptake inhibitors (e.g., paroxetine, venlafaxine, and fluoxetine).[53]

Chronic Daily Headache

The term *chronic daily headache* (CDH) is used to refer to headaches that occur 15 days or more a month, including those due to medication overuse.[54,55] Little is known about the prevalence and incidence of CDH. Diagnostic criteria for CDH are not provided in the IHS Classification System. The cause of CDH is unknown, although there are several hypotheses. They include transformed migraine headache, evolved tension-type headache, new daily persistent headache, and posttraumatic headache. In many persons, CDH retains certain characteristics of migraine, whereas in others it resembles chronic tension-type headache. CDH may be associated with chronic and episodic tension-type headache. New daily persistent headache may have a fairly rapid onset, with no history of migraine, tension-type headache, trauma, or psychological stress. Although overuse of symptomatic medications (e.g., analgesics, ergotamine) has been related to CDH, there is a group of patients in whom CDH is unrelated to excessive use of medications.

For patients with CDH, a combination of pharmacologic and behavioral interventions may be necessary. As with tension-type headaches, nonpharmacologic techniques, such as biofeedback, massage, acupuncture, relaxation, imagery, and physical therapy, may be helpful. Measures to reduce or eliminate medication, including caffeine, overuse may be helpful. If the patient is abusing medications, the overuse must be managed before prophylactic agents will be effective. Most of the medications used for prevention of CDH have not been examined in well-designed, double-blind studies.

Temporomandibular Joint Pain

A common cause of head pain is temporomandibular joint (TMJ) syndrome. It usually is caused by an imbalance in joint movement because of poor bite, bruxism (i.e., teeth grinding), or joint problems such as inflammation, trauma, and degenerative changes.[56] The pain almost always is referred and commonly presents as facial muscle pain, headache, neck ache, or earache. Referred pain is aggravated by jaw function. Headache associated with this syndrome is common in adults and children and can cause chronic pain problems.

Treatment of TMJ pain is aimed at correcting the problem, and in some cases this may be difficult. The initial therapy for TMJ pain should be directed toward relief of pain and improvement in function. Pain relief often can be achieved with use of the NSAIDs. Muscle relaxants may be used when muscle spasm is a problem. In some cases, the selected application of heat or cold, or both, may provide relief. Referral to a dentist who is associated with a team of therapists, such as a psychologist, physical therapist, or pain specialist, may be indicated.

In summary, head pain is a common disorder that is caused by a number of conditions. Some headaches represent primary disorders and others occur secondary to another disease state in which head pain is a symptom. Primary headache disorders include migraine headache, tension-type headache, cluster headache, and chronic daily headache. Although most causes of secondary headache are benign, some are indications of serious disorders such as meningitis, brain tumor, or cerebral aneurysm. TMJ syndrome is one of the major causes of headaches. It usually is caused by an imbalance in joint movement because of poor bite, teeth grinding, or joint problems such as inflammation, trauma, and degenerative changes.

Pain in Children and Older Adults

Pain frequently is underrecognized and undertreated in both children and the elderly. In addition to the common obstacles to adequate pain management, such as concern about the effects of analgesia on respiratory status and the potential for addiction to opioids, there are additional deterrents to adequate pain management in children and the elderly. With regard to both children and the elderly, there are stereotypic beliefs that they feel less pain than other patients. In very young children and confused elderly, there are several additional factors. These include the extreme difficulty of assessing the location and intensity of pain in individuals who are cognitively immature or cognitively impaired, and the argument that even if they feel pain, they do not remember it. Research during the past few decades has added a great deal to the body of knowledge about pain in children and the elderly.

Pain in Children

Human responsiveness to painful stimuli begins in the neonatal period and continues through the life span. Although the specific and localized behavioral reactions are less marked in the neonate, protective or withdrawal reflexes in response to nociceptive stimuli are clearly demonstrated. Pain pathways, cortical and subcortical centers, and neurochemical responses associated with pain transmission are developed and functional by the last trimester of pregnancy. Neonates clearly perceive pain, as demonstrated by their integrated physiologic response to nociceptive stimuli.[57–59] In fact, pain may be accentuated because descending inhibitory pathways to the dorsal horn are not as well developed at birth.[58] Furthermore, dorsal horn neurons in neonates have a wider receptive field and lower excitatory threshold than those in older children.

As infants and children mature, their responses to pain become more complex and reflective of their maturing cognitive and developmental processes. Children do feel pain and have been shown to reliably and accurately report pain at as young as 3 years of age.[59] They also remember pain, as evidenced in studies of children with cancer, whose distress during painful procedures increases over time without intervention, and in newborns in the neonatal intensive care (NICU), who demonstrate protective withdrawal responses to a heel stick after repeated episodes. The recognition that untreated pain can lead to serious short- and long-term consequences has resulted in a shift to the more liberal use of opioids for treatment of pain in the newborn, particularly those in the NICU.[59]

To manage pain adequately, ongoing assessment of the presence of pain and response to treatment is essential.[58,59] Behavior and physiologic signs are useful, but can be misleading. A toddler may scream during an ear examination because of fear rather than pain, and a child with inadequately relieved cancer pain may withdraw from his or her surroundings. Investigators have devised a range of behavioral distress scales for infants and young children, mostly emphasizing the child's facial expressions, crying, and bodily movements. Children 3 to 7 years of age become more articulate in describing the intensity, location, and severity of the pain. There are self-report measures for children of this age, including

scales with faces of actual children or cartoon faces. With children 8 years of age or older, numeric scales (i.e., 1 to 10) and word graphic scales (i.e., "none," "a little," "most I have ever experienced") can be used. Another supplementary strategy for assessing a child's pain is to use a body outline and ask the child to indicate where the hurt is located. Some physiologic measures, such as heart rate, are convenient to measure and respond rapidly to brief nociceptive stimuli, but they are nonspecific. Relying on indicators of sympathetic nervous system activity and behaviors can also be problematic because they can be caused by things other than pain (e.g., anxiety and activity) and they do not always accompany pain, particularly chronic pain.

The management of children's pain basically falls into two categories: pharmacologic and nonpharmacologic. In terms of pharmacologic interventions, many of the analgesics used in adults can be used safely and effectively in children and adolescents. However, it is critical when using specific medications to determine that the medication has been approved for use with children and that it is dosed appropriately according to the child's weight and level of physiologic development. Age-related differences in physiologic functioning, notably in neonates, will affect drug action. Neonates have decreased fat and muscle and increased water, which increases the duration of action for some water-soluble drugs; neonates also have decreased concentration of plasma proteins (albumin and α_1-glycoprotein), which increases the unbound concentration of protein-bound drugs.[58] Neonates and infants also have decreased levels of the hepatic enzymes needed for metabolism of many analgesics. The levels of these hepatic enzymes quickly increase to adult levels in the first few months of life. Drug clearance in the 2- to 6-year-old age group is actually higher than adult levels because of the larger hepatic mass relative to body weight.[58,60] The renal excretion of drugs depends on renal blood flow, glomerular filtration rate, and tubular secretion, all of which are decreased in neonates, particularly premature neonates. Renal function reaches adult levels by 1 year of age.[58,60]

As with any person in pain, the type of analgesic used should be matched to the type and intensity of pain; whether the patient is a child or adult, the management of chronic pain may require a multidisciplinary team.[60] The overriding principle in all pediatric pain management is to treat each child's pain on an individual basis and to match the analgesic agent with the cause and the level of pain. A second principle involves maintaining the balance between the level of side effects and pain relief such that pain relief is obtained with as little opioid and sedation as possible. One strategy toward this end is to time the administration of analgesia so that a steady blood level is achieved and, as much as possible, pain is prevented. This requires that the child receive analgesia on a regular dosing schedule, not "as needed." Also, most drugs are packaged primarily for adult use, and dose calculations and serial dilutions may predispose to medication errors. Common errors include milligram–microgram errors, decimal point errors, confusion between daily dose and fractional dose (e.g., 100 mg/kg per day divided by 6 hours versus 100 mg/kg per dose every 6 hours), and dilution errors.[60]

Nonpharmacologic strategies can be very effective in reducing the overall amount of pain and amount of analgesia used. In addition, some nonpharmacologic strategies can reduce anxiety and increase the child's level of self-control during pain. Pacifiers and sucrose are being used in the NICU. The effects of sucrose (sweet taste) are believed to be opioid mediated because its effects are reversed by naloxone (an opioid antagonist).[59] Distraction helps children of any age divert their attention away from pain and onto other activities. Common attention diverters include bubbles, music, television, conversation, and games. Relaxation techniques and massage therapy are particularly useful in children with chronic pain. Other nonpharmacologic techniques can be taught to the child to provide psychological preparation for a painful procedure or surgery. These include positive self-talk, imagery, play therapy, modeling, and rehearsal. The nonpharmacologic interventions must be developmentally appropriate and, if possible, the child and parent should be taught these techniques when the child is not in pain (e.g., before surgery or a painful procedure) so that it is easier to practice the technique.

Pain in Older Adults

Among adults, the prevalence of pain in the general population increases with age. Prevalence reports for persistent pain in older adults ranges from 25% to 80%, depending on whether the older adults are community dwelling or reside in a nursing home.[61] Among the common causes of pain in older adults are musculoskeletal disorders such as osteoarthritis and chronic low back pain; rheumatologic diseases such as rheumatoid arthritis and polymyalgia rheumatica; and neurologic conditions such as diabetic neuropathy, postherpetic neuralgia, and central post-stroke pain.

Unrelieved pain can have significant functional, cognitive, emotional, and societal effects in the elderly.[61,62] Decreased activity because of pain can lead to myofascial deconditioning and gait disturbances, which in turn can result in injuries from falls. Pain in the elderly has been associated with impaired appetite, increased sleep disturbances, and in some cases a decrease in cognitive function. These consequences can lead to less than optimal participation in rehabilitation efforts and decreased quality of life. Increased costs because of health care use have also been attributed to unrelieved pain in the elderly.

The assessment of pain in the elderly can range from relatively simple in a well-informed, alert, cognitively intact individual with pain from a single source and no comorbidities to extraordinarily difficult in a frail individual with severe dementia and many concurrent health problems.[61,63,64] When possible, a patient's report of pain is the gold standard, but behavioral signs of pain should be considered as well. Accurately diagnosing pain when the individual has many health problems or some decline in cognitive function can be particularly challenging. In recent years, there has been increased awareness of the

need to address issues of pain in individuals with dementia. The Assessment for Discomfort in Dementia Protocol is one example of the efforts to improve assessment and pain management in these individuals. It includes behavioral criteria for assessing pain and recommended interventions for pain. Its use has been shown to improve pain management.[65]

When prescribing pharmacologic and nonpharmacologic methods of pain management for the older population, care must be taken to consider the cause of the pain, the patient's health status, concurrent therapies, and mental status. In the older population, where the risk of adverse events is higher, the nonpharmacologic options are usually less costly and cause fewer side effects.

Common nonpharmacologic interventions include application of cold (which suppresses the release of products from tissue damage) and heat (which promotes the release of endogenous endorphins).[66] The role of mental focus and anxiety is important, and relaxation techniques, massage, and biofeedback may be useful. Physical therapy and occupational therapy bring a variety of modalities, including the use of braces or splints, changes in biomechanics, and exercise, all of which have been shown to promote pain relief.[65]

Although efficacy is important when considering the use of pharmacologic agents for pain relief in the elderly population, cost and safety must also be considered. Safety issues that must be considered among older adults include changes in drug metabolism, other disease comorbidity, and polypharmacy. The elderly may have physiologic changes that affect the pharmacokinetics of medications prescribed for pain management. These changes include decreased blood flow to organs, delayed gastric motility, reduced kidney function, and decreased albumin related to poor nutrition.[66] The elderly also often have many coexisting health problems, leading to polypharmacy. On average, a 70-year-old takes seven different medications.[66] The addition of analgesics to a complex medication regimen is even more likely to cause drug interactions and complicate compliance in the elderly. However, these considerations should not preclude the appropriate use of analgesic drugs to achieve pain relief. Nonopioids are generally the first line of therapy for mild to moderate pain, and acetaminophen is usually the first choice because it is relatively safe for older adults.[66] Opioids are used for more severe pain and for palliative care. As with younger persons, adjuvant analgesics are effectively used for treatment of pain in older adults. The use of some assessment tool to evaluate the level of pain and effectiveness of treatment is essential. Monitoring for side effects is also critical.

In summary, children experience and remember pain, and even fairly young children are able to accurately and reliably report their pain. Recognition of this has changed the clinical practice of health professionals involved in the assessment of children's pain. Pharmacologic (including opioids) and nonpharmacologic pain management interventions have been shown to be effective in children. Nonpharmacologic techniques must be based on the developmental level of the child and should be taught to both children and parents.

Pain is a common symptom in the elderly. Assessment, diagnosis, and treatment of pain in the elderly can be complicated. The elderly may be reluctant or cognitively unable to report their pain. Diagnosis and treatment can be complicated by comorbidities and age-related changes in cognitive and physiologic function.

REVIEW EXERCISES

1. A 25-year-old man is admitted to the emergency department with acute abdominal pain that began in the epigastric area and has now shifted to the lower right quadrant of the abdomen. There is localized tenderness and guarding or spasm of the muscle over the area. His heart rate and blood pressure are elevated, and his skin is moist and cool from perspiring. He is given a tentative diagnosis of appendicitis and referred for surgical consultation.

A. Describe the origin of the pain stimuli and the neural pathways involved in the pain that this man is experiencing.
B. Explain the neural mechanisms involved in the spasm of the overlying abdominal muscles.
C. What is the significance of his cool, moist skin and increased heart rate and blood pressure?

2. A 65-year-old woman with breast cancer is receiving hospice care in her home. She is currently receiving a long-acting opioid analgesic supplemented with a short-acting combination opioid and nonnarcotic medication for breakthrough pain.

A. Explain the difference between the mechanisms and treatment of acute and chronic pain.
B. Describe the action of opioid drugs in the treatment of pain.
C. Define the term *tolerance* as it refers to the use of opioids for treatment of pain.

3. A 42-year-old woman presents with sudden, stabbing-type facial pain that arises near the right side of her mouth and then shoots toward the right ear, eye, and nostril. She is holding her hand to protect her face because the pain is "triggered by touch, movement, and drafts." Her initial diagnosis is trigeminal neuralgia.

A. Explain the distribution and mechanisms of the pain, particularly the triggering of the pain by stimuli applied to the skin.
B. What are possible treatment methods for this woman?

4. A 21-year-old woman presents to the student health center with complaints of a throbbing pain on the left side of her head, nausea and vomiting, and extreme sensitivity to light, noise, and head movement. She also tells you she had a similar headache 3 months ago that lasted for 2 days and states that she thinks she is developing migraine headaches like her mother. She is concerned because she has been unable to attend classes and has exams next week.

A. Are this woman's history and symptoms consistent with migraine headaches? Explain.
B. Use the distribution of the trigeminal nerve and the concept of neurogenic inflammation to explain this woman's symptoms.

5. A 48-year-old man presents with complaints of severe pain in his right foot after a crush injury. He reports that although he had his ankle pinned surgically, it still causes severe pain now, almost 1 year after injury. He states that he cannot stand to have the sheets touch his foot, and even wearing shoes is painful. His physician has diagnosed chronic regional pain syndrome type I.

A. Differentiate chronic regional pain syndrome type I from type II.
B. Explain the proposed theories of why this pain syndrome develops.

REFERENCES

1. Guyton A., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 572–609). Philadelphia: Elsevier Saunders.
2. Kandel E.R., Schwartz J.H., Jessell T.M. (2000). *Principles of neural science* (5th ed., pp. 430–479). New York: McGraw-Hill.
3. Vanderah T.W. (2007). Pathophysiology of pain. *Medical Clinics of North America* 91, 1–12.
4. Polomano R.C., Dunwoody C.J., Krenzischek D.A., et al. (2008). Perspectives on pain management in the 21st century. *Journal of Perioperative Nursing* 25(1A), S4–S14.
5. Bonica J.J. (1991). History of pain concepts and pain theory. *Mount Sinai Journal of Medicine* 58, 191–202.
6. Melzack R., Wall P.D. (1965). Pain mechanisms: A new theory. *Science* 150, 971–979.
7. Melzack R. (2005). Evolution of the matrix theory of pain. The Prithvi Raz lecture: presented at the third World Conference Institute of Pain, Barcelona 2004. *Pain Practice* 5(2), 85–94.
8. Julius D., Basbaum A.I. (2001). Molecular mechanisms of nociception. *Nature* 413, 203–210.
9. Grady K., Severn A., Eldridge P. (2007). *Key topics in pain medicine* (3rd ed.). United Kingdom: Informa Healthcare.
10. D'Mello R., Dickenson A.H. (2008). Spinal cord mechanisms of pain. *British Journal of Anesthesia* 101(1), 8–16.
11. Ploner M., Gross J., Timmerman L., et al. (2002). Cortical representation of first and second pain sensation in humans. *Proceedings of the National Academy of Sciences of the United States of America* 99, 12444–12448.
12. Fields H.L., Heinricher M.M., Mason P. (1991). Neurotransmitters in nociceptive modulatory circuits. *Review of Neuroscience* 14, 219–245.
13. Stein C. (2003). Opioid receptors on peripheral sensory neurons. In Machelska H., Stein C. (Eds.), *Immune mechanisms of pain and analgesia* (pp. 69–76). New York: Kluwer Academic/Plenum.
14. Cervero F., Laird J.M. (1999). Visceral pain. *Lancet* 353, 2145–2148.
15. Al-Chaer E.D., Traub R.J. (2002). Biological basis of visceral pain: Recent developments. *Pain* 96, 221–225.
16. Turk D.C., Okikfuji A. (2001). Pain terms and taxonomies of pain. In Loser J.D. (Ed.), *Bonica's management of pain* (3rd ed., pp. 17–25). Philadelphia: Lippincott Williams & Wilkins.
17. Fink W.A. (2005). The pathophysiology of acute pain. *Emergency Medicine Clinics of North America* 23, 277–284.
18. Peterson-Felix S., Curatolo M. (2002). Neuroplasticity—an important factor in acute and chronic pain. *Swiss Medical Weekly* 132, 273–278.
19. Polomano R.C., Rathwell J.P., Krenzischeck D.A., et al. (2008). Emerging trends and new approaches to acute pain management. *Journal of Perianesthesia Nursing* 25(1A), S45–S53.
20. Jacobson L., Mariano A.J. (2001). General considerations in chronic pain. In Loser J.D. (Ed.), *Bonica's management of pain* (3rd ed., pp. 241–254). Philadelphia: Lippincott Williams & Wilkins.
21. Hainline B. (2005). Chronic pain: Physiologic, diagnostic, and management considerations. *Psychiatric Clinics of North America* 28, 713–735.
22. Canavero S., Bonicalzi V. (2007). *Central pain syndrome: Pathophysiology, diagnosis and management*. New York: Cambridge University Press.
23. Rustoen T., Gaardsrud T., Leegaard M., et al. (2009). Nursing pain management: A qualitative interview study of patients with pain, hospitalized for cancer treatment. *Pain Management Nursing* 10(1), 48–55.
24. DePinto M., Dunbar P.J., Edwards W.T. (2006). Pain management. *Anesthesia Clinics of North America* 24, 19–37.
25. DeSancire P.L., Quest T.E. (2009). Management of cancer-related pain. *Emergency Medicine Clinics of North America* 27, 179–194.
26. World Health Organization. (1986). *Cancer pain relief*. Geneva, Switzerland: World Health Organization.
27. Katzung H. (Ed.). (2007). *Basic and clinical pharmacology* (10th ed., pp. 489–510, 575–583). New York: Lange Medical Books/McGraw-Hill.
28. Maizels M., McCarberg B. (2005). Antidepressant and antiepileptic drugs for chronic non-cancer pain. *American Family Physician* 71, 483–490.
29. Campbell J.N., Meyer R.A. (2006). Mechanisms of neuropathic pain. *Neuron* 52, 77–92.
30. Rozen T.D. (2004). Trigeminal neuralgia and glossopharyngeal neuralgia. *Neurologic Clinics* 22, 185–206.
31. Liu J.K., Apfelbaum R.I. (2004). Treatment of trigeminal neuralgia. *Neurosurgical Clinics of North America* 15, 319–334.
32. Schmader K. (2007). Herpes zoster and postherpetic neuralgia in older adults. *Clinics in Geriatric Medicine* 23, 615–632.
33. Kimberlin D.W., Whitley R.J. (2007). Varicella-zoster vaccine for the prevention of herpes zoster. *New England Journal of Medicine* 356, 1338–1343.
34. Pham T., Lafforgue P. (2003). Reflex sympathetic dystrophy syndrome and neuromediators. *Joint, Bone, Spine* 70, 12–17.
35. Campell J., Basbaum A., Dray A., et al. (2006). *Emerging strategies for the treatment of neuropathic pain*. Seattle: IASP Publications.
36. Stanton-Hicks M. (2003). Complex regional pain syndrome. *Anesthesia Clinics of North America* 21, 733–744.
37. Blaes F., Schmitz K., Tschernatsch M. (2004). Autoimmune etiology of chronic regional pain syndrome. *Neurology* 63, 1734–1736.
38. Melzack R. (1992). Phantom limb. *Scientific American* 226, 120–126.

39. Kaniecki R. (2003). Headache assessment and management. *Journal of the American Medical Association* 289, 1430–1433.
40. Headache Classification Subcommittee of the International Headache Committee. (2004). The International Classification of headache disorders, 2nd edition. *Cephalalgia* 24(Suppl 1), 1–152.
41. Lipton R.B., Biglal M.E., Stiener T.J., et al. (2004). Classification of primary headaches. *Neurology* 63, 427–435.
42. Mathew N.T. (2001). Pathophysiology, epidemiology, and impact of migraine. *Clinical Cornerstone* 4, 1–17.
43. Cady R., Schreiber C. (2003). Sinus headache or migraine? Considerations in making a differential diagnosis. *Headache* 43, 305.
44. Lewis D.J. (2002). Headaches in children and adolescents. *American Family Physician* 65, 625–632.
45. Haslam R.H.A. (2007). Headaches. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2479–2483). Philadelphia: Saunders Elsevier.
46. Tepper S.J., Rapoport A., Sheftell F. (2001). The pathophysiology of migraine. *The Neurologist* 7, 279–786.
47. Snow V., Weiss K., Wall E.M., et al. (2002). Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Annals of Internal Medicine* 137, 840–849.
48. Silberstein S.D. (2000). Practice parameter: Evidence-based guidelines for migraine headache. *Neurology* 55, 754–763.
49. Ekbom K., Hardebo J.E. (2002). Cluster headache aetiology, diagnosis and management. *Drugs* 62, 61–69.
50. May A. (2005). Cluster headache: Pathogenesis, diagnosis, and management. *Lancet* 366, 843–855.
51. Beck E., Sieber W.J., Trejo R. (2005). Management of cluster headache. *American Family Physician* 71, 717–728.
52. Gladstein J. (2006). Headache. *Medical Clinics of North America* 90, 275–290.
53. Millea P.J., Brodie J.J. (2002). Tension-type headache. *American Family Physician* 66, 797–804.
54. Biondi D.M. (2005). Chronic daily headache. *Clinics in Family Practice* 7, 463–491.
55. Maizels M. (2004). The patient with daily headaches. *American Family Physician* 70, 2299–2306, 2313–2314.
56. Lobbezoo F. (2004). Topical review: New insights into the pathology and diagnosis of disorders of the temporomandibular joint. *Journal of Orofacial Pain* 18, 181–191.
57. Howard R.F. (2003). Current status of pain management in children. *Journal of the American Medical Association* 290, 2464–2469.
58. Brislin R.P., Rose J.B. (2005). Pediatric acute pain management. *Anesthesia Clinics of North America* 23, 789–814.
59. Zeltzer L.K., Krell H. (2007). Pediatric pain management. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 475–484). Philadelphia: Saunders Elsevier.
60. Berde C.B., Sethna N.F. (2002). Analgesics for the treatment of pain in children. *New England Journal of Medicine* 347, 1094–1103.
61. Bruckenthal P. (2008). Assessment of pain in the elderly adult. *Clinical Geriatric Medicine* 24, 213–236.
62. Deane G., Smith H.S. (2008). Overview of pain management in older persons. *Clinics in Geriatric Medicine* 24, 185–201.
63. Kovach C.R., Weissman D.E., Griffie J., et al. (1999). Assessment and treatment of discomfort for people with late-stage dementia. *Journal of Pain and Symptom Management* 18, 412–419.
64. Hutt E., Pepper G.A., Vojir C., et al. (2006). Assessing the appropriateness of pain medication prescribing practices in nursing homes. *Journal of the American Geriatrics Society* 54, 231–239.
65. Barkin R.L., Barkin S.J., Barkin D.S. (2005). Perception, assessment, treatment, and management of pain in the elderly. *Clinics in Geriatric Medicine* 21, 465–490.
66. Katzung B.G. (2007). Special aspects of geriatric pharmacology. In Katzung H. (Ed.), *Basic and clinical pharmacology* (10th ed., pp. 983–990). New York: Lange Medical Books/McGraw-Hill.

Organization and Control of Motor Function
Organization of Movement
The Spinal Cord
The Brain Stem
The Motor Cortex
The Cerebellum and Basal Ganglia
The Motor Unit
Spinal Reflexes
Motor Pathways
Assessment of Motor Function
Muscle Strength, Bulk, and Tone
Spinal Reflex Activity
Coordination of Movement
Disorders of the Motor Unit
Skeletal Muscle Disorders
Muscle Atrophy
Muscular Dystrophy
Disorders of the Neuromuscular Junction
Drug- and Toxin-Induced Disorders
Myasthenia Gravis
Peripheral Nerve Disorders
Peripheral Nerve Injury and Repair
Mononeuropathies
Polyneuropathies
Back Pain and Spinal Nerve Root Disorders
Disorders of the Cerebellum and Basal Ganglia
Disorders of the Cerebellum
Cerebellum-Associated Movement Disorders
Disorders of the Basal Ganglia
Basal Ganglia–Associated Movement Disorders
Parkinson Disease
Upper Motor Neuron Disorders
Amyotrophic Lateral Sclerosis
Demyelinating Disorders of the Central Nervous System
Multiple Sclerosis
Vertebral and Spinal Cord Injury
Injury to the Vertebral Column
Acute Spinal Cord Injury
Types and Classification of Spinal Cord Injury
Disruption of Somatosensory and Skeletal Muscle Function
Disruption of Autonomic Nervous System Function
Disruption of Bladder, Bowel, and Sexual Function
Disruption of Other Functions
Future Directions in Repair of the Injured Spinal Cord

Chapter 36

Disorders of Neuromuscular Function

Just as our perceptual skills reflect the ability of our sensory systems to detect, analyze, and estimate the significance of our physical environment, the ability to carry out skilled movements requires skeletal muscles that contract and neural pathways that plan, coordinate, and execute these contractions in a manner that provides for smooth, purposeful, and coordinated movement. In some cases, purposeless and disruptive movements can be almost as disabling as relative or complete absence of movement. This chapter provides an introduction to the organization and control of motor function, followed by a discussion of disorders of motor function, including muscular dystrophy, and disorders of the neuromuscular junction, peripheral nerves, the basal ganglia and cerebellum, and upper motor neurons.

Organization and Control of Motor Function

Motor function, whether it involves walking, running, or precise finger movements, requires movement and maintenance of posture. Posture can be described as the relative position of various parts of the body with respect to one another (limb extension, flexion) or to the environment (standing, supine).[1] Posture also can be described as the active muscular resistance to the displacement of the body by gravity or acceleration. The structures that control posture and movement are located throughout the neuromuscular system. The system consists of the motor unit (motor neuron and the muscle fibers it innervates); the spinal cord, which contains the basic reflex circuitry for posture and movement; and the descending pathways from brain stem circuits, the cerebellum, the basal ganglia, and the motor cortex.

Organization of Movement

As with other parts of the nervous system, the motor systems are organized in a functional hierarchy, each concerned with increased levels of complexity.[2] The lowest

Motor Systems

- Motor systems require upper motor neurons (UMNs) that project from the motor cortex to the brain stem or spinal cord, where they directly or indirectly innervate the lower motor neurons (LMNs) of the contracting muscles; sensory feedback from the involved muscles that is continuously relayed to the cerebellum, basal ganglia, and sensory cortex; and a functioning neuromuscular junction that links nervous system activity with muscle contraction.
- The pyramidal motor system originating in the motor cortex provides control of delicate muscle movement, and the extrapyramidal system originating in the basal ganglia provides the background for the more crude, supportive movement patterns.
- The efficiency of the movement by the motor system depends on a background of muscle tone provided by the stretch reflex and vestibular system input to maintain stable postural support.

level of the hierarchy occurs at the spinal cord, which contains the basic reflex circuitry needed to coordinate the function of the motor units. Above the spinal cord is the brain stem, and above the brain stem are the cerebellum and basal ganglia, structures that modulate the actions of the brain stem systems. Overseeing these supraspinal structures are the motor centers in the cerebral cortex. The highest level of function, which occurs at the level of the frontal cortex, is concerned with the purpose and planning of motor movements. The efficiency of movement depends on input from sensory systems that operate in parallel with the motor systems.

The Spinal Cord

The spinal cord is the lowest level of motor hierarchical organization.[2] It contains the neuronal circuits that mediate a variety of reflexes and automatic rhythmic movements. Similar circuits governing reflex movements of the face and mouth are located in the brain stem. The simplest circuits are monosynaptic, containing only a primary motor neuron. However, most reflexes are polysynaptic, involving one or more interposed interneurons. Interneurons and motor neurons also receive input from axons descending from higher centers. These supraspinal signals can modify reflex responses to peripheral stimuli by facilitating or inhibiting different populations of interneurons. They also coordinate movements through these interneurons.

The Brain Stem

The next level of motor hierarchy is in the brain stem. The brain stem contains, in addition to the facial nerves,

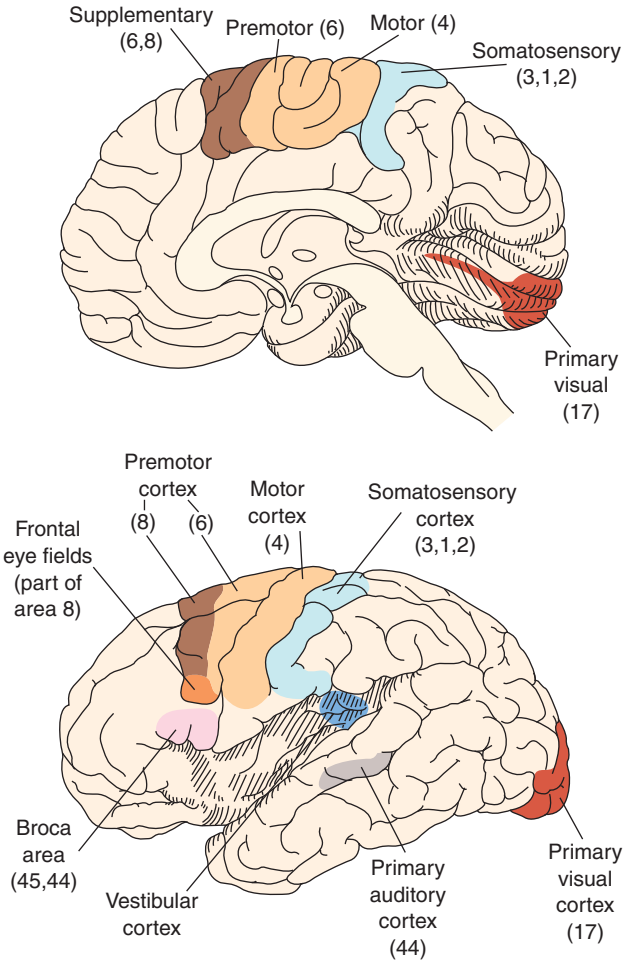


FIGURE 36-1. Primary motor cortex. (*Top*) The location of the primary, premotor, and supplementary cortex on the medial surface of the brain. (*Bottom*) The location of the primary and premotor cortex on the lateral surface of the brain.

many groups of neurons that project from the spinal gray matter. These projections are grouped into two main systems: the medial and lateral brain stem systems, which receive input from the cerebral cortex and subcortical nuclei and project to the spinal cord.[2] The medial descending systems contribute to the control of posture by integrating visual, vestibular, and somatosensory information. The lateral descending systems control more distal limb muscles and are thus more concerned with goal-directed movements, especially of the arm and hand. Brain stem circuits also control movements of the eyes and head.

The Motor Cortex

The cortex represents the highest level of motor function. Precise, skillful, and intentional movements of the distal and especially flexor muscles of the limbs and speech apparatus are initiated and controlled by the primary, premotor, and supplementary motor cortices located in the posterior part of the frontal lobe[1,3] (Fig. 36-1). These motor areas receive information from the thalamus and somatosensory cortex and, indirectly, from the cerebellum and basal ganglia.

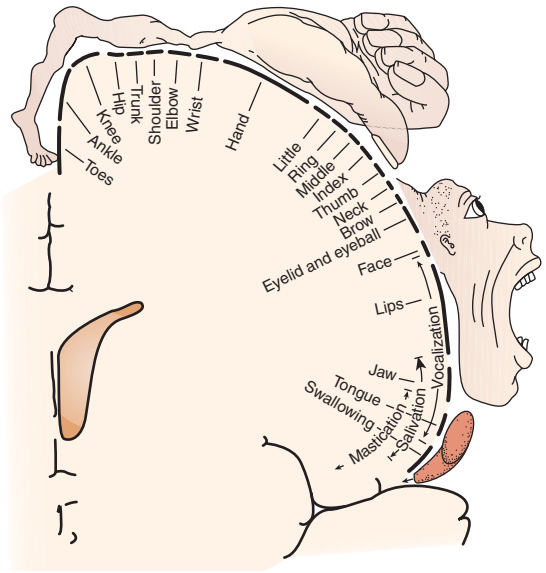


FIGURE 36-2. Representation of the relative extent of motor cortical area 4 devoted to muscles of the various body regions. Medial surface is at the left, lateral fissure is at the right, with pharyngeal and laryngeal muscle representation extending toward the insula. (From Penfield E., Rasmussen T. [1968]. *The cerebral cortex in man: A clinical study of localization of function.* New York: Macmillan.)

The primary motor cortex (area 4), also called the *motor strip,* is located on the rostral surface and adjacent portions of the central sulcus. The primary motor cortex controls specific muscle movement sequences and is the first level of descending control for precise motor movements. The neurons in the primary motor cortex are arranged in a somatotopic array or distorted map of the body called the *motor homunculus*[4] (Fig. 36-2). The areas of the body that require the greatest dexterity have the largest cortical areas devoted to them. More than half of the primary motor cortex is concerned with controlling the muscles of the hands, of facial expression, and of speech.

The premotor cortex (areas 6 and 8), which is located just anterior to the primary motor cortex, sends some fibers into the corticospinal tract but mainly innervates the primary motor strip. Nerve signals generated by the premotor cortex produce much more complex "patterns" of movement than the discrete patterns generated by the primary motor cortex. For example, the movement pattern to accomplish a particular objective, such as throwing a ball or picking up a fork, is programmed by the prefrontal association cortex and associated thalamic nuclei.

The supplementary motor cortex, which contains representations of all parts of the body, is located on the medial surface of the hemisphere in the premotor region (areas 6 and 8). It is intimately involved in the performance of complex, skillful movements that involve both sides of the body.

The Cerebellum and Basal Ganglia

In addition to the brain stem and cerebral cortex, two other parts of the brain assist in the planning and execution of motor movements. The cerebellum and basal ganglia provide feedback circuits that regulate cortical and brain stem motor areas.[2] They receive input from various areas of the cortex and project to the motor cortex through the thalamus. The cerebellum and basal ganglia do not send significant output directly to the spinal cord, but act directly on motor neurons in the brain stem.

Although the precise contributions of the cerebellum and basal ganglia are still unclear, both are necessary for smooth movement and posture. The basal ganglia provide the gracefulness of performance as well as the supportive posture for highly skilled movements. As will be discussed, degenerative diseases of the basal ganglia such as Parkinson disease produce involuntary movements. Cerebellar circuits are involved with the timing and coordination of movements that are in progress and with learning of motor skills. Damage to the cerebellum by vascular lesions of certain familial degenerative disorders produces cerebellar ataxia, a characteristic loss of coordination and accuracy of limb movement.

The Motor Unit

The neurons that control motor function are referred to as *motor neurons* or sometimes as *alpha motor neurons*.[3] The motor neuron and the group of muscle fibers it innervates in a muscle is called a *motor unit*. When the motor neuron develops an action potential, all of the muscle fibers in the motor unit it innervates develop action potentials, causing them to contract simultaneously. Thus, a motor neuron and the muscle fibers it innervates function as a single unit—the basic unit of motor control.

Each motor neuron undergoes multiple branchings, making it possible for a single motor neuron to innervate a few to thousands of muscle fibers. In general, large muscles—those containing hundreds or thousands of muscle fibers and providing gross motor movement—have large motor units. This contrasts sharply with those that control the hand, tongue, and eye movements, for which the motor units are small and permit very precise control.

The motor neurons supplying a motor unit are located in the ventral horn of the spinal cord and are called *lower motor neurons* (LMNs). Upper motor neurons (UMNs), which exert control over LMNs, project from the motor strip in the cerebral cortex to the ventral horn and are fully contained in the central nervous system (CNS; Fig. 36-3).

Spinal Reflexes

Reflexes are coordinated, involuntary motor responses that are initiated by a stimulus applied to peripheral receptors.[3,5] Some reflexes, such as the flexor-withdrawal reflex, initiate movements to avoid hazardous situations, whereas others, such as the stretch reflex or crossed-extensor reflex, serve to integrate motor movements so they function in a coordinated manner. The anatomic basis of a reflex consists of an afferent neuron that synapses either directly with an effector neuron that innervates a muscle or with an interneuron that synapses with an effector neuron. Reflexes are essentially "wired into" the CNS so that

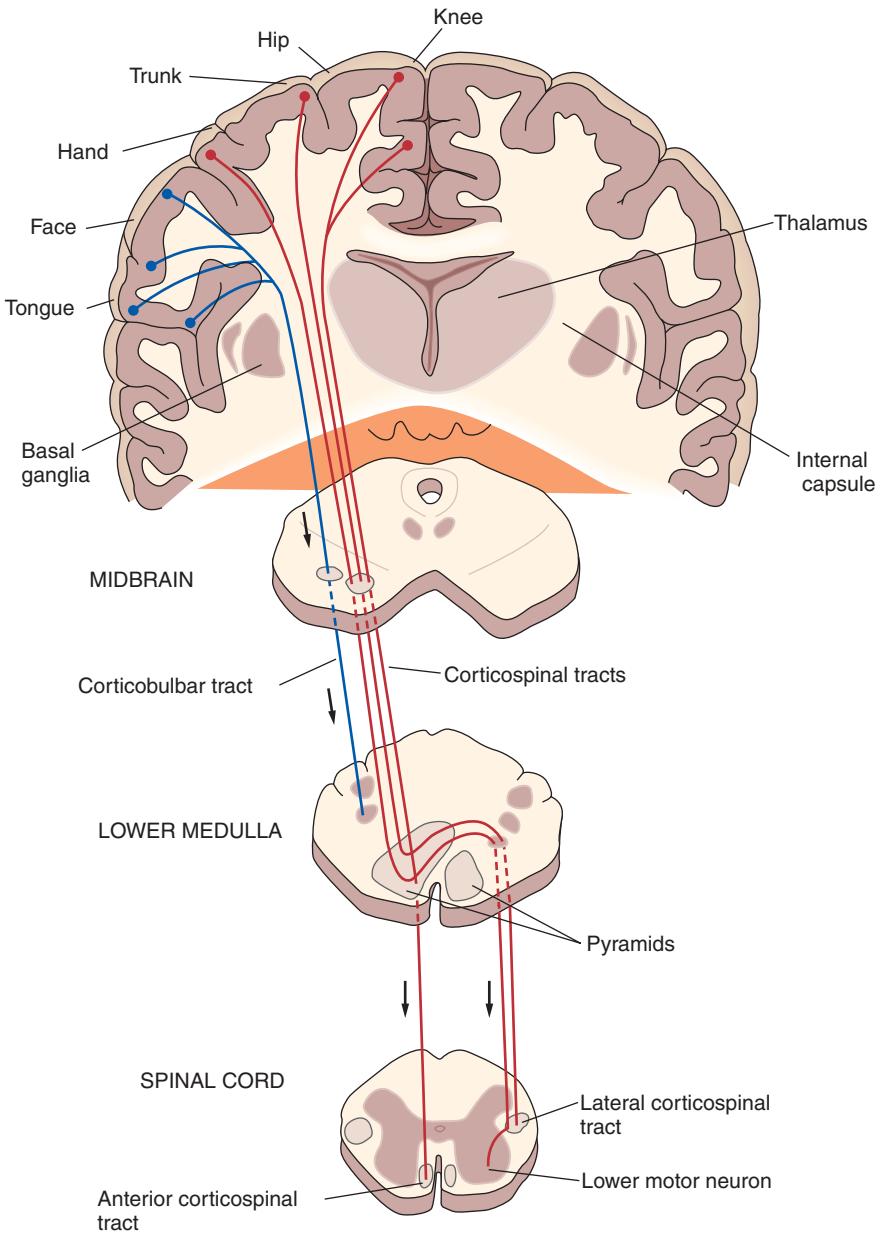


FIGURE 36-3. Upper motor neuron pathways: corticospinal (red) and corticobulbar tracts (blue). (Modified from Bickley L.S. [2003]. *Bates guide to physical examination and history taking* [8th ed., p. 543]. Philadelphia: Lippincott Williams & Wilkins.)

they are always ready to function; with training, most reflexes can be modulated to become parts of more complicated movements. A reflex may involve neurons in a single cord segment (i.e., segmental reflexes), several or many segments (i.e., intersegmental reflexes), or structures in the brain (i.e., suprasegmental reflexes).

In most cases, reflex activities go on without our conscious awareness. There is a significant amount of reflex circuitry in the spinal cord for the coordinated control of movements, particularly stereotyped movements concerned with locomotion. Many of these reflexes work equally well in decerebrate animals (those in which the brain has been destroyed) as long as the spinal cord is intact. Other spinal reflexes require the activity of the brain for their successful completion. In addition, the brain is advised of many types of spinal cord reflex activities and can either inhibit or facilitate them.

The Stretch and Deep Tendon Reflexes. If the skeletal muscles of the body are to perform normally, the brain must be continually informed of the current state of contraction, and the muscles must exhibit healthy tone (resistance to active and passive stretch at rest). The first requirement depends on the transmission of information regarding the sense of body position, movement, and muscle tone to the CNS. Information from these sensory afferents is relayed to the cerebellum and cerebral cortex and is experienced as *proprioception* or the sense of body movement and position, independent of vision. To provide this information, the muscles and their tendons are supplied with two types of receptors: muscle spindles and Golgi tendon organs. The *muscle spindles*, which are distributed throughout the belly of a muscle, relay information about muscle length and rate of stretch. The *Golgi tendon organs* are found in muscle

tendons and transmit information about muscle tension or force of contraction at the junction of the muscle and the tendon that attaches to bone.

Normal muscle tone depends on stretch reflexes initiated by the muscle spindles, which monitor changes in muscle length (see Understanding the Stretch Reflex and Muscle Tone). The neural circuits responsible for stretch reflexes provide higher centers of the nervous system with a mechanism for adjusting muscle tone under different circumstances. Disorders of muscle tone are frequently associated with lesions of the motor system, especially those that interfere with descending pathways. Stretch reflexes are hyperactive when lesions of the corticospinal tract (e.g., stroke or spinal cord injury) reduce or disrupt the inhibitory effect of the brain on the spinal cord, and they are hypoactive or absent in cases of peripheral nerve damage or anterior spinal cord injury.

The muscle spindles consist of a group of specialized miniature skeletal muscle fibers called *intrafusal fibers* that are encased in a connective tissue capsule and attached to the extrafusal fibers of a skeletal muscle. In the center of the receptor area, a large sensory neuron spirals around the intrafusal fiber, forming the so-called *primary* or *annulospiral ending*. The intrafusal muscle fibers function as stretch receptors that increase their firing when the muscle is stretched. Axons of these spindle fiber neurons enter the spinal cord through several branches of the dorsal root. Some branches end in the segment of entry; others ascend to adjacent segments, influencing intersegmental reflex function; and still others ascend in the dorsal column of the cord to the brain stem. Segmental branches establish monosynaptic contact with each of the LMNs that have motor units in the muscle containing the spindle receptor. This produces an opposing muscle contraction. Another segmental branch of the same afferent neuron innervates an internuncial neuron that is inhibitory to motor units of antagonistic muscle groups. This disynaptic inhibitory pathway is the basis for the reciprocal activity of agonist and antagonist muscles (i.e., when an agonist muscle is stretched, the antagonists relax). Reciprocal innervation is useful not only for the stretch reflex, but also for voluntary movements. Relaxation of the antagonist muscle during movements enhances the speed and efficiency because the muscles that act as prime movers are not working against contraction of the opposing muscle.[1]

Another function of the stretch reflex is to inform the CNS of the status of muscle length. Ascending impulses from stretch receptors in the contracting muscle fibers ultimately provide information about muscle length to higher centers in the cerebellum and cerebral cortex. When a skeletal muscle lengthens or shortens against tension, a feedback mechanism needs to be available for readjustment such that the spindle apparatus remains sensitive to moment-to-moment changes in muscle stretch, even while changes in muscle length are occurring. This is accomplished by the *gamma motor neurons* that adjust spindle fiber length to match the length of the extrafusal muscle fiber. Descending fibers of motor pathways synapse with and simultaneously activate both alpha and gamma motor neurons so that the sensitivity of the spindle fibers is coordinated with muscle movement.

Central control over the gamma motor neurons also permits increases or decreases in muscle tone in anticipation of changes in the muscle force. The CNS, through its coordinated control of the muscle's alpha and the spindle's gamma motor neurons, can suppress the stretch reflex. This occurs during centrally programmed movements, such as pitching a baseball, that require a muscle to produce a full range of unopposed motion. Without this programmed adjustability of the stretch reflex, any movement is immediately opposed and prevented.

Motor Pathways

The primary motor cortex contains many layers of pyramid-shaped output neurons that project to the premotor and somatosensory areas on the same side of the cortex, project to the opposite side of the cortex, or descend to subcortical structures such as the basal ganglia and thalamus. The large pyramidal cells located in the fifth layer project to the brain stem and spinal cord. The axons of these UMNs project through the subcortical white matter and internal capsule to the deep surface of the brain stem, through the ventral bulge of the pons, and to the ventral surface of the medulla, where they form a ridge or pyramid (see Fig. 36-3). The majority of corticospinal UMNs cross the midline in the pyramidal decussation at the junction of the medulla and cervical spinal cord to form the lateral corticospinal tract in the white matter of the spinal cord. A few of the fibers do not cross to the opposite side of the cord, but pass down the ventral column of the cord, mainly to cervical levels, where they cross and innervate contralateral LMNs.

Traditionally, motor tracts have been classified as belonging to one of two motor systems: the pyramidal and extrapyramidal systems. According to this classification system, the *pyramidal* system consists of the motor pathways originating in the motor cortex and terminating in the corticobulbar fibers in the brain stem and the corticospinal fibers in the spinal cord. Other fibers from the cortex and basal ganglia project to the brain stem reticular formation and reticulospinal systems, following a more ancient pathway to LMNs of proximal and extensor muscles. These fibers do not decussate in the pyramids, hence the name *extrapyramidal system*. Disorders of the pyramidal tracts (e.g., stroke) are characterized by spasticity and paralysis, whereas those affecting the extrapyramidal tracts (e.g., Parkinson disease) result in involuntary movements, muscle rigidity, and immobility without paralysis. As increased knowledge regarding motor pathways has emerged, it has become evident that the extrapyramidal and pyramidal systems are extensively interconnected and cooperate in the control of movement.[1]

Assessment of Motor Function

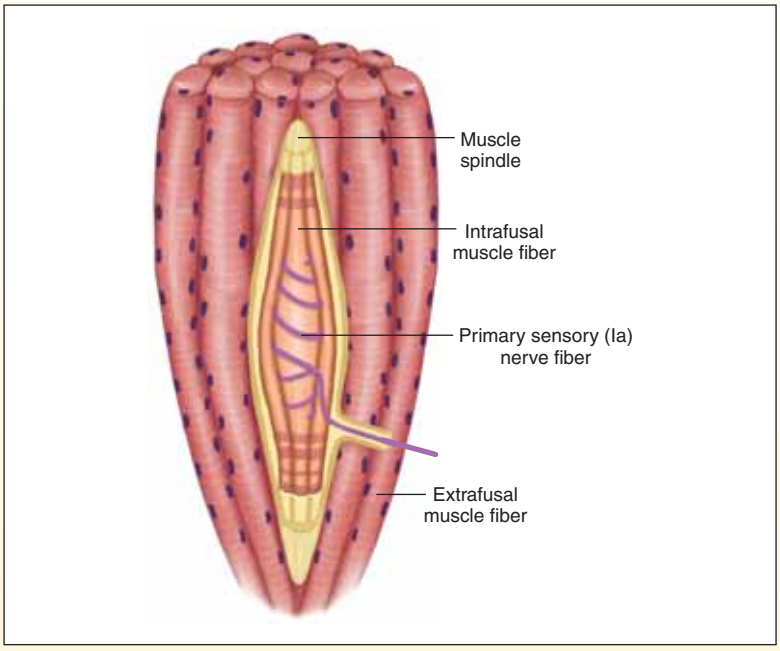
Disorders of the motor system produce signs and symptoms that can be used in localizing the disorder. These

UNDERSTANDING → The Stretch Reflex and Muscle Tone

Muscle tone is controlled by the stretch reflex, which monitors changes in muscle length. The activity of the stretch reflex can be divided into three steps: (1) activation of the stretch receptors, (2) integration of the reflex in the spinal cord, and (3) regulation of reflex sensitivity by higher centers in the brain. Testing the (4) knee-jerk reflex provides a means of assessing that reflex.

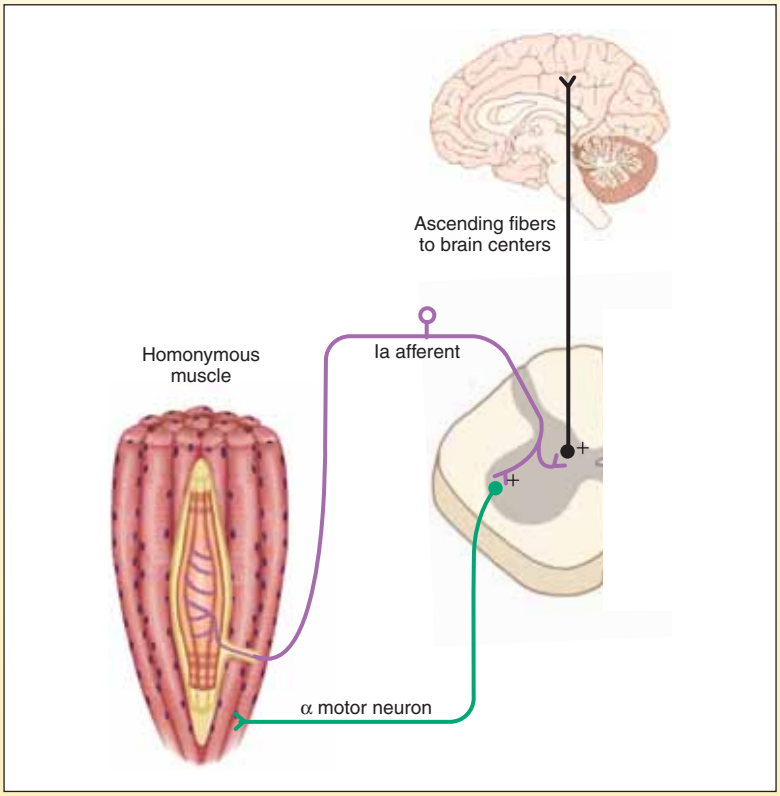
1

Stretch Reflex Receptors. Skeletal muscle is composed of two types of muscle fibers: a large number of extrafusal fibers, which control muscle movement, and a smaller number of intrafusal fibers, which control muscle tone. The intrafusal fibers are encapsulated in sheaths, forming a muscle spindle that runs parallel to the extrafusal fibers. Each intrafusal fiber is innervated by a large Ia sensory nerve fiber, which encircles the central noncontractile portion of the fiber to form the so-called *annulospiral ending*. Because the spindles are oriented parallel to the extrafusal muscle fibers, stretching of the extrafusal fibers also stretches the spindle fibers and stimulates the receptive endings of the Ia afferent neuron.



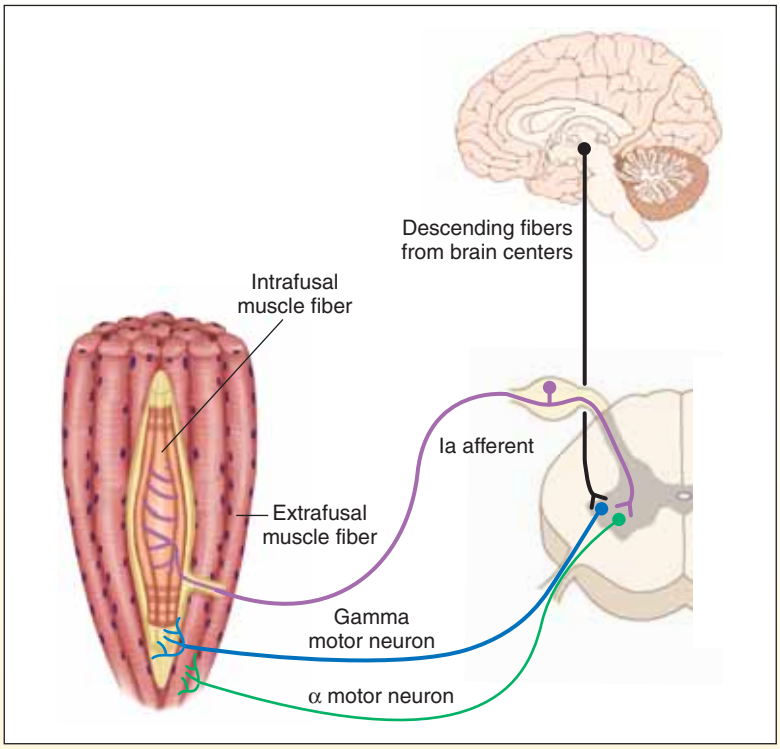
2

Spinal Reflex Centers. Afferent impulses from the Ia sensory fiber of the muscle spindle are transmitted to the spinal cord, where they synapse with alpha motor neurons of the stretched muscle to form a monosynaptic reflex arc—"monosynaptic" because only one synapse separates the primary sensory input from the motor neuron output. The reflex muscle contraction that follows resists further stretching of the muscle. As this spinal reflex activity is occurring, impulses providing information on muscle length are transmitted to higher centers in the brain. It is the coordinated activity of all the monosynaptic reflexes supplying the extrafusal fibers in a skeletal muscle that provides the muscle tone needed for organized movement.



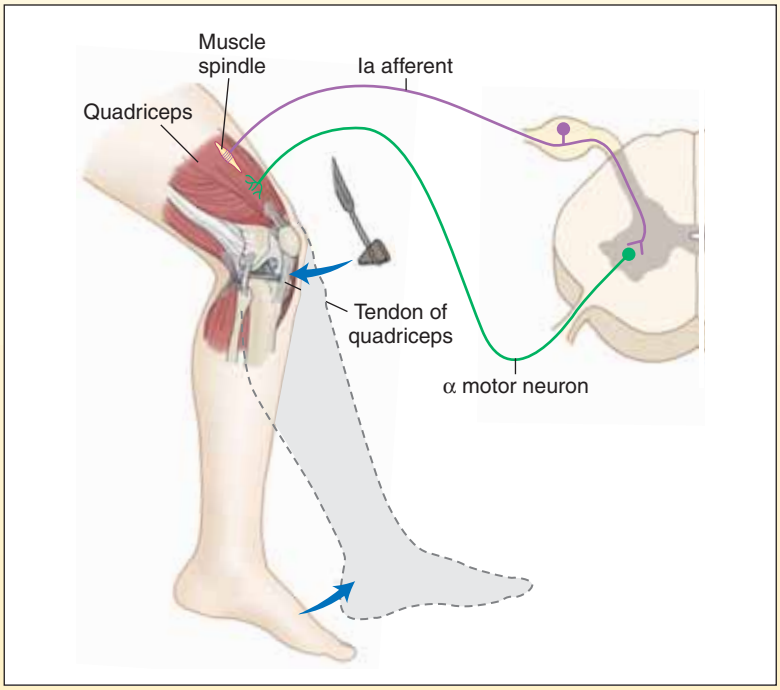
3

Brain Center Connections. Although a spinal reflex can function independently, its sensitivity is adjusted by higher centers in the brain. Both types of muscle fibers are supplied with motor neurons—the extrafusal fibers with large alpha motor neurons, which produce muscle contraction; and the intrafusal fibers with smaller gamma motor neurons, which control the sensitivity of the stretch reflex. Descending fibers of motor pathways synapse with both alpha and gamma motor neurons, and the impulses are sent simultaneously to the large extrafusal fibers and to the intrafusal fibers to maintain muscle spindle tension (and sensitivity) during muscle contraction.



4

The Knee-Jerk Reflex. The knee-jerk reflex that occurs when the knee is tapped with a reflex hammer tests for the intactness of the stretch reflex arc in the quadriceps muscle. Stretching of the extrafusal fibers by tapping with a reflex hammer leads to lengthening of the intrafusal fibers and increased firing of the type Ia afferent neuron. Impulses from the Ia fiber enter the dorsal horn of the spinal cord and make monosynaptic contact with the ventral horn alpha motor neuron supplying the extrafusal fibers in the quadriceps muscle. The resultant reflex contraction (shortening) of the quadriceps muscle is responsible for the knee jerk. These muscle reflexes are called *deep tendon reflexes* (DTRs). They can be checked at the wrists, elbows, knees, and ankles as a means of assessing the components of the stretch reflex at different spinal cord segments.



signs and symptoms include changes in muscle characteristics (strength, bulk, and tone), spinal reflex activity, and motor coordination.[6] For diagnostic purposes, clinicians often use the terms *LMN,* referring to neurons that are located in the spinal cord and brain stem and directly innervate skeletal muscle, and *UMN,* referring to neurons that originate in higher regions of the brain, such as the motor cortex, and synapse with motor neurons. The distinction between LMNs and UMNs is important because each class of neurons produces distinctive symptoms.

Muscle Strength, Bulk, and Tone

Muscle Strength. Abnormalities in any part of the motor pathway can produce impaired strength or muscle weakness. *Paralysis* refers to loss of movement, and *paresis* to weakness or incomplete loss of strength. The pattern of weakness may be helpful in the localization of the lesion. *Monoparesis* or *monoplegia* results from the destruction of pyramidal UMN innervation of one limb; *hemiparesis* or *hemiplegia,* both limbs on one side; *diparesis* or *diplegia* or *paraparesis* or *paraplegia,* both upper or lower limbs; and *tetraparesis* or *tetraplegia,* also called *quadriparesis* or *quadriplegia,* all four limbs (Fig. 36-4).

Paresis or paralysis can be further designated as of UMN or LMN origin. UMN lesions of the motor cortex or corticospinal tract typically affect the extensors in the upper extremities more than the flexors, whereas in the lower extremities, the flexors are more affected. In LMN or peripheral nerve disorders, the weakness is predominantly in the distal limb, whereas in muscle disorders, such as muscular dystrophy, proximal limb function may be affected sooner than distal limb function.

Muscle Bulk. The size of muscle (whether muscles are normal sized, enlarged, or atrophied) also helps localize the lesion, and sometimes provides helpful hints to the pathologic process. Muscular atrophy, or loss of muscle bulk, usually results from LMN lesions as well as diseases of the muscles themselves. Hypertrophy refers to an increase in muscle bulk with a proportionate increase in strength. Pseudohypertrophy, as occurs with Duchenne muscular dystrophy, refers to an increase in bulk without an accompanying increase in strength.

Muscle Tone. Muscle tone is the normal state of muscle tension. It is assessed by palpating the muscle while at rest and during passive stretching. With the person at rest, the joints are put through the normal range of motion (flexion and extension) by the examiner. Disorders of skeletal muscle tone are characteristic of many nervous system lesions. Any interruption of the myotatic or stretch reflex circuitry by peripheral nerve injury, pathologic process of the neuromuscular junction, injury to the spinal cord, or damage to the corticospinal system can result in disturbances of muscle tone.

Abnormalities of muscle tone may be described as hypotonia (less than normal), flaccidity (absent), or hypertonia, rigidity, spasticity, or tetany (all indicating higher-than-normal tone). Typically, UMN lesions produce increased tone, whereas LMN lesions produce decreased tone. Increased resistance that varies and commonly becomes worse at the extremes of the range of motion is called *spasticity.* Resistance that becomes worse throughout the range and in both directions is called *lead-pipe rigidity.* Decreased resistance suggests disease of the LMNs or the acute stages of spinal cord injury. Marked floppiness indicates hypotonic or flaccid muscles.

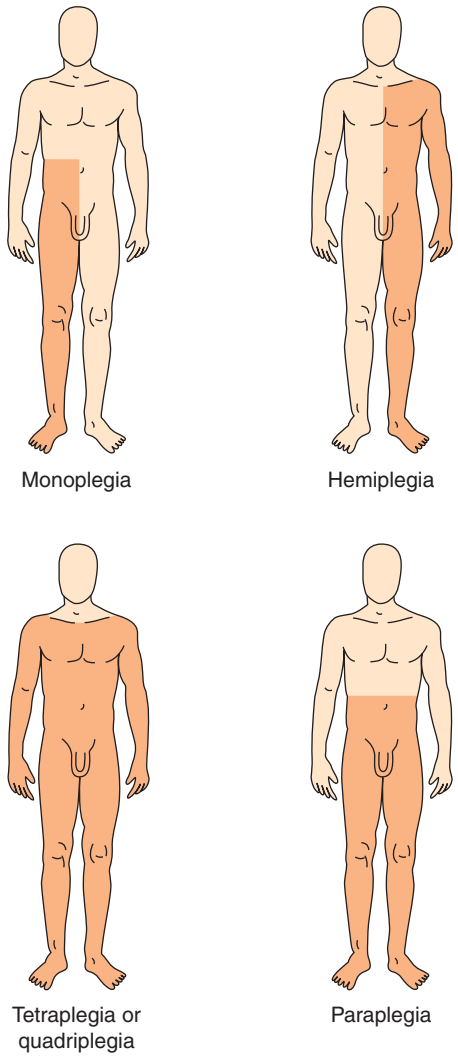


FIGURE 36-4. Areas of the body affected by monoplegia, hemiplegia, tetraplegia or quadriplegia, and paraplegia. The *shaded area* shows the extent of motor and sensory loss. (From Hickey J.V. [1997]. *The clinical practice of neurological and neurosurgical nursing* [3rd ed.]. Philadelphia: J.B. Lippincott.)

Fasciculations. Fasciculations are visible squirming and twitching movements of muscle fibers that can be seen as flickers under the skin.[7] They are caused by spontaneous contractions of all the muscle fibers in a motor unit due to irritation and hyperexcitability of the cell body and its motor neuron, and suggest LMN disease.

Spinal Reflex Activity

Testing of deep tendon reflexes (see Understanding the Stretch Reflex and Muscle Tone) can provide important

information about the status of the CNS in controlling muscle function. Hyperactive reflexes are suggestive of a UMN disorder. *Clonus* is the rhythmic contraction and alternate relaxation of a limb that is caused by suddenly stretching a muscle and gently maintaining it in the stretched position. It is seen in the hypertonia of spasticity associated with UMN lesions, such as spinal cord injury. *Hyporeflexia* or *areflexia* suggests the presence of an LMN lesion. The distribution of abnormality in the reflexes is also helpful in determining the location of the lesion. For example, hyperreflexia in both lower extremities would suggest a lesion in the spinal cord, whereas hyperreflexia on one side of the body would suggest a lesion in the UMN along the motor pathway (e.g., in the motor cortex or internal capsule).

Coordination of Movement

Coordination of muscle movement requires that four areas of the nervous system function in an integrated manner—the motor system for muscle strength, the cerebellar system for rhythmic movement and steady posture, the vestibular system for posture and balance, and the sensory system for position sense.

In cerebellar disease, one movement cannot be followed quickly by its opposite movement and movements are slow, irregular, clumsy, unsteady, and inappropriately varying in their speed, force, and direction. *Dysdiadochokinesia* is the failure to accurately perform rapid alternating movements. *Ataxia* is a term used to describe a wide-based, unsteady gait. *Dysmetria* is a term used to describe inaccuracies of movements leading to a failure to reach a specified target. This can be tested by having the person touch the examiner's finger and then alternately touch his or her finger. These movements are normally smooth and accurate. Asking the person to touch the examiner's finger with an outstretched arm and finger, first with the eyes open and then closed, provides a test for position sense. Repetitive and consistent deviation to one side (referred to as past pointing), which is worse with the eyes closed, suggests cerebellar or vestibular disease.

Chorea (abnormal writhing movements), *dystonia* (abnormal simultaneous contractions of agonist and antagonist muscles, leading to abnormal postures), *tremor* (rhythmic movements of a particular body part), *bradykinesia* (slowness of movements), and *myoclonus* (involuntary jerking movement) indicate abnormalities in the basal ganglia, although the exact localization may be difficult to determine.

In summary, motor function, whether it involves walking, running, or precise finger movements, requires movement and maintenance of posture. The system consists of the LMNs, which are located in the ventral horn of the spinal cord and the group of muscle fibers it innervates in the muscle; spinal cord circuitry and reflexes; and the descending UMNs, which project from the motor cortex to the opposite side of the medulla, where they form a pyramid before crossing the midline to form the lateral corticospinal tract in the spinal cord. Voluntary control of motor function is directed by the motor cortex, which consists of the primary, premotor, and supplementary motor cortex. The primary motor cortex is responsible for execution of a movement, the premotor cortex for generating a plan of movement, and the supplemental motor cortex for rehearsing the motor sequences of a movement, including those involving both sides of the body. As with other parts of the nervous system, the motor systems are organized in a functional hierarchy of, from bottom to top, the spinal cord, brain stem, and motor cortex, each with circuits that, through their input and output connections, can contribute to the organization and regulation of complex motor responses.

Proper control of muscle function requires not only excitation of the muscle by the LMNs located in the spinal cord, but also the function of reflex circuitry that monitors the functional status of the muscle fibers on a moment-by-moment basis. The muscle spindles of the stretch reflex function to monitor and correct for changes in muscle length when extrafusal fibers are either shortened (by contraction) or lengthened (by stretch).

Assessments of muscle strength and muscle bulk, muscle tone and motor reflexes, and patterns of motor movement and posture provide the means for determining the location of disorders of motor function. Paresis (weakness) and paralysis (loss of muscle movement) reflect a loss of muscle strength. UMN lesions tend to produce spastic paralysis, and LMN lesions flaccid paralysis. Changes in muscle bulk are characterized by a loss of muscle mass (atrophy) or an increase in muscle mass (hypertrophy). Muscle tone is maintained through the combined function of the spinal cord stretch reflex and higher centers that monitor and buffer UMN innervation of the LMNs. Hypotonia is a condition of less-than-normal muscle tone, and hypertonia or spasticity is a condition of excessive tone. Abnormal and uncoordinated movements and postures are suggestive of a cerebellar or basal ganglia pathologic process.

Disorders of the Motor Unit

Most of the diseases of the motor unit cause weakness and wasting of skeletal muscles. The distinguishing features of these diseases vary depending on which of the components of the motor unit is primarily affected—the cell body of the motor neuron, its axon, the neuromuscular junction, or the muscle fibers.[7–9] Disorders affecting the nerve cell body are often referred to as *lower motor neuron disorders*, those affecting the nerve axon as *peripheral neuropathies*, and primary disorders affecting the muscle fibers as *myopathies*.

Skeletal Muscle Disorders

Muscle Atrophy

Maintenance of muscle strength requires relatively frequent movements against resistance. Reduced use results in muscle atrophy, which is characterized by a reduction in the diameter of the muscle fibers because of a loss of protein filaments.[8] When a normally innervated muscle is not used for long periods, the muscle cells shrink in diameter, and although the muscle cells do not die, they lose much of their contractile proteins and become weakened. This is called *disuse atrophy,* and it occurs with conditions such as immobilization and chronic illness.

The most extreme examples of muscle atrophy are found in persons with disorders that deprive muscles of their innervation. This is called *denervation atrophy.* During early embryonic development, outgrowing skeletal nerves innervate partially mature muscle cells. If the developing muscle cells are not innervated, they do not mature and eventually die. In the process of innervation, randomly contracting muscle cells become enslaved by the innervating neurons, and from then on, the muscle cell contracts only when stimulated by that particular neuron. If the LMN dies or its axon is destroyed, the skeletal muscle cell is again free of neural domination. When this occurs, it begins to have temporary spontaneous contractions, called *fibrillations.* In contrast to previously described fasciculations, fibrillations are not visible clinically and can be detected only by electromyography.[7] The muscle also begins to lose its contractile proteins and, after several months, if not reinnervated, it is replaced by fibrous connective tissue, which makes rehabilitation difficult. Atrophy of denervation can often be delayed by periodic electrical stimulation while waiting to determine if the damaged nerve fiber regenerates.

Muscular Dystrophy

Muscular dystrophy is a term applied to a number of genetic disorders that produce progressive degeneration and necrosis of skeletal muscle fibers and eventual replacement with fat and connective tissue. They are primary diseases of muscle tissue and probably do not involve the nervous system. As the muscle undergoes necrosis, fat and connective tissue replace the muscle fibers, which increases muscle size and results in muscle weakness. The increase in muscle size resulting from connective tissue infiltration is called *pseudohypertrophy.* The muscle weakness is insidious in onset but continually progressive, varying with the type of disorder.

The two most common forms of muscular dystrophy are Duchene muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), both of which are inherited as an X-linked recessive trait. DMD is the most common and severe form of muscular dystrophy, with an incidence of 1 in every 3500 to 3600 live male births.[8,10] Despite the X-lined inheritance in DMD, about 30% of cases are new mutations, and the mother is not a carrier. Female carriers are usually asymptomatic; affected girls are occasionally encountered, but usually have much milder symptoms than boys. BMD, which shares the same genetic locus as DMD, manifests later in childhood or adolescence and has a slower and less severe course of progression.

Both DMD and BMD are caused by mutations in the dystrophin gene, located on the short arm of the X chromosome. Dystrophin is a large protein that is expressed in a variety of tissues, including all types of muscle cells.[8–11] It attaches portions of the sarcomere to the cell membrane, maintaining the structural integrity of skeletal and cardiac muscle cells. The role of dystrophin in transferring the force of contraction to the extracellular connective tissue matrix has been proposed as the basis for muscle cell degeneration that occurs with dystrophin defects or changes in other proteins that interact with dystrophin. The dystrophin gene is one of the largest in the human genome, spanning 2.3 million base pairs, a factor that is thought to make it particularly vulnerable to mutations that affect different aspects of dystrophin synthesis. Muscle biopsy specimens from individuals with DMD show little or no dystrophin. In comparison, individuals with BMD, who also have mutations in the dystrophin gene, show diminished amounts of dystrophin, usually of an abnormal molecular weight, reflecting mutations that allow synthesis of an abnormal protein of smaller size.[8]

Clinical Course. Boys with DMD are usually asymptomatic at birth and during infancy.[8,10] Early gross movements such as rolling, sitting, and standing are usually achieved at the proper age. The postural muscles of the hips and shoulders are usually the first to be affected. Pseudohypertrophy (enlargement of the muscle due to excessive replacement of muscle fibers with fibroadipose tissue) of the calf muscle eventually develops (Fig. 36-5). Signs of muscle weakness usually become evident beginning at 2 to 3 years, when frequent falling begins to occur. Imbalances between agonist and antagonist muscles lead to abnormal postures and the development of contractures and joint immobility. Scoliosis is common. Wheelchairs usually are needed at approximately 7 to 12 years of age.[10] The function of the distal muscles usually is preserved well enough that the child can continue

FIGURE 36-5. A boy with Duchenne muscular dystrophy demonstrating pseudohypertrophy of his calves and climbing from a sitting position because of proximal muscle weakness. (From Bird T., Sumi S. [2002]. *Atlas of clinical neurology.* Edited by Roger N. Rosenberg. © Current Medicine, Inc.)

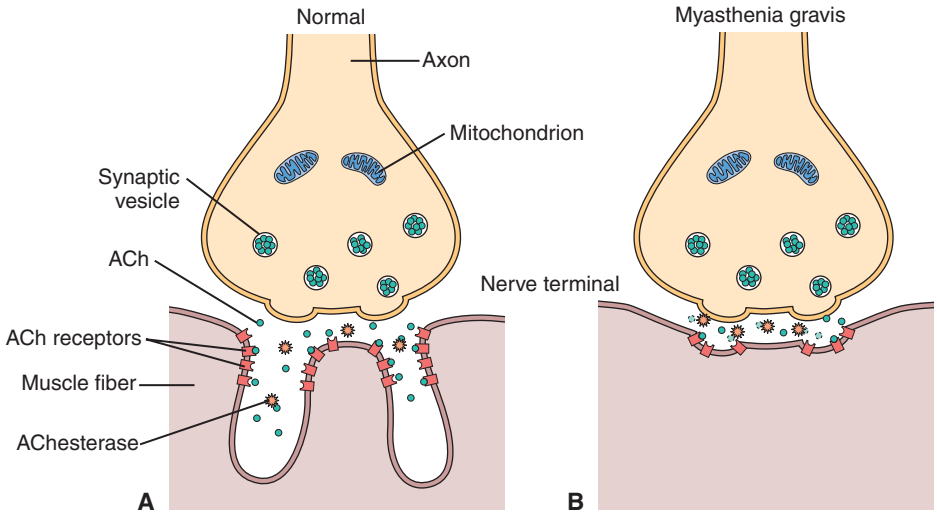


FIGURE 36-6. Neuromuscular junction. **(A)** Acetylcholine (ACh) released from the motor neurons in the myoneural junction crosses the synaptic space to reach receptors that are concentrated in the folds of the endplate of the muscle fiber. Once released, ACh is rapidly broken down by the enzyme acetylcholinesterase (AChesterase). **(B)** Decrease in ACh receptors in myasthenia gravis.

to use eating utensils and a computer keyboard. The function of the extraocular muscles also is well preserved, as is the function of the muscles controlling urination and defecation. Incontinence is an uncommon and late event. Respiratory muscle involvement results in weak and ineffective cough, frequent respiratory infections, and decreasing respiratory reserve. Cardiomyopathy is a common feature of the disease. The severity of cardiac involvement, however, does not necessarily correlate with skeletal muscle weakness. Some persons die early as the result of severe cardiomyopathy, whereas others maintain adequate cardiac function until the terminal stages of the disease. Death from respiratory and cardiac muscle involvement usually occurs in young adulthood.

Observation of the child's voluntary movement and a complete family history provide important diagnostic data for the disease. Serum levels of the enzyme creatine kinase, which leaks out of damaged muscle fibers, can be used to confirm the diagnosis. Muscle biopsy, which shows a mixture of muscle cell degeneration and regeneration and reveals fat and scar tissue replacement, is diagnostic of the disorder. Echocardiography, electrocardiography, and chest radiography are used to assess cardiac function. A specific molecular genetic diagnosis is possible by demonstrating defective dystrophin through the use of immunohistochemical staining of sections of muscle biopsy tissue or by deoxyribonucleic acid (DNA) analysis from the peripheral blood. The same methods of DNA analysis may be used on blood samples to establish carrier status in female relatives at risk, such as sisters and cousins. Prenatal diagnosis is possible as early as 12 weeks' gestation by sampling chorionic villi for DNA analysis[10] (see Chapter 6).

Management of the disease is directed toward maintaining ambulation and preventing deformities. Passive stretching, correct or counterposturing, and splints help to prevent deformities. Precautions should be taken to avoid respiratory infections. Although there have been exciting advances in identifying the gene and gene product involved in DMD, there is no known cure.

Disorders of the Neuromuscular Junction

The neuromuscular junction serves as a synapse between a motor neuron and a skeletal muscle fiber.[3] It consists of the axon terminals of a motor neuron and a specialized region of the muscle membrane called the *endplate*. The transmission of impulses at the neuromuscular junction is mediated by the release of the neurotransmitter *acetylcholine* from the axon terminals. Acetylcholine binds to specific receptors in the endplate region of the muscle fiber surface to cause muscle contraction (Fig. 36-6A). Acetylcholine is active in the neuromuscular junction only for a brief period, during which an action potential is generated in the innervated muscle cell. Some of the transmitter diffuses out of the synapse, and the remaining transmitter is rapidly inactivated by an enzyme called *acetylcholinesterase* (see Chapter 34, Fig. 34-25A). The rapid inactivation of acetylcholine allows repeated muscle contractions and gradations of contractile force.

Drug- and Toxin-Induced Disorders

A number of drugs and agents can alter neuromuscular function by changing the release, inactivation, or receptor binding of acetylcholine. Curare acts on the postjunctional membrane of the motor endplate to prevent the depolarizing effect of the neurotransmitter. Neuromuscular transmission is blocked by curare-type drugs during many types of surgical procedures to facilitate relaxation of involved musculature. Drugs such as physostigmine and neostigmine inhibit the action of acetylcholinesterase and allow acetylcholine released from the motor neuron to accumulate. These drugs are used in the treatment of myasthenia gravis.

Neurotoxins from the botulism organism (*Clostridium botulinum*) produce paralysis by blocking acetylcholine release.[3] Clostridia are anaerobic, gram-positive, spore-forming bacilli found worldwide in soils, marine and fresh water sediments, and the intestines of many animals. Classic food-borne botulism occurs through ingestion of

soil-grown foods that are not properly cooked or preserved.[12] Spores can be dormant, are resistant to heat, and germinate in low-acidity and low-nitrate environments. Canned vegetables, items preserved in garlic oil, and soups are usually the cause of sporadic outbreaks. Ingestion of the spores leads to toxin synthesis and absorption of the toxins from the intestinal tract. Wound botulism occurs through colonization of wounds with *C. botulinum*.

Pharmacologic preparations of the botulinum toxin (botulinum type A toxin [Botox] and botulinum type B toxin [Myobloc]) have become available for use in treating eyelid and eye movement disorders such as blepharospasm and strabismus.[13] These agents also are used for treatment of spasmodic torticollis, spasmodic dysphonias (laryngeal dystonia), and other dystonias. The drug is injected into the target muscle using the electrical activity recorded from the tip of a special electromyographic injection needle to guide the injection. The treatment is not permanent and usually needs to be repeated approximately every 3 months.

The aminoglycoside antibiotics (e.g., gentamicin) may produce a clinical disturbance similar to botulism by preventing the release of acetylcholine from nerve endings. The symptoms usually subside rapidly once the drug is eliminated from the body. These drugs are particularly dangerous in persons with preexisting disturbances of neuromuscular transmission, such as myasthenia gravis.

The organophosphates (e.g., malathion, parathion) that are used in some insecticides bind acetylcholinesterase to prevent the breakdown of acetylcholine. They produce excessive and prolonged acetylcholine action with a depolarization block of cholinergic receptors, including those of the neuromuscular junction.[13] The organophosphates are well absorbed from the skin, lungs, gut, and conjunctiva of the eye, making them particularly effective as insecticides but also potentially dangerous to humans. Malathion and certain other organophosphates are rapidly metabolized to inactive products in humans and are considered safe for sale to the general public. The sale of other insecticides, such as parathion, which is not effectively metabolized to inactive products, has been banned. Other organophosphate compounds (e.g., soman) were developed as "nerve gases"; if absorbed in high enough concentrations, they produce lethal effects through depolarization block and loss of respiratory muscle function.

Myasthenia Gravis

Myasthenia gravis is a disorder of the neuromuscular junction that affects impulse transmission between the motor neuron and the innervated muscle cell.[8,14–16] Women are affected nearly three times more commonly than men during early adulthood (age <40 years), whereas the incidence is roughly equal during puberty and after the age of 40 years. After 50 years of age, the incidence is higher in men. The Lambert-Eaton myasthenic syndrome is a special type of myasthenic syndrome that develops in association with neoplasms, particularly small cell carcinoma of the lung[8] (see Chapter 7).

Now recognized as an autoimmune disease, the disorder is caused by an antibody-mediated loss of acetylcholine receptors in the neuromuscular junction[8,14–16] (see Fig. 36-6B). Three mechanisms are thought to underlie the loss of functional acetylcholine receptors: (1) complement-mediated injury to the postsynaptic muscle membrane, (2) accelerated acetylcholine receptor degradation by receptor specific antibodies, and (3) blockade of the receptors by antibodies attached to the acetylcholine-binding sites. The pathogenic antibodies are immunoglobulin G (IgG) and are T-cell dependent. Neonatal myasthenia gravis, caused by placental transfer of the acetylcholine receptor antibody, occurs in about 10% to 15% of infants born to mothers with the disease.[14,15] Spontaneous resolution of symptoms usually occurs within a few months of birth.

The trigger or inciting factor leading to the autoimmune derangement in myasthenia gravis remains unclear, but several lines of evidence implicate the thymus gland in the process. Approximately 75% of persons with myasthenia gravis also have thymic abnormalities, such as a thymoma (i.e., thymus tumor) or thymic hyperplasia (i.e., increased thymus weight from an increased number of thymus cells).[16]

Clinical Manifestations. In persons with myasthenia gravis who have a loss of functional acetylcholine receptors, each release of acetylcholine from the presynaptic membrane results in diminished motor response. This results in both muscle weakness and fatigability with sustained effort. Most commonly affected are the eye and periorbital muscles, with ptosis due to eyelid weakness or diplopia due to weakness of the extraocular muscles as an initial symptom.[14–16] The disease may progress from ocular muscle weakness to generalized weakness, including respiratory muscle weakness. Chewing and swallowing may be difficult. Weakness in limb movement usually is more pronounced in proximal than in distal parts of the extremity, so that climbing stairs and lifting objects are difficult. As the disease progresses, the muscles of the lower face are affected, causing speech impairment. In most persons, symptoms are least evident when arising in the morning, but grow worse with effort and as the day proceeds.

Persons with myasthenia gravis may experience a sudden exacerbation of symptoms and weakness known as *myasthenic crisis*. Myasthenic crisis occurs when muscle weakness becomes severe enough to compromise ventilation to the extent that ventilatory support and airway protection are needed. This usually occurs during a period of stress, such as infection, emotional upset, pregnancy, alcohol ingestion, cold exposure, or surgery. It also can result from inadequate or excessive doses of the anticholinesterase drugs used in treatment of the disorder.

Diagnosis and Treatment. The diagnosis of myasthenia gravis is based on history and physical examination and confirmed by the response to a short-acing anticholinesterase test. Edrophonium (Tensilon) commonly is used for the test.[14–16] The drug, which is administered intravenously, decreases the breakdown of acetylcholine in the neuromuscular junction. When weakness is caused by myasthenia gravis, a dramatic transitory improvement in muscle function occurs. Electrophysiologic studies can be done to demonstrate a decremental

muscle response to repetitive 2- or 3-Hz stimulation of motor nerves. An immunoassay test can be used to detect the presence of antiacetylcholine receptor antibodies circulating in the blood.

Treatment methods include the use of pharmacologic agents; immunosuppressive therapy, including corticosteroid drugs; management of myasthenic crisis; thymectomy; and plasmapheresis or intravenous immunoglobulin.[14–16] Medications that may exacerbate myasthenia gravis, such as the aminoglycoside antibiotics, should be avoided. Pharmacologic treatment with reversible anticholinesterase drugs (i.e., neostigmine, pyridostigmine) inhibits the breakdown of acetylcholine at the neuromuscular junction by acetylcholinesterase. Corticosteroid drugs, which suppress the immune response, are used in cases of a poor response to anticholinesterase drugs and thymectomy. Immunosuppressant drugs (e.g., azathioprine, cyclosporine) also may be used, often in combination with plasmapheresis.

Plasmapheresis removes antibodies from the circulation and provides short-term clinical improvement. It is used primarily to stabilize the condition of persons in myasthenic crisis or for short-term treatment in persons undergoing thymectomy. Intravenous immunoglobulin also produces improvement in persons with myasthenia gravis. Although the effect is temporary, it may last for weeks to months. Intravenous immunoglobulin therapy is very expensive, which limits its use.

Thymectomy, or surgical removal of the thymus, may be used as a treatment for myasthenia gravis. Because the mechanism whereby surgery exerts its effect is unknown, the treatment is controversial. Thymectomy is performed in persons with thymoma, regardless of age, and in persons with generalized myasthenia gravis with onset before 50 years of age.[16]

Peripheral Nerve Disorders

Peripheral nervous system (PNS) disorders involve neurons that are located outside the CNS. They include disorders of the motor and sensory branches of the somatic and visceral nervous systems and the peripheral branches of the autonomic nervous system (see Chapter 34). The result usually is muscle weakness, with or without atrophy, and sensory changes. The disorder can involve a single nerve (mononeuropathy) or multiple nerves (polyneuropathy).

Unlike the nerves of the CNS, peripheral nerves are fairly strong and resilient. They contain a series of connective tissue sheaths that enclose their nerve fibers. An outer fibrous sheath called the *epineurium* surrounds the medium-sized to large nerves; inside, a sheath called the *perineurium* invests each bundle of nerve fibers; and within each bundle, a delicate sheath of connective tissue known as the *endoneurium* surrounds each nerve fiber (see Chapter 34, Fig. 34-2). Inside the endoneurial sheath are the Schwann cells that produce the myelin sheath that surrounds the peripheral nerves. Each Schwann cell can myelinate only one segment of a single axon—the one that it covers—so that myelination of an entire axon requires the participation of a long line of these cells.

Peripheral Nerve Injury and Repair

There are two main types of peripheral nerve injury based on the target of the insult: segmental demyelination involving the Schwann cell and axonal degeneration involving the neuronal cell body or its axon.[8,17] The peripheral nerve disorders can affect a spinal nerve, a peripheral nerve trunk (mononeuropathies), or multiple peripheral nerves (polyneuropathies).

Segmental Demyelination. Segmental demyelination occurs when there is a disorder of the Schwann cell (as in hereditary motor and sensory neuropathies) or damage to the myelin sheath (e.g., Guillain-Barré syndrome) without a primary abnormality of the axon. It typically affects some Schwann cells while sparing others. The disintegrated myelin is engulfed initially by Schwann cells and then by macrophages. The denuded axon provides a stimulus for remyelination and the population of cells within the endoneurium has the capacity to replace the injured Schwann cells. These cells proliferate and encircle the axon, and in time remyelinate the denuded portion. However, the new myelin sheath is thin in proportion to the axon, and in time, many chronic demyelinating neuropathies give way to axonal injury.

Axonal Degeneration. Axonal degeneration is caused by primary injury to a neuronal cell body or its axon. Damage to the axon may be due either to a focal event occurring at some point along the length of the nerve (e.g., trauma or ischemia) or to a more generalized abnormality affecting the neuronal cell body (neuropathy).

Damage to a peripheral nerve axon, whether by injury or neuropathy, results in degenerative changes, followed by breakdown of the myelin sheath and Schwann cells. In distal axonal degeneration, the proximal axon and neuronal cell body, which synthesizes the material required for nourishing and maintaining the axon, remain intact. In neuropathies and crushing injuries, in which the endoneurial tube remains intact, the outgrowing fiber grows down this tube to the structure that was originally innervated by the neuron (Fig. 36-7). However, it can take weeks or months for the regrowing fiber to reach its target organ and for communicative function to be reestablished. More time is required for the Schwann cells to form new myelin segments and for the axon to recover its original diameter and conduction velocity.

The successful regeneration of a nerve fiber in the PNS depends on many factors. If a nerve fiber is destroyed relatively close to the neuronal cell body, the chances are that the nerve cell will die, and if it does, it will not be replaced. If a crushing type of injury has occurred, partial or often full recovery of function occurs. Cutting-type trauma to a nerve is an entirely different matter. Connective scar tissue forms rapidly at the wound site, and when it does, only the most rapidly regenerating axonal branches are able to get through to the intact distal endoneurial tubes. A number of scar-inhibiting agents have been used in an effort to reduce this hazard, but have met with only moderate success. In another attempt to improve nerve regeneration, various types of tubular

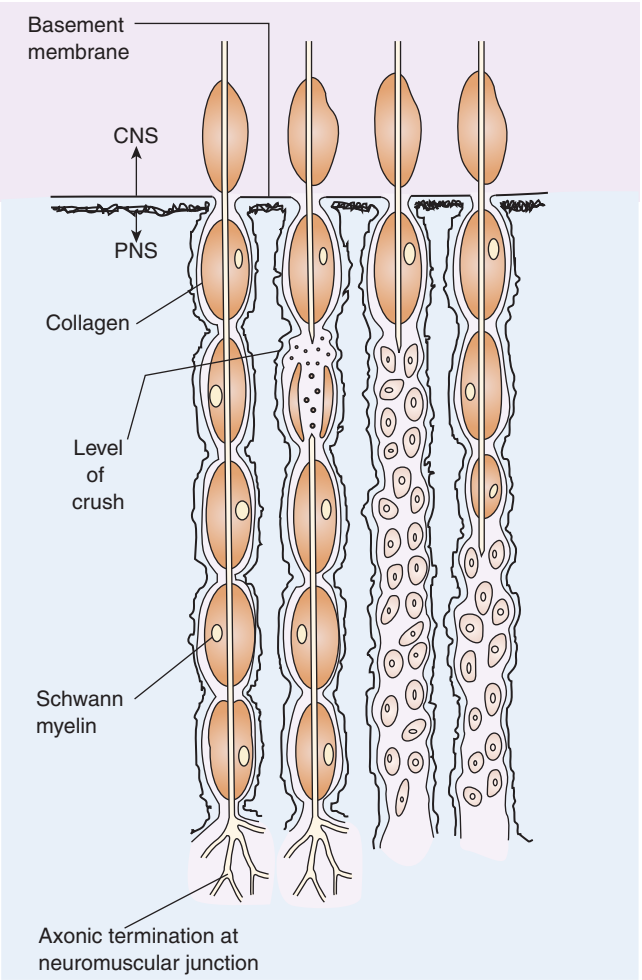


FIGURE 36-7. Sequential stages of efferent axon degeneration and regeneration within its endoneurial tube, after peripheral nerve crush injury.

implants have been placed to fill longer gaps in the endoneurial tube.

Neuropathies involving the neuronal cell body are much less common than those affecting the axons. In these cases, there is little potential for recovery of function because death of the neuronal cells precludes axonal regeneration.

Mononeuropathies

Mononeuropathies usually are caused by localized conditions such as trauma, compression, or infections that affect a single spinal nerve, plexus, or peripheral nerve trunk. Fractured bones may lacerate or compress nerves, excessively tight tourniquets may injure nerves directly or produce ischemic injury, and infections such as herpes zoster may affect a single segmental afferent nerve. Recovery of nerve function usually is complete after compression lesions and incomplete or faulty after nerve transection.

Carpal Tunnel Syndrome. Carpal tunnel syndrome is a relatively common entrapment mononeuropathy.[18–20] It

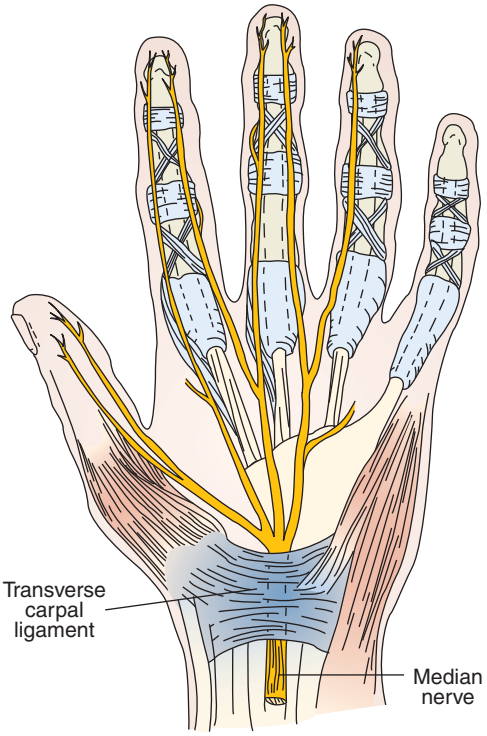


FIGURE 36-8. Carpal tunnel syndrome: compression of the median nerve by the transverse carpal ligament. (Courtesy of Carole Russell Hilmer, C.M.I.)

is caused by compression of the median nerve as it travels with the flexor tendons through a canal made by the carpal bones and transverse carpal ligament (Fig. 36-8). The condition can be caused by a variety of conditions that produce a reduction in the capacity of the carpal tunnel (i.e., bony or ligamentous changes) or an increase in the volume of the tunnel contents (i.e., inflammation of the tendons, synovial swelling, or tumors). Carpal tunnel syndrome may be a feature of a number of systemic diseases, such as rheumatoid arthritis, hyperthyroidism, acromegaly, and diabetes mellitus. Most cases, however, are due to repetitive use of the wrist (i.e., flexion–extension movements and stress associated with pinching and gripping motions).

Carpal tunnel syndrome is characterized by pain, paresthesia (tingling), and numbness of the thumb and first, second, third, and half of the fourth digits of the hand; pain in the wrist and hand, which worsens at night; atrophy of the abductor pollicis muscle; and weakness in precision grip. All of these abnormalities may contribute to clumsiness of fine motor activity.

Diagnosis usually is based on sensory disturbances confined to median nerve distribution and a positive Tinel or Phalen sign.[18,20] The *Tinel sign* is the development of a tingling sensation radiating into the palm of the hand that is elicited by light percussion over the median nerve at the wrist. The *Phalen maneuver* is performed by having the person hold the wrist in complete flexion for approximately a minute; if numbness and paresthesia along the median nerve are reproduced or

exaggerated, the test result is considered to be positive. Electromyography and nerve conduction studies often are done to confirm the diagnosis and exclude other causes of the disorder.

Treatment includes a variety of options including nonsteroidal anti-inflammatory agents, injection of corticosteroids, immobilization of the wrist with splints, rehabilitation modalities (e.g., ultrasound, stretching, and strengthening exercises), and surgery. Measures to decrease the causative repetitive movements should be initiated. Splints may be confined to nighttime use. When splinting is ineffective, corticosteroids may be injected into the carpal tunnel to reduce inflammation and swelling. Surgical intervention consists of operative division of the volar carpal ligaments as a means of relieving pressure on the median nerve.

Polyneuropathies

Polyneuropathies involve demyelination or axonal degeneration of multiple peripheral nerves that leads to symmetric sensory, motor, or mixed sensorimotor deficits. Typically, the longest axons are involved first, with symptoms beginning in the distal part of the extremities. If the autonomic nervous system is involved, there may be postural hypotension, constipation, and impotence. Polyneuropathies can result from immune mechanisms (e.g., Guillain-Barré syndrome), toxic agents (e.g., arsenic polyneuropathy, lead polyneuropathy, alcoholic polyneuropathy), and metabolic diseases (e.g., diabetes mellitus, uremia). Different causes tend to affect axons of different diameters and to affect sensory, motor, or autonomic neurons to different degrees.

Guillain-Barré Syndrome. Guillain-Barré syndrome is an acute life-threatening polyneuropathy.[18,21–24] The syndrome defines a clinical entity that is characterized by rapidly progressive limb weakness and loss of tendon reflexes. It has been described as the most common cause of acute, flaccid paralysis in developed countries of the world, now that poliomyelitis has been eliminated. As a syndrome, there are several subtypes of the disorder, including pure motor axonal degeneration, axonal degeneration of both motor and sensory nerves, and a variant characterized by ophthalmoplegia, ataxia, and areflexia.

Guillain-Barré syndrome is thought to be an acute-onset immune-mediated demyelinating neuropathy. Approximately two thirds of patients report having had an acute, influenza-like illness before the onset of symptoms.[18] Controlled epidemiologic studies have linked it to infection with *Campylobacter jejuni,* cytomegalovirus, Epstein-Barr virus, and mycoplasma pneumoniae. A *C. jejuni* infection is often an antecedent to symptoms. In a few cases, the patient reports receiving a vaccination prior to onset of Guillain-Barré syndrome.

The disorder is characterized by progressive ascending muscle weakness of the limbs, producing a symmetric flaccid paralysis. Symptoms of paresthesia and numbness often accompany the loss of motor function. The rate of disease progression varies, and there may be disproportionate involvement of the upper or lower extremities. Paralysis may progress to involve the respiratory muscles. Autonomic nervous system involvement that causes postural hypotension, arrhythmias, facial flushing, abnormalities of sweating, and urinary retention is common. Pain is another common feature of Guillain-Barré syndrome. It is most common in the shoulder girdle, back, and posterior thighs and occurs with even the slightest of movements.

Guillain-Barré syndrome usually is a medical emergency. There may be a rapid development of ventilatory failure and autonomic disturbances that threaten circulatory function. Treatment includes support of vital functions and prevention of complications such as skin breakdown and thrombophlebitis. Clinical trials have shown the effectiveness of plasmapheresis in decreasing morbidity and shortening the course of the disease. Treatment is most effective if initiated early in the course of the disease. High-dose intravenous immunoglobulin therapy also has proved effective. Approximately 80% to 90% of persons with the disease achieve a full and spontaneous recovery within 6 to 12 months.[23]

Back Pain and Spinal Nerve Root Disorders

Back pain is a common problem that affects an estimated two thirds of people at least once in their lifetime.[25] Back pain can result from a number of causes, including problems involving the vertebrae and intervertebral joints, back muscles and ligaments, and disorders of the spinal nerve roots. Perhaps the most common are musculoligamentous injuries and age-related degenerative changes in the intervertebral disks and facet joints.[26] Other causes include spinal nerve root compression due to intervertebral disk herniation and narrowing of the central canal due to spinal stenosis.

The spinal cord and spinal nerve roots are located within the vertebral canal. The anterior portion of the spine consists of cylindrical vertebral bodies separated by intervertebral disks and held together by the anterior and posterior longitudinal ligaments (Fig. 36-9A).

The posterior portion of the spine consists of the vertebral arches, each consisting of paired transverse processes, one posterior spinous process, and two superior articular facets. The functions of the posterior spine are to protect the spinal cord and nerves within the spinal canal and to stabilize the spine by providing sites for the attachment of muscles and ligaments.

Pain-sensitive structures in the spine include the periosteum of the vertebrae, dura, facet joints, annulus fibrosus of the intervertebral disk, and posterior longitudinal ligament. Pain sensation is conveyed through afferent fibers in the spinal nerves. Local pain is caused by stretching of pain-sensitive structures that compress or irritate sensory nerve endings. Pain referred to the back may arise from abdominal or pelvic structures. Pain associated with muscle spasm is usually dull, and often accompanied by abnormal posture and stiff paraspinal muscles.

Nerve root injury (radiculopathy) is a common cause of neck, arm, low back, and leg pain. The pain is typically

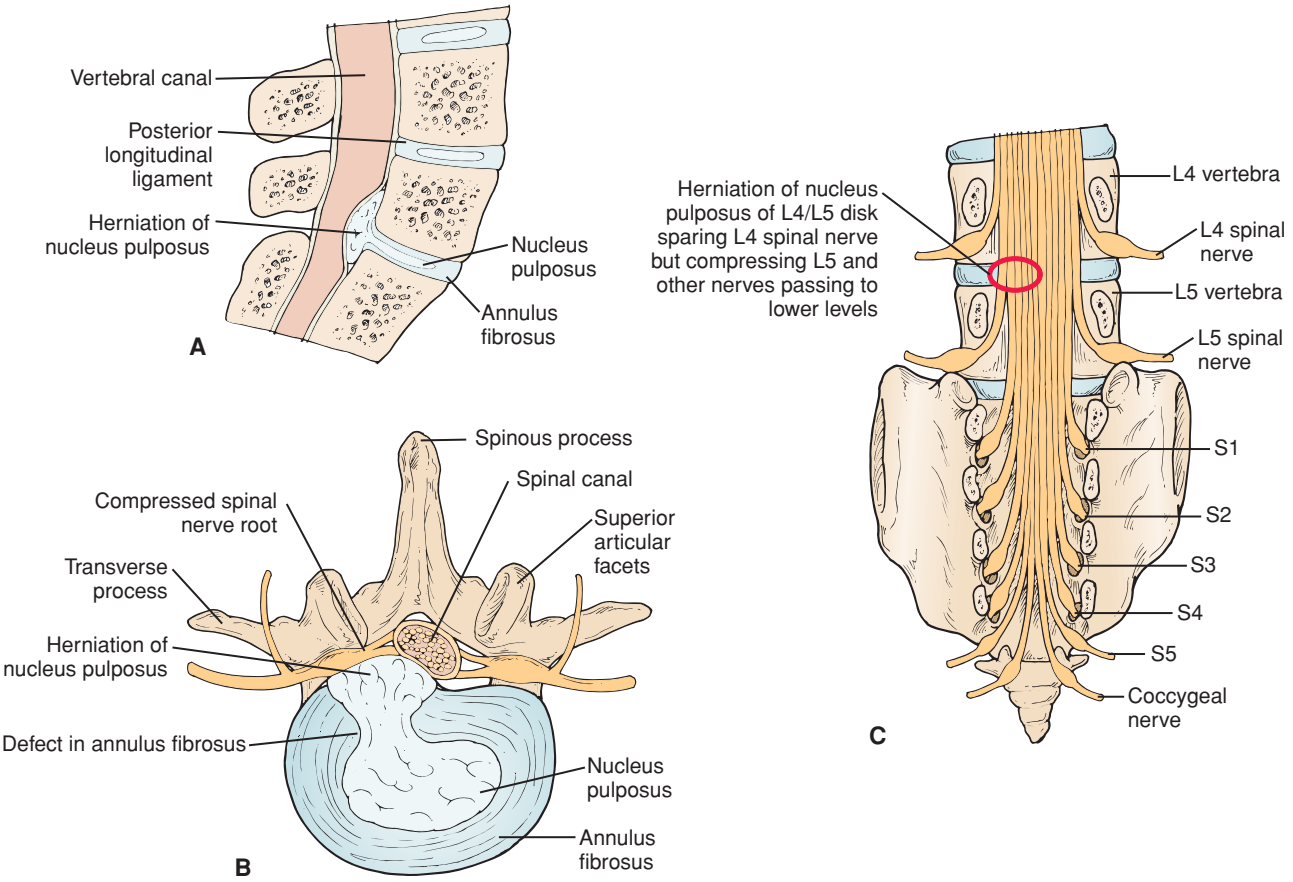


FIGURE 36-9. Herniated intervertebral disk. **(A)** Longitudinal section. **(B)** Cross-section. **(C)** Location of L4 to L5 and S1 to S5 spinal nerves, with site of L4/L5 herniation of nucleus pulposus indicated. (Modified from Moore K.L., Dalley A.F. [2006]. *Clinically oriented anatomy* [5th ed., p. 503]. Philadelphia: Lippincott Williams & Wilkins.)

sharp and radiates to the arm or leg within the territory of the spinal root. Disorders affecting the upper lumbar segments tend to be referred to the lumbar area, groin, or anterior thigh; and those affecting the lower lumbar and upper sacral segments, to the buttocks and posterior thighs.

Diagnosis and Treatment. Although back problems are commonly attributed to a herniated disk, most acute back disorders are cause by less serious problems.[18,25–28] The diagnostic challenge is to identify those persons who require further evaluation for more serious problems such as malignancies, compression fractures, and vascular disorders. The diagnostic measures used in the evaluation of back pain include history and physical examination, including a thorough neurologic examination. Other diagnostic methods may include radiographs of the back and magnetic resonance imaging (MRI).

Treatment of back pain usually is conservative and consists of analgesic medications, muscle relaxants, and instruction in the correct mechanics for lifting and methods of protecting the back. Pain relief is usually provided using nonsteroidal anti-inflammatory drugs. Muscle relaxants may be used on a short-term basis. Bed rest, once the mainstay of conservative therapy, is now understood to be ineffective for acute back pain. Conditioning exercises of the trunk muscles, particularly the back extensors, are often recommended.

Intervertebral Disk Disorders. The intervertebral disk is considered the most critical component of the load-bearing structures of the spinal column. It consists of a soft, gelatinous center called the *nucleus pulposus,* which is encircled by a strong, ringlike collar of fibrocartilage called the *annulus fibrosus.*[29] The structural components of the disk make it capable of absorbing shock and changing shape while allowing movement. With dysfunction, the nucleus pulposus can be squeezed out of place and herniate through the annulus fibrosus, a condition referred to as a *herniated* or *slipped disk* (see Fig. 36-9A, B).

The intervertebral disk can become dysfunctional because of trauma, the effects of aging, or degenerative disorders of the spine. Protrusion of the nucleus pulposus usually occurs posteriorly and toward the intervertebral foramen and its contained spinal nerve root, where the annulus fibrosus is relatively thin and poorly supported by either the posterior or anterior ligaments[28,29] (see Fig. 36-9A). Trauma results from activities such as lifting while in the flexed position, slipping, falling on the buttocks or back, or suppressing a sneeze. With aging,

the gelatinous center of the disk dries out and loses much of its elasticity.

The level at which a herniated disk occurs is important (see Fig. 36-9C). The cervical and lumbar regions are the most flexible areas of the spine and are most often involved in disk herniations. Usually, herniation occurs at the lower levels of the lumbar spine, where the mass being supported and the bending of the vertebral column are greatest. When the injury occurs in the lumbar area, only the nerve fibers of the cauda equina are involved. Because these elongated dorsal and ventral roots contain endoneurial tubes of connective tissue, regeneration of the nerve fibers is likely. However, months may be required for full recovery to occur because of the distance to the innervated muscle or skin of the lower limbs.

The signs and symptoms of a herniated disk are localized to the area of the body innervated by the spinal nerve roots and include both motor and sensory manifestations (Fig. 36-10). Pain is the first and most common symptom of a herniated disk. The nerve roots of L4, L5, S1, S2, and S3 give rise to a syndrome of back pain, sometimes referred to as *sciatica*, which spreads down the back of the leg and over the sole of the foot. The pain is usually intensified with coughing, sneezing, straining, stooping, standing, and the jarring motions that occur during walking or riding. Slight motor weakness may occur, although major weakness is rare. The most common sensory deficits from spinal nerve root compression are paresthesias and numbness, particularly of the leg and foot. Knee and ankle reflexes also may be diminished or absent.

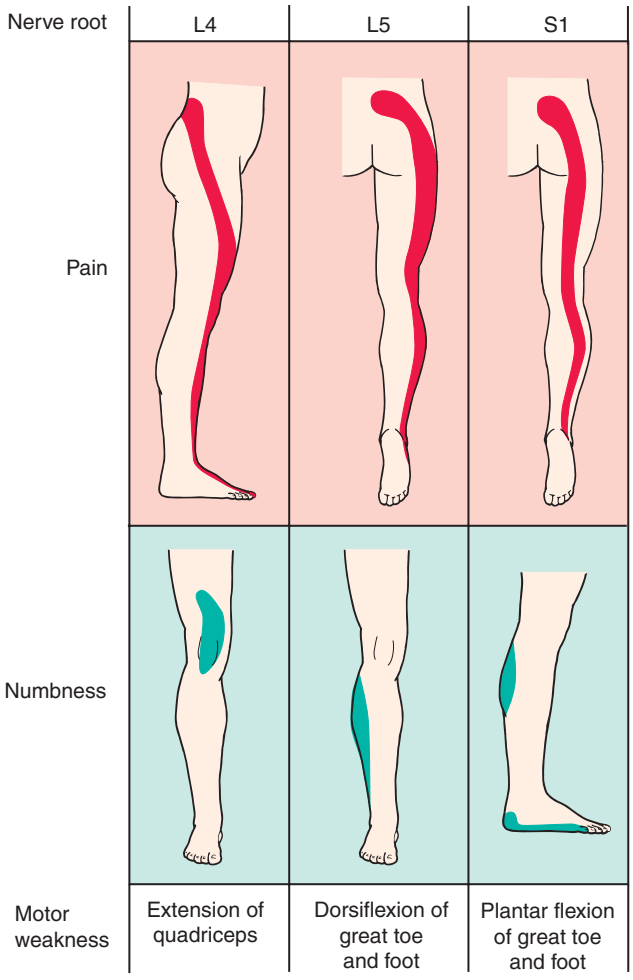


FIGURE 36-10. Dermatomes of the leg (L1 through S5) where pain and numbness would be experienced with spinal root irritation.

A herniated disk must be differentiated from other causes of acute back pain. Diagnostic measures include history and physical examination. Neurologic assessment includes testing of muscle strength and reflexes. The straight-leg test is an important diagnostic maneuver. It is done in the supine position and is performed by passively raising the person's leg. The test can also be done by slowly extending the knee while the person sits on a table, with both hip and knee flexed at 90 degrees. The maneuver is designed to apply traction along the nerve root, which exacerbates pain if the nerve root is acutely inflamed. Normally, it is possible to raise the leg approximately 90 degrees without causing discomfort of the hamstring muscles. The test result is positive if pain is produced when the leg is raised to 60 degrees or less. Other diagnostic methods include radiographs of the back, MRI, computed tomography (CT), and CT myelography.

Treatment usually is similar to that for back pain. Surgical treatment may be indicated when there is documentation of herniation by an imaging procedure, consistent pain, or consistent neurologic deficit that failed to respond to conservative therapy.

Back Pain Emergencies. Although acute back pain is usually a non–life-threatening condition, in 5% to 10% of persons it is a manifestation of a more serious pathologic process.[30] Vascular catastrophes (ruptured abdominal aortic aneurysms and dissecting aortic aneurysms), malignancy, spinal cord compression syndromes, and infectious processes may all present as acute back pain.

Clinical findings, commonly referred to as *red flags,* that indicate the possibility of more serious disease include gradual onset of pain; age younger than 20 years or older than 50 years; thoracic back pain; history of trauma, fever, chills, night sweats, immunosuppression, or malignancy; unintentional weight loss; recent procedure known to cause bacteremia; and history of intravenous drug use.[30] The gradual onset of pain may be indicative of malignancy or infection. Back pain that begins before 20 years of age suggests congenital or developmental disorders, and new-onset pain in persons 50 years of age or older is more likely to be a manifestation of serious conditions such as an aortic aneurysm, malignancy, or compression fracture. Pain that is aggravated by lying down is a red flag for malignancy or infection, and pain that improves with sitting or slight flexion of the spine suggests the presence of spinal stenosis. Persons with symptoms of large or rapidly evolving neurologic deficits require urgent evaluation for possible cauda equina masses, epidural abscess, or central disk herniation. Signs and symptoms that suggest possible cauda equina syndrome are low back pain associated with bilateral leg weakness (from multiple lumbar nerve root compressions), saddle area numbness, bowel and bladder

incontinence, or impotence (indicating multiple sacral nerve compressions).[25,30] Reports of neurologic symptoms such as paresthesia, motor weakness, and gait abnormalities also require additional diagnostic tests to rule out spinal cord compression.

In summary, the motor unit consists of the LMN, the neuromuscular junction, and the skeletal muscle that the nerve innervates. Disorders of the neuromuscular unit include muscular dystrophy, myasthenia gravis, and peripheral nerve disorders. *Muscular dystrophy* is a term used to describe a number of disorders that produce progressive deterioration of skeletal muscle. Muscle necrosis is followed by fat and connective tissue replacement. One form, Duchenne muscular dystrophy, is inherited as an X-linked trait and transmitted by the mother to her male offspring. Myasthenia gravis is a disorder of the neuromuscular junction resulting from a deficiency of functional acetylcholine receptors, which causes weakness of the skeletal muscles. Because the disease affects the neuromuscular junction, there is no loss of sensory function. The most common manifestations are weakness of the eye muscles, with ptosis and diplopia.

Peripheral nerve disorders involve motor and sensory neurons outside the CNS. There are two main types of peripheral nerve injury based on the target of the insult: segmental demyelination involving the Schwann cell and axonal degeneration involving the nerve axon or its cell body. Peripheral nerve disorders include mononeuropathies, involving a single spinal nerve, plexus, or peripheral nerve, and polyneuropathies, involving demyelination or axonal degeneration of multiple peripheral nerves that leads to symmetric sensory, motor, or mixed sensorimotor deficits. Carpal tunnel syndrome, a mononeuropathy, is caused by compression of the medial nerve as it passes through the carpal tunnel in the wrist. Guillain-Barré syndrome is a subacute polyneuropathy, probably due to immune mechanisms, that causes progressive ascending motor, sensory, and autonomic nervous system manifestations. Respiratory involvement may occur and necessitate mechanical ventilation.

Back pain can result from a number of causes, including muscle and ligament strains, age-related degenerative spine disorders, disk herniation, and narrowing of the central vertebral canal due to spinal stenosis. Most cases of back pain are thought to be due to muscular or ligamentous injuries that are self-limited and treated conservatively. Herniation or protrusion of the gelatinous pulposus through the anulus fibrosus of an intervertebral disk causes pain and numbness related to the area of the body that is innervated by the affected nerve root. Although back pain is most commonly caused by nonspecific conditions such as muscle strain, the diagnostic challenge is to identify persons who require urgent evaluation for conditions such as vascular disorders (ruptured abdominal aneurysm, aortic dissection), osteomyelitis, malignancies, compression fractures, and cauda equina syndrome.

Disorders of the Cerebellum and Basal Ganglia

Disorders of the Cerebellum

The cerebellum is a cauliflower-shaped structure located in the posterior fossa and attached to the pons, medulla, and midbrain by the three paired cerebellar peduncles[3,31] (see Chapter 34). It has sometimes been referred to as the *silent area* of the brain because electrical stimulation does not produce any conscious sensation and rarely causes any motor movements.[3] However, removal or damage to the cerebellum causes movements to become highly abnormal. The cerebellum is especially vital during rapid muscular activities such as running, typing, and even talking. Loss of cerebellar function can result in total incoordination of these functions even though paralysis does not occur.

The functions of the cerebellum are integrated into many connected afferent and efferent pathways throughout the brain. An extensive and important afferent pathway is the *corticopontocerebellar* pathway, which originates in the cerebral motor and premotor cortices as well as the somatosensory cortex. Other important afferent pathways link the cerebellum to input from the basal ganglia, muscle and joint tension information from the stretch receptors, visual input from the eyes, and balance and equilibrium sensation from the vestibular system in the inner ear. There are three general efferent pathways leading out of the cerebellum: (1) the *vestibulocerebellar pathway* that functions in close association with the brain stem vestibular nuclei to maintain equilibrium and posture; (2) the *spinocerebellar pathway* that provides the circuitry for coordinating the movements of the distal portions of the limbs, especially the hands and fingers; and (3) the *cerebrocerebellar pathway* that transmits output information in the upward direction to the cerebral cortex, functioning in a feedback manner with the motor and somatosensory systems to coordinate sequential body and limb movements.

Cerebellum-Associated Movement Disorders

The signs of cerebellar dysfunction can be grouped into three classes: vestibulocerebellar disorders, cerebellar ataxia or decomposition of movement, and cerebellar tremor. These disorders occur on the side of cerebellar damage, whether because of congenital defect, vascular accident, or growing tumor. Visual monitoring of movement cannot compensate for cerebellar defects, and the movement abnormalities occur whether the eyes are open or closed.

Damage to the part of the cerebellum associated with the vestibular system leads to difficulty or inability to maintain a steady posture of the trunk, which normally requires constant readjusting movements. This is seen as an unsteadiness of the trunk, called *truncal ataxia,* and can be so severe that standing is not possible. The ability to fix the eyes on a target also can be affected. Constant conjugate readjustment of eye position, called *nystagmus,* results and makes reading extremely difficult,

especially when the eyes are deviated toward the side of cerebellar damage.

Cerebellar ataxia and tremor are different aspects of defects in the smooth, continuously correcting functions. Cerebellar dystaxia or, if severe, ataxia is characterized by a decomposition of movement, with each succeeding component of a complex movement occurring separately instead of being blended into a smoothly proceeding action. Because ethanol specifically affects cerebellar function, persons who are inebriated often walk with a staggering and unsteady gait. Rapid alternating movements such as supination–pronation–supination of the hands are jerky and performed slowly. Reaching to touch a target breaks down into small sequential components, each going too far, followed by overcorrection. The finger moves jerkily toward the target, misses, corrects in the other direction, and misses again, until the target is finally reached. This is called *over- and underreaching* or *dysmetria*.

Cerebellar tremor is a rhythmic back-and-forth movement of a finger or toe that worsens as the target is approached. The tremor results from the inability of the damaged cerebellar system to maintain ongoing fixation of a body part and to make smooth, continuous corrections in the trajectory of the movement; overcorrection occurs, first in one direction and then the other. Often, the tremor of an arm or leg can be detected during the beginning of an intended movement. The common term for cerebellar tremor is *intention tremor.* Cerebellar function, as it relates to tremor, can be assessed by asking a person to touch one heel to the opposite knee, to gently move the toes along the back of the opposite shin, or to touch the nose with a finger.

Cerebellar function also can affect the motor skills of chewing, swallowing, and speech. Normal speech requires smooth control of respiratory muscles and highly coordinated control of the laryngeal, lip, and tongue muscles. Cerebellar dysarthria is characterized by slow, slurred speech of continuously varying loudness. Rehabilitative efforts directed by speech therapists include learning to slow the rate of speech and to compensate as much as possible through the use of less affected muscles.

Disorders of the Basal Ganglia

The basal ganglia are a group of deep, interrelated subcortical nuclei that play an essential role in control of movement. They function in the organization of inherited and highly learned and rather automatic movement programs, especially those affecting the trunk and proximal limbs. The basal ganglia are thought to be particularly important in starting, stopping, and monitoring movements executed by the cortex, especially those that are relatively slow and sustained, or stereotyped. They also help to regulate the intensity of these movements, and they act to inhibit antagonistic or unnecessary movements. The function of the basal ganglia is not limited to motor functions; they also are involved in cognitive and perceptual functions.

The structural components of the basal ganglia include the caudate nucleus, putamen, and globus pallidus.[3,32] They are located lateral and caudal to the thalamus, occupying a large portion of the interior of both cerebral hemispheres. The caudate and putamen are collectively referred to as the *striatum,* and the putamen and globus pallidus form a wedge-shaped region called the *lentiform nucleus.* Two other structures, the *substantia nigra* of the midbrain and the *subthalamic nucleus* of the diencephalon, are considered part of the basal ganglia (Fig. 36-11). The dorsal part of the substantia nigra contains cells that synthesize dopamine and are rich in a black pigment called *melanin.* The high concentration of melanin gives the structure a black color, hence the name *substantia nigra.* The axons of the substantia nigra form the *nigrostriatal pathway,* which supplies dopamine to the striatum. The subthalamic nucleus lies just below the thalamus and above the anterior portion of the substantia nigra. The glutaminergic cells of this nucleus are the only excitatory projections to the basal ganglia.

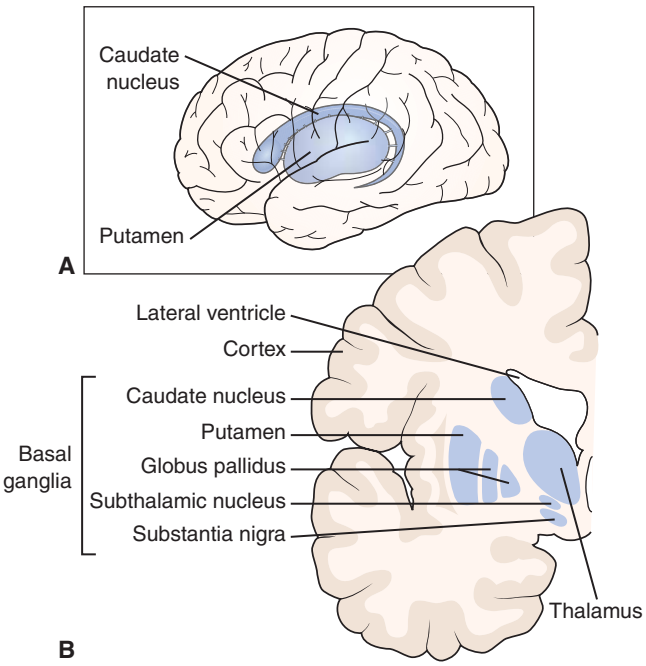


FIGURE 36-11. **(A)** Lateral view of the basal ganglia. **(B)** Coronal section showing the basal ganglia in relation to surrounding structures.

The basal ganglia have input structures that receive afferent information from the cerebral cortex and thalamus, internal circuits that connect the various structures of the basal ganglia, and output structures that deliver information to other brain centers. The neostriatum represents the major input structure for the basal ganglia. Virtually all areas of the cortex and afferents from the thalamus project to the neostriatum. The output areas of the basal ganglia, including the lateral globus pallidus, have both ascending and descending components. The major ascending output is transmitted to thalamic nuclei, which process all incoming information that is transmitted to the cerebral cortex. Descending output is directed to the midbrain, brain stem, and spinal cord.

The output functions of the basal ganglia are mainly inhibitory. Looping circuits from specific cortical areas

pass through the basal ganglia to modulate the excitability of specific thalamic nuclei and control the cortical activity involved in highly learned, automatic, and stereotyped motor functions. The most is known about the inhibitory basal ganglia loop that is involved in modulating cortical motor control. This loop regulates the release of stereotyped movement patterns that add efficiency and gracefulness to cortically controlled movements. These movements include inherited patterns that add precision, efficiency, and balance to motion, such as the swinging of the arms during walking and running and the highly learned automatic postural and follow-through movements of throwing a ball or swinging a bat.

The basal ganglia also have a cognitive function in that they monitor sensory information coming into the brain and apply it to information stored in memory as a means of planning and sequencing motor movements.[3] The cognitive control of motor activities determines, subconsciously and within seconds, which patterns of movement will be needed to achieve a goal. The caudate nucleus, which receives large amounts of input from the association areas of the brain, plays a major role in the cognitive control of motor activity.

Multiple pathways provide excitatory signals that balance the large number of inhibitory signals transmitted by γ-aminobutyric acid (GABA) and dopaminergic neurons. One of these circuits involves a *neostriatal inhibitory projection* on the substantia nigra. The substantia nigra projects dopaminergic axons back on the striatum. A deficiency in the dopaminergic projection of this modulating circuit is implicated in parkinsonism. The function of the striatum also involves local excitatory cholinergic interneurons, and their destruction is thought to be related to the choreiform movements of Huntington disease, another basal ganglia–related syndrome (see Chapter 37).

Basal Ganglia–Associated Movement Disorders

Disorders of the basal ganglia comprise a complex group of motor disturbances characterized by tremor and other involuntary movements, changes in posture and muscle tone, and poverty and slowness of movement. They include tremors and tics, hypokinetic disorders, and hyperkinetic disorders[1] (Table 36-1).

Unlike disorders of the motor cortex and corticospinal (pyramidal) tract, lesions of the basal ganglia disrupt movement but do not cause paralysis. The various types of involuntary movements often occur in combination and appear to have a common underlying cause. Recent studies indicate that hypokinetic and hyperkinetic disorders can be explained as specific disturbances in the indirect and direct pathways that link the basal ganglia with the thalamocortical motor circuit.[32] Accordingly, overactivity of the indirect pathway relative to the direct pathway would result in hypokinetic disorders such as Parkinson disease, and underactivity of the indirect pathway would result in hyperkinetic disorders such as chorea and ballismus.

Parkinson Disease

Parkinson disease is a progressive degenerative disorder of basal ganglia function that results in variable combinations of tremor, rigidity, and bradykinesia.[33,34] Parkinson disease is the second most common neurodegenerative disease

TABLE 36-1 Characteristics of Basal Ganglia–Associated Movement Disorders

Movement Disorder	Characteristics
Tremor	Involuntary, oscillating contractions of opposing muscle groups around a joint Usually fairly uniform in frequency and amplitude Can occur as resting tremors and postural tremors, which occur when the part is maintained in a stable position
Hypokinetic disorders	Slowness in initiating movement, and reduced range and force of the movement (bradykinesia)
Chorea	Irregular wriggling and writhing movements Accentuated by movement and by environmental stimulation; they often interfere with normal movement patterns May be grimacing movements of the face, raising the eyebrows, rolling of the eyes, and curling, protrusion, withdrawal of the tongue In the limbs, the movements largely are distal; there may be piano playing–type movements with alternating extension and flexion of the fingers
Athetosis	Continuous, wormlike, twisting and turning motions of the joints of a limb or the body
Ballismus	Violent, sweeping, flinging motions, especially of the limbs on one side of the body (hemiballismus)
Dystonia	Abnormal maintenance of a posture resulting from a twisting, turning movement of the limbs, neck, or trunk Often the result of simultaneous contraction of agonist and antagonist muscles Can result in grotesque and twisted postures
Dyskinesias	Bizarre wriggling and writhing movements Frequently involve the face, mouth, jaw, and tongue, causing grimacing, pursing of the lips, or protrusion of the tongue Limbs affected less often Tardive dyskinesia is an untoward reaction that can develop with long-term use of some antipsychotic medications

after Alzheimer disease. It usually begins after 50 years of age, with the prevalence increasing to 4% to 5% in those older than 85 years of age.[33]

The clinical syndrome arising from the degenerative changes in basal ganglia function often is referred to as *parkinsonism*. Parkinson disease, the most common form of parkinsonism, is named after James Parkinson, a British physician who first described the disease in a paper he published in 1817 on the "shaking palsy."[35] In Parkinson disease, also known as *idiopathic parkinsonism,* dopamine depletion results from degeneration of the dopamine nigrostriatal system. Parkinsonism can also develop as a postencephalitic syndrome, as a side effect of therapy with antipsychotic drugs that block dopamine receptors, as a toxic reaction to a chemical agent, or as an outcome of severe carbon monoxide poisoning.[36] Postencephalitic parkinsonism was a particular problem in the 1930s and 1940s as a result of an outbreak of lethargic encephalitis (sleeping sickness) that occurred in 1914 to 1918. Drug-induced parkinsonism can follow the administration of antipsychotic drugs in high doses (e.g., phenothiazines, butyrophenones). These drugs block dopamine receptors and dopamine output by the cells of the substantia nigra. Symptoms of parkinsonism also may accompany conditions such as cerebral vascular disease, brain tumors, repeated head trauma, or degenerative neurologic diseases that structurally damage the nigrostriatal pathway.

The primary brain abnormality found in persons with Parkinson disease is degeneration of the nigrostriatal pathway, with subsequent reduction in striatal concentrations of dopamine. Other brain areas are affected to a lesser extent.[37,38] Although the cause of Parkinson disease is still unknown, it is widely believed that most cases are caused by an interaction of environmental and genetic factors. Over the past several decades, several pathologic processes (e.g., oxidative stress, apoptosis, and mitochondrial disorders) that might lead to degeneration have been identified. Of interest in terms of research was the development of Parkinson disease in several persons who had attempted to make a narcotic drug and instead synthesized a compound called *MPTP (1-methyl-phenyl-2,3,6-tetrahydropyridine)*.[36] This compound selectively destroys the dopaminergic neurons of the substantia nigra. This incident prompted investigations into the role of toxins that are produced by the body as a part of metabolic processes and those that enter the body from outside sources in the pathogenesis of Parkinson disease. One theory is that the auto-oxidation of catecholamines such as dopamine may injure neurons in the substantia nigra. There is increasing evidence that the development of Parkinson disease may be related to oxidative metabolites of this process and the inability of neurons to render these products harmless. MPTP is an inhibitor of the mitochondrial electron transport system that functions in the inactivation of these metabolites, suggesting that it may produce Parkinson disease in a manner similar to that of the naturally occurring disease.[36,37]

The recent discovery of inherited forms of Parkinson disease suggests that genetic factors may also play a role in the pathogenesis of early-onset Parkinson disease.[37–39] The first genetic mutation associated with Parkinson disease was found in the gene encoding α-*synuclein*, a member of a small family of proteins that are expressed preferentially in the substantia nigra.[37,38] Although mutations in this gene cause a very rare, autosomal dominant form of the disease, the mutation has received considerable attention because α-synuclein is one of the major components of the Lewy bodies that are found in the brain tissue of persons with Parkinson disease. Mutations in a second gene that encodes the protein *parkin* is associated with an autosomal recessive, early-onset form of Parkinson disease.[37] Numerous other genetic loci have been linked to Parkinson disease, but the genes remain to be mapped. Thus, the genetics of Parkinson disease are beginning to provide molecular clues that help explain the etiology of parkinsonism, just as epidemiologic studies have delineated an array of environmental modulators of susceptibility, which can now be explored in the context of gene expression.[39]

Clinical Manifestations. The cardinal manifestations of Parkinson disease are tremor, rigidity, and bradykinesia or slowness of movement (Fig. 36-12).[40,41] Tremor is the most visible manifestation of the disorder. The tremor

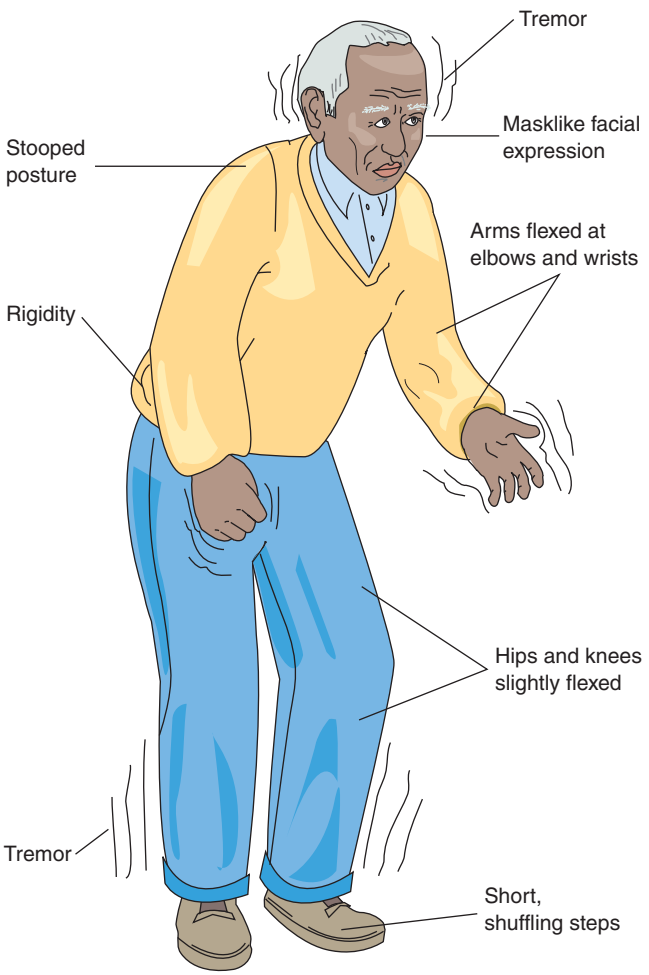


FIGURE 36-12. The clinical features of Parkinson disease. (From Timby B.K., Smith N.E. [2003]. *Introductory medical–surgical nursing* [8th ed., p. 626]. Philadelphia: Lippincott Williams & Wilkins.)

affects the distal segments of the limbs, mainly the hands and feet; head, neck, face, lips, and tongue; or jaw. It is characterized by rhythmic, alternating flexion and contraction movements (four to six beats per minute) that resemble the motion of rolling a pill between the thumb and forefinger. The tremor usually is unilateral, occurs when the limb is supported and at rest, and disappears with movement and sleep. The tremor eventually progresses to involve both sides of the body.

Rigidity is defined as resistance to movement of both flexors and extensors throughout the full range of motion. It is most evident during passive joint movement and involves jerky, cogwheel-type or ratchetlike movements that require considerable energy to perform. Flexion contractions may develop as a result of the rigidity. As with tremor, rigidity usually begins unilaterally but progresses to involve both sides of the body.

Bradykinesia is characterized by slowness in initiating and performing movements and difficulty with sudden, unexpected stopping of voluntary movements. Unconscious associative movements occur in a series of disconnected steps rather than in a smooth, coordinated manner. This is the most disabling of the symptoms of Parkinson disease. Persons with the disease have difficulty initiating walking and difficulty turning. While walking, they may freeze in place and feel as if their feet are glued to the floor, especially when moving through a doorway or preparing to turn. When they walk, they lean forward to maintain their center of gravity and take small, shuffling steps without swinging their arms, and they have difficulty changing their stride.

Manifestations of advanced-stage parkinsonism include falls, fluctuations in motor function, neuropsychiatric disorders, and sleep disorders. Loss of postural reflexes predisposes to falling, often backward. Emotional and voluntary facial movements become limited and slow as the disease progresses, and facial expression becomes stiff and masklike. There is loss of the blinking reflex and a failure to express emotion. The tongue, palate, and throat muscles become rigid; the person may drool because of difficulty in moving the saliva to the back of the mouth and swallowing it. The speech becomes slow and monotonous, without modulation, and poorly articulated.

Because the basal ganglia also influence the autonomic nervous system, persons with Parkinson disease often have excessive and uncontrolled sweating, sebaceous gland secretion, and salivation. Autonomic symptoms, such as lacrimation, dysphagia, orthostatic hypotension, thermal regulation, constipation, impotence, and urinary incontinence, may be present, especially late in the disease.

Cognitive dysfunction may also be an important feature associated with Parkinson disease. It occurs in approximately 20% to 30% of persons with the disease and develops late in the course of the disease.[40] Deficits in executive functioning may be among the earliest signs of cognitive decline, as evidenced by difficulty in planning, starting, and carrying out tasks. Dementia, when it does occur, is usually a late manifestation of the disease, and the rate of decline is slow compared with Alzheimer disease.

Treatment. The approach to treatment of Parkinson disease must be highly individualized. It includes nonpharmacologic, pharmacologic, and, when indicated, surgical methods.[33,34,41] Nonpharmacologic interventions offer group support, education, daily exercise, and adequate nutrition. Botulinum toxin injections may be used in the treatment of dystonias such as eyelid spasm and limb dystonias that frequently are associated with Parkinson disease. Persons with parkinsonism other than idiopathic Parkinson disease usually do not respond significantly to medications developed for Parkinson disease.

Pharmacologic treatment usually is determined by the severity of symptoms. Antiparkinson drugs act by increasing the functional ability of the underactive dopaminergic system, or by reducing the excessive influence of excitatory cholinergic neurons. Drugs that improve the function of the dopaminergic system include those that increase dopamine levels (levodopa), stimulate dopamine receptors (dopamine receptor agonists), or retard the breakdown of dopamine (monoamine oxidase inhibitors). Dopamine does not cross the blood-brain barrier. Levodopa does cross the blood-brain barrier, but only in small amounts due to its high metabolism outside the brain. However, when levodopa (a decarboxylase inhibitor) is given in combination with carbidopa, the peripheral metabolism of levodopa is reduced, plasma levels of levodopa are increased and its half-life is longer, more levodopa is available for entry into the brain, and a smaller dose is needed. A later adverse effect of levodopa treatment is the so-called *on–off phenomenon*, in which frequent, abrupt, and unpredictable fluctuations in motor performance occur during the day. These fluctuations include "on" periods without dyskinesia, "on" periods with dyskinesia, and periods of bradykinesia (the "off" response). Some fluctuations reflect the timing of drug administration, in which case the "on" response coincides with peak drug levels and the "off" response with low drug levels.

Bromocriptine, pramipexole, and ropinirole are dopamine agonists that act directly to stimulate dopamine receptors.[13] Rotigotine is a dopamine agonist that is supplied in a transdermal system. The dopamine agonists can be used as initial or adjunctive therapy in Parkinson disease and can be given in combination with carbidopa/levodopa. Apomorphine is another dopamine agonist that can be given intravenously. Rotigotine is only approved by the U.S. Food and Drug Administration (FDA) for initial treatment of Parkinson disease, whereas apomorphine is used as a rescue medication in patients experiencing sudden "off" periods or delayed "on" periods. Amantadine is thought to augment release of dopamine from the remaining intact dopaminergic terminals in the nigrostriatal pathway of persons with Parkinson disease. It is used to treat persons with mild symptoms but no disability. Selegiline and rasagiline are monoamine oxidase type B inhibitors that inhibit the metabolic breakdown of dopamine. Selegiline and rasagiline may be used as adjunctive treatment to reduce mild on–off fluctuations in the responsiveness of persons who are receiving levodopa.

Because dopamine transmission is disrupted in Parkinson disease, there is a preponderance of cholinergic activity,

which may be treated with anticholinergic drugs. Anticholinergic drugs (e.g., trihexyphenidyl, benztropine) are thought to restore a "balance" between reduced dopamine and uninhibited cholinergic neurons in the striatum. They are more useful in alleviating tremor and rigidity than bradykinesia. The anticholinergic drugs lessen the tremors and rigidity and afford some improvement of function. However, their potency seems to decrease over time, and increasing the dosage merely increases side effects such as blurred vision, dry mouth, bowel and bladder problems, cognitive dysfunction, and hallucinations.

Before the advent of deep brain stimulation, surgical treatment for Parkinson disease was limited to thalamotomy and pallidotomy performed using stereotactic surgery.[39–41] With these procedures, part of the thalamus or globus pallidus in the basal ganglia is destroyed using an electrical stimulator or supercooled tip of a metal probe (cryothalamotomy). Brain mapping is done during the surgery to identify and prevent injury to sensory and motor tracts. Thalamotomy and pallidotomy are generally confined to one side of the brain because of adverse effects associated with bilateral lesioning procedures. Surgical transplantation of adrenal medullary tissue or fetal substantia nigra tissue was studied in clinical trials, but neither was proven to be helpful.

Today, deep brain stimulation, which involves the implantation of electrodes into the subthalamic nuclei or the pars interna of the globus pallidus, is performed more frequently for treatment of Parkinson disease in the United States.[39,42] The electrodes are connected to a surgically implanted impulse generator that delivers electrical simulation to block the abnormal nerve activity that causes tremor and abnormal motor activity in Parkinson disease. The deep brain stimulation system allows the stimulation to be programmed to control the individual patient's symptoms, and the stimulation parameters can be changed over time as the disease progresses. Deep brain stimulation is used for persons with Parkinson disease who respond to levodopa but experience side effects associated with it (e.g., motor fluctuation or dyskinesia). It is not a cure but serves to increase the duration of the "on" periods, allows for a reduction in medication dosages (in subthalamic nuclei stimulation), and improves function. Of note, other movement disorders can be treated by placing electrodes in different target sites (e.g., thalamus for tremor and globus pallidus internus for dystonia).

In summary, alterations in coordination of muscle movements and abnormal muscle movements result from disorders of the cerebellum and basal ganglia. The functions of the cerebellum, which are especially vital during rapid muscular movements, use afferent input from various sources, including stretch receptors, proprioceptors, tactile receptors in the skin, visual input, and the vestibular system. Cerebellar disorders include vestibulocerebellar dysfunction, cerebellar ataxia, and cerebellar tremor.

The basal ganglia organize basic movement patterns into more complex patterns and release them when commanded by the motor cortex, contributing gracefulness to cortically initiated and controlled skilled movements. Disorders of the basal ganglia are characterized by involuntary movements, alterations in muscle tone, and disturbances in posture. These disorders include tremor, tics, hemiballismus, chorea, athetosis, dystonias, and dyskinesias.

Parkinsonism, a disorder of the basal ganglia, is characterized by destruction of the nigrostriatal pathway, with a subsequent reduction in striatal concentrations of dopamine. This results in an imbalance between the inhibitory effects of dopaminergic basal ganglia functions and an increase in the excitatory cholinergic functions. The disorder is manifested by resting tremor, increased muscle tonus and rigidity, slowness of movement (i.e., bradykinesia), gait disturbances, and impaired autonomic postural responses. The disease usually is slowly progressive over several decades, but the rate of progression varies from 2 to 30 years. The tremor often begins in one or both hands and then becomes generalized. Postural changes and gait disturbances continue to become more pronounced, resulting in significant disability.

Upper Motor Neuron Disorders

Upper motor neuron disorders involve neurons that are fully contained within the CNS. They include the motor neurons arising in the motor areas of the cortex and their fibers as they project through the brain and descend in the spinal cord. Disorders that affect UMNs include multiple sclerosis and spinal cord injury. Stroke, which is a common cause of UMN damage, is discussed in Chapter 37. Amyotrophic lateral sclerosis is a mixed UMN and LMN disorder.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as *Lou Gehrig disease* after the famous New York Yankees baseball player, is a devastating neurologic disorder that selectively affects motor function. ALS has an annual incidence of about 2 cases per 100,000 population.[37] It is primarily a disorder of middle to late adulthood, with men being affected more frequently than women. The disease typically follows a progressive course, with a mean survival period of 2 to 5 years from the onset of symptoms.

ALS affects motor neurons in three locations: the anterior horn cells (LMNs) of the spinal cord; the motor nuclei of the brain stem, particularly the hypoglossal nuclei; and the UMNs of the cerebral cortex.[37,38,43–45] The fact that the disease is more extensive in the distal parts of the affected tracts in the lower spinal cord rather than the proximal parts suggests that affected neurons first undergo degeneration at their distal terminals and that the disease proceeds in a centripetal direction until ultimately the parent

nerve cell dies. The death of LMNs leads to denervation, with subsequent shrinkage of musculature and muscle fiber atrophy. It is this fiber atrophy, called *amyotrophy,* that appears in the name of the disease. The loss of nerve fibers in lateral columns of the white matter of the spinal cord, along with fibrillary gliosis, imparts a firmness or sclerosis to this CNS tissue; the term *lateral sclerosis* designates these changes. A remarkable feature of the disease is that the entire sensory system, the regulatory mechanisms of control and coordination of movement, and the intellect remain intact. The neurons for ocular motility and the parasympathetic neurons in the sacral spinal cord also are spared.

The etiology of ALS is largely unknown. Five percent to 10% of cases are familial; the others are believed to be sporadic, with no family history of the disease.[18,37] The gene for a subset of familial ALS has been mapped to superoxide dismutase 1 (*SOD1*) gene on chromosome 21. Possible targets of *SOD1*-induced toxicity include the neurofilament proteins, which function in the axonal transport of molecules necessary for maintenance of the axon.[44] Another suggested mechanism of pathogenesis in ALS is exotoxic injury through activation of glutamate-gated ion channels, which are distinguished by their sensitivity to *N*-methyl-D-aspartic acid (see Chapter 37). Although autoimmunity has been suggested as a cause of ALS, the disease does not respond to the immunosuppressant agents that normally are used in treatment of autoimmune disorders.

The symptoms of ALS may be referable to UMN or LMN involvement. Manifestations of UMN lesions include weakness, spasticity or stiffness, and impaired fine motor control.[43–45] Manifestations of LMN destruction include fasciculations, weakness, muscle atrophy, and hyporeflexia. Muscle cramps involving the distal legs often are an early symptom. The most common clinical presentation is slowly progressive weakness and atrophy in distal muscles of one upper extremity. This is followed by regional spread of clinical weakness, reflecting involvement of neighboring areas of the spinal cord. Eventually, UMNs and LMNs involving multiple limbs and the head are affected. In the more advanced stages, muscles of the palate, pharynx, tongue, neck, and shoulders become involved, causing impairment of chewing, swallowing (dysphagia), and speech. Dysphagia with recurrent aspiration and weakness of the respiratory muscles produces the most significant acute complications of the disease. Death usually results from involvement of cranial nerves and respiratory musculature.

Currently, there is no cure for ALS. The treatment of persons with ALS, which requires management of medical problems, severe disability, and psychosocial problems, is best provided by a multidisciplinary team.[43–45] Measures to assist persons with the disorder to manage their symptoms (e.g., weakness and muscle spasms, dysphagia, communication difficulty, excessive watery saliva, and emotional lability), nutritional status, and respiratory muscle weakness allow people with the disorder to survive longer than would otherwise have been the case. An antiglutamate drug, riluzole, is the only drug approved for the treatment of ALS.[43] The drug is designed to decrease glutamate accumulation and slow the progression of the disease.

Demyelinating Disorders of the Central Nervous System

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disorder characterized by inflammation and selective destruction of CNS myelin.[37,38,46–52] The peripheral nervous system is spared and there is usually no evidence of an associated systemic disease. It is the most common of the demyelinating disorders, having a prevalence of approximately 1 per 1000 persons in the United States and Europe.[37] The age of onset is typically between 20 and 40 years, with women being affected twice as frequently as men.

Multiple sclerosis is thought to be an immune-mediated disorder that occurs in genetically susceptible people. Although the target antigen has not been identified, the data suggest an immune response against the components of the myelin sheath. As with other autoimmune disorders, the pathogenesis appears to involve both genetic and environmental influences. The risk for developing MS is 15-fold higher when the disease is present in a first-degree relative, and is even greater in monozygotic twins.[37] People with the human leukocyte antigen (HLA)-DR2 haplotype (see Chapter 15) are particularly susceptible.

Pathophysiology. The pathophysiology of MS involves the demyelination of nerve fibers in the white matter of the brain, spinal cord, and optic nerve. In the CNS, myelin is formed by the oligodendrocytes, chiefly those lying among the nerve fibers in the white matter. This function of the oligodendrocytes is equivalent to that of the Schwann cells in the peripheral nervous system (see Chapter 34). The properties of the myelin sheath—high electrical resistance and low capacitance—permit it to function as an electrical insulator. Demyelinated nerve fibers display a variety of conduction abnormalities, ranging from decreased conduction velocity to conduction blocks.

The lesions of MS consist of hard, sharp-edged, demyelinated or sclerotic patches that are macroscopically visible throughout the white matter of the CNS (Fig. 36-13). These lesions, which represent the end result of acute myelin breakdown, are called *plaques*. The lesions have a predilection for the optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter. In an active plaque, there is evidence of ongoing myelin breakdown. The sequence of myelin breakdown is not well understood, although it is known that the lesions contain small amounts of myelin basic proteins and increased amounts of proteolytic enzymes, macrophages, lymphocytes, and plasma cells. Oligodendrocytes are decreased in number and may be absent, especially in older lesions. Acute, subacute, and chronic lesions often are seen at multiple sites throughout the CNS.

MRI, which has had a major impact on the diagnosis and subsequent follow-up of MS, has shown that the lesions of MS may occur in two stages: a first stage that involves the sequential development of small inflammatory

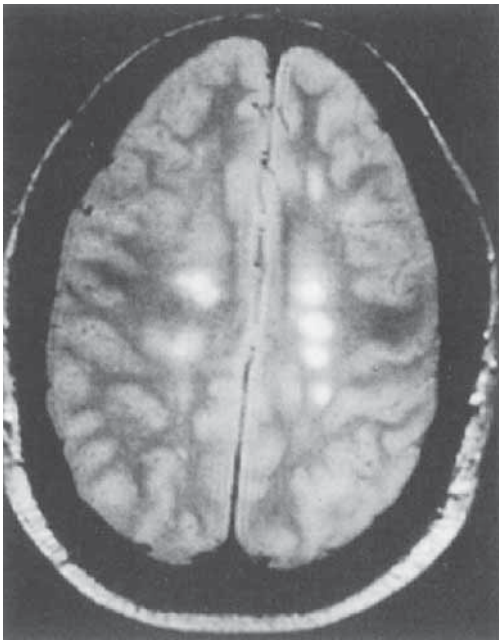


FIGURE 36-13. Axial T2-weighted image shows ovoid hyperintense lesions of multiple sclerosis in both hemispheres. (From Hickey J.V. [2008]. *The clinical practice of neurological & neurosurgical nursing* [6th ed., p. 699]. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.)

lesions, and a second stage during which the lesions extend and consolidate and when demyelination and gliosis (scar formation) occur. It is not known whether the inflammatory process, present during the first stage, is directed against myelin or against the oligodendrocytes that produce myelin. Remyelination of the nervous system was considered to be impossible until the late 1990s. Evidence now suggests that remyelination can occur in the CNS if the process that initiated the demyelination is halted before the oligodendrocyte dies.[50]

Manifestations and Clinical Course. The interruption of neural conduction in the demyelinated nerves in MS is manifested by a variety of symptoms, depending on the location and extent of the lesion.[48,51,52] Areas commonly affected are the optic nerve (visual field), corticobulbar tracts (speech and swallowing), corticospinal tracts (muscle strength), cerebellar tracts (gait and coordination), spinocerebellar tracts (balance), medial longitudinal fasciculus (conjugate gaze function of the extraocular eye muscles), and posterior cell columns of the spinal cord (position and vibratory sensation). Typically, an otherwise healthy person presents with an acute or subacute episode of paresthesias, optic neuritis (i.e., visual clouding or loss of vision in part of the visual field with pain on movement of the globe), diplopia, or specific types of gaze paralysis.

Paresthesias are evidenced as numbness, tingling, burning sensations, or pressure on the face or involved extremities, with symptoms ranging from annoying to severe. The *Lhermitte sign* is an electric shock–like tingling down the back and onto the legs that is produced by flexion of the neck. Pain from spasticity also may be a factor that can be alleviated by appropriate stretching exercises. Other common symptoms are abnormal gait, bladder and sexual dysfunction, vertigo, nystagmus, fatigue, and speech disturbance. These symptoms usually last for several days to weeks, and then completely or partially resolve. After a period of normal or relatively normal function, new symptoms appear. Psychological manifestations, such as mood swings, may represent an emotional reaction to the nature of the disease or, more likely, involvement of the white matter of the cerebral cortex. Depression, euphoria, inattentiveness, apathy, forgetfulness, and loss of memory may occur.

Fatigue is one of the most common problems for persons with MS. Fatigue often is described as a generalized low-energy feeling not related to depression and different from weakness. Fatigue has a harmful impact on activities of daily living and sustained physical activity. Interventions such as spacing activities and setting priorities often are helpful.

The course of the disease may fall into one of four categories: relapsing-remitting, secondary progressive, primary progressive, or progressive relapsing.[47] The *relapsing-remitting* form of the disease is characterized by episodes of acute worsening with recovery and a stable course between relapses. *Secondary progressive disease* involves a gradual neurologic deterioration with or without superimposed acute relapses in a person with previous relapsing-remitting disease. *Primary progressive disease* is characterized by nearly continuous neurologic deterioration from onset of symptoms. The *progressive relapsing* category of disease involves gradual neurologic deterioration from the onset of symptoms but with subsequent superimposed relapses.

Diagnosis. The diagnosis of MS is based on evidence of CNS lesions that are disseminated in time and space (i.e., occur in different parts of the CNS at least 3 months apart), with no explanation for the disease process.[51,52] MRI is a sensitive diagnostic tool that is used as an adjunct to clinical diagnosis. MRI studies can detect lesions even when CT scans appear normal. A computer-assisted method of MRI can measure lesion size. Many new areas of myelin abnormality are asymptomatic. Serial MRI studies can be done to detect asymptomatic lesions, monitor the progress of existing lesions, and evaluate the effectiveness of treatment. Although MRI can be used to provide evidence of disseminated lesions in persons with the disease, normal findings do not exclude the diagnosis. Electrophysiologic evaluations (e.g., evoked potential studies) and CT scans may assist in the identification and documentation of lesions.

Although no laboratory test can be used to diagnose MS, examination of the cerebrospinal fluid is helpful. A large percentage of patients with MS have elevated IgG levels, and some have oligoclonal patterns (i.e., discrete electrophoretic bands) even with normal IgG levels. Total

protein or lymphocyte levels may be mildly elevated in the cerebrospinal fluid. These test results can be altered in a variety of inflammatory neurologic disorders and are not specific for MS.

Treatment. Most treatment measures for MS are directed at modifying the course and managing the primary symptoms of the disease.[48,51,52] The variability in symptoms, unpredictable course, and lack of specific diagnostic methods has made the evaluation and treatment of MS difficult. Persons who are minimally affected by the disorder require no specific treatment. The person should be encouraged to maintain as healthy a lifestyle as possible, including good nutrition and adequate rest and relaxation. Physical therapy may help maintain muscle tone. Every effort should be made to avoid excessive fatigue, physical deterioration, emotional stress, viral infections, and extremes of environmental temperature, which may precipitate an exacerbation of the disease.

The pharmacologic agents used in the treatment of MS fall into three categories: those used to (1) treat acute attacks or initial demyelinating episodes, (2) modify the course of the disease, and (3) treat symptoms of the disorder. Corticosteroids are the mainstay of treatment for acute attacks of MS. These agents are thought to reduce the inflammation, improve nerve conduction, and have important immunologic effects. Long-term administration does not, however, appear to alter the course of the disease and can have harmful side effects. Adrenocorticotropic hormone (ACTH) also may be used in the treatment of MS. Plasmapheresis has also proved beneficial in some cases.

Disease-modifying agents include interferon-β1a, glatiramer acetate, and mitoxantrone.[48,51,53] These agents have shown some benefit in reducing exacerbations in persons with relapsing-remitting MS. Interferon-β is a cytokine that acts as an immune enhancer. Two forms of recombinant interferon have been approved by the FDA for treatment of MS—interferon-β1a and interferon-β1b. Both types of interferon are administered by injection, and both are usually well tolerated. Glatiramer acetate is a synthetic polypeptide that simulates parts of the myelin basic protein. Although the exact mechanism of action is unknown, the drug appears to block myelin-damaging T cells by acting as a myelin decoy. The drug is given daily by subcutaneous injection. Mitoxantrone, an anticancer drug, is recommended for persons with worsening forms of the disease. Because it is an anticancer drug, it is recommended that it only be administered by experienced health care professionals. Recently, natalizumab has also been approved for relapsing-remitting MS. Natalizumab is a monoclonal antibody against leukocyte α4 integrins, and its primary mechanism of action is suppression of leukocyte entry into the CNS. Other promising therapies that focus on immune-mediated disease mechanisms are currently in the development stages.

Among the medications used to manage the chronic problems associated with MS are dantrolene, baclofen, or diazepam for spasticity; cholinergic drugs for bladder problems; and antidepressant drugs for depression.

Vertebral and Spinal Cord Injury

Spinal cord injury (SCI) represents damage to the neural elements of the spinal cord. SCI is primarily a disorder of young people, with most injuries occurring in the 16- to 30-year age group.[54] The most common cause of SCI is motor vehicle accidents, followed by falls, violence (primarily gunshot wounds), and recreational sporting activities.[54] Life expectancy for persons with SCI continues to increase, but is somewhat below life expectancy for those without SCI. Mortality rates are significantly higher during the first year after injury than during subsequent years, particularly for severely injured persons.[54]

Most SCIs involve damage to the vertebral column or supporting ligaments as well as the spinal cord. Because of extensive tract systems that connect sensory afferent neurons and LMNs with higher brain centers, SCIs commonly involve both sensory and motor function. Although the discussion in this section of the chapter focuses on traumatic SCI, much of the content is applicable to SCI caused by other disorders, such as congenital deformities (e.g., spina bifida), tumors, ischemia and infarction, and bone disease with pathologic fractures of the vertebrae.

Injury to the Vertebral Column

Injuries to the vertebral column include fractures, dislocations, and subluxations. A fracture can occur at any part of the bony vertebrae, causing fragmentation of the bone. It most often involves the pedicle, lamina, or processes (e.g., facets). Dislocation or subluxation (partial dislocation) injury causes the vertebral bodies to become displaced, with one overriding another and preventing correct alignment of the vertebral column. Damage to the ligaments or bony vertebrae may make the spine unstable. In an unstable spine, further unguarded movement of the spinal column can impinge on the spinal canal, causing compression or overstretching of neural tissue.

Most injuries result from some combination of compressive force or bending movements.[18] Flexion injuries occur when forward bending of the spinal column exceeds the limits of normal movement. Typical flexion injuries result, for example, when the head is struck from behind, as in a fall with the back of the head as the point of impact. Extension injuries occur with excessive forced bending (i.e., hyperextension) of the spine backward. A typical extension injury involves a fall in which the chin or face is the point of impact, causing hyperextension of the neck. Injuries of flexion and extension occur more commonly in the cervical spine (C4 to C6) than in any other area. Limitations imposed by the ribs, spinous processes, and joint capsules in the thoracic and lumbar spine make this area less flexible and less susceptible to flexion and extension injuries than the cervical spine.

A compression injury, causing the vertebral bones to shatter, squash, or even burst, occurs when there is spinal loading from a high-velocity blow to the top of the head or when landing forcefully on the feet or buttocks[18] (Fig. 36-14A). This typically occurs at the cervical level (e.g., diving injuries) or in the thoracolumbar area (e.g., falling from a distance and landing on the

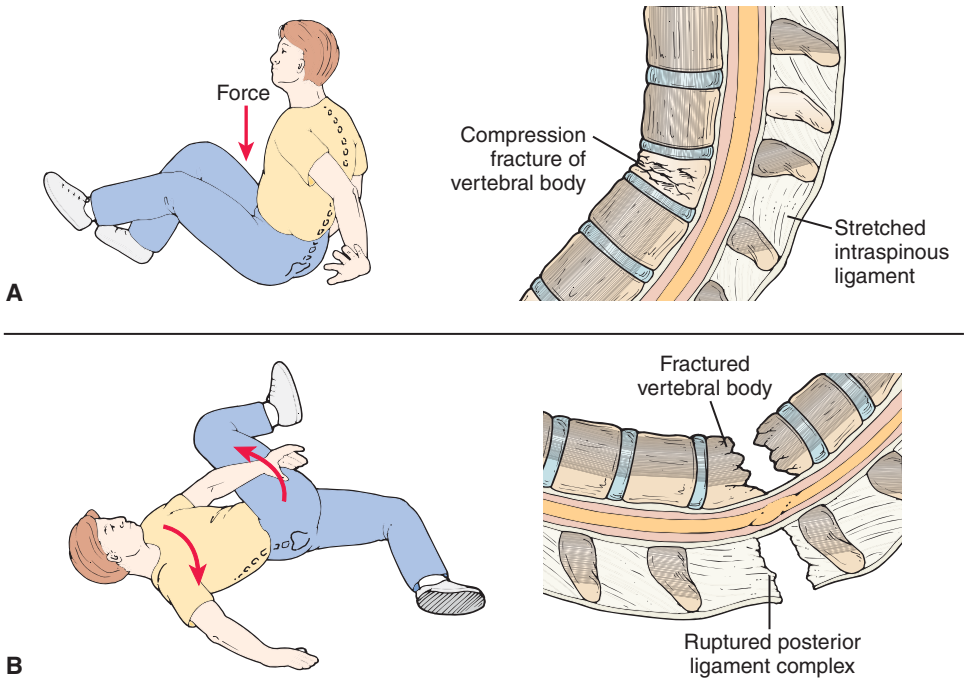


FIGURE 36-14. **(A)** Compression vertebral fracture secondary to axial loading as occurs when a person falls from a height and lands on the buttocks. **(B)** Rotational injury, in which there is concurrent fracture and tearing of the posterior ligamentous complex, is caused by extreme lateral flexion or twisting of the head or neck. (Modified from Hickey J.V. [2003]. *The clinical practice of neurological and neurosurgical nursing* [5th ed., pp. 411–412]. Philadelphia: Lippincott Williams & Wilkins.)

buttocks). Compression injuries may occur when the vertebrae are weakened by conditions such as osteoporosis and cancer with bone metastasis. Axial rotation injuries can produce highly unstable injuries. Maximal axial rotation occurs in the cervical region, especially between C1 and C2, and at the lumbosacral joint[18] (see Fig. 36-14B). Coupling of vertebral motions is common in injury when two or more individual motions occur (e.g., lateral bending and axial rotation).

Acute Spinal Cord Injury

Spinal cord injury involves damage to the neural elements of the spinal cord. The damage may result from direct trauma to the cord from penetrating wounds or indirect injury resulting from vertebral fractures, fracture-dislocations, or subluxations of the spine. The spinal cord may be contused, not only at the site of injury but also above and below the trauma site.[18] Traumatic injury may be complicated by the loss of blood flow to the cord, with resulting infarction.

Sudden, complete transection of the spinal cord results in complete loss of motor, sensory, reflex, and autonomic function below the level of injury. The immediate response to SCI is often referred to as *spinal cord shock*. It is characterized by flaccid paralysis with loss of tendon reflexes below the level of injury, absence of somatic and visceral sensations below the level of injury, and loss of bowel and bladder function. Loss of systemic sympathetic vasomotor tone may result in vasodilation, increased venous capacity, and hypotension. These manifestations occur regardless of whether the level of the lesion eventually will produce spastic (UMN) or flaccid (LMN) paralysis. The basic mechanisms accounting for transient spinal shock are unknown. Spinal shock may last for hours, days, or weeks. Usually, if reflex function returns by the time the person reaches the hospital, the neuromuscular changes are reversible. This type of reversible spinal shock may occur in football-type injuries, in which jarring of the spinal cord produces a concussion-like syndrome with loss of movement and reflexes, followed by full recovery within days. In persons in whom the loss of reflexes persists, hypotension and bradycardia may become critical but manageable problems. In general, the higher the level of injury, the greater is the effect.

Pathophysiology. The pathophysiology of acute SCI can be divided into two types: primary and secondary.[18,55–59] The *primary neurologic injury* occurs at the time of mechanical injury and is irreversible. It is characterized by small hemorrhages in the gray matter of the cord, followed by edematous changes in the white matter that lead to necrosis of neural tissue. This type of injury results from the forces of compression, stretch, and shear associated with fracture or compression of the spinal vertebrae, dislocation of vertebrae (e.g., flexion, extension, subluxation), and contusions due to jarring of the cord in the spinal canal. Penetrating injuries produce lacerations and direct trauma to the cord and may occur with or without spinal column damage. Lacerations occur when there is cutting or tearing of the spinal cord, which injures nerve tissue and causes bleeding and edema.

Secondary injuries follow the primary injury and promote the spread of injury. Although there is considerable debate about the pathogenesis of secondary injuries, the tissue destruction that occurs ends in progressive neurologic damage. After SCI, several pathologic mechanisms come into play, including vascular damage, neuronal injury that leads to loss of reflexes below the level of injury, and release of vasoactive agents and cellular enzymes. Vascular lesions (i.e., vessel trauma and hemorrhage) can lead to

ischemia, increased vascular permeability, and edema. Blood flow to the spinal cord may be further compromised by spinal shock that results from a loss of vasomotor tone and neural reflexes below the level of injury. The release of vasoactive substances (i.e., norepinephrine, serotonin, dopamine, and histamine) from the wound tissue causes vasospasm and impedes blood flow in the microcirculation, producing further necrosis of blood vessels and neurons. The release of proteolytic and lipolytic enzymes from injured cells causes delayed swelling, demyelination, and necrosis in the neural tissue in the spinal cord.

Management. The goal of management of acute SCI is to reduce the neurologic deficit and prevent any additional loss of neurologic function. The specific steps in resuscitation and initial evaluation can be carried out at the trauma site or in the emergency department, depending on the urgency of the situation.[18] Most traumatic injuries to the spinal column render it unstable, mandating measures such as immobilization with collars and backboards and limiting the movement of persons at risk for or with known SCI. Every person with multiple trauma or head injury, including victims of traffic and sporting accidents, should be suspected of having sustained an acute SCI.

The nature of the injury determines further methods of stabilization and treatment. In unstable injuries of the cervical spine, cervical traction improves or restores spinal alignment, decompresses neural structures, and facilitates recovery. Fractures and dislocations of the thoracic and lumbar vertebrae may be initially stabilized by restricting the person to bed rest and turning him or her in a log-rolling manner to keep the spine rigid. Gunshot or stab wounds of the spinal column may not produce structural instability and may not require immobilization.

The goal of early surgical intervention for an unstable spine is to provide internal skeletal stabilization so that early mobilization and rehabilitation can occur. One of the more important aspects of early SCI care is the prevention and treatment of spinal or systemic shock and the hypoxia associated with compromised respiration. Correcting hypotension or hypoxia is essential to maintaining circulation to the injured cord.[60]

The recognition that much of the posttraumatic degeneration of the spinal cord following injury is caused by secondary injuries has led to the search for neuroprotective strategies that would prevent or minimize these processes. Randomized controlled trials in the 1990s reported beneficial effects from a high-dose regimen of the glucocorticoid methylprednisolone administered soon after spinal cord injury.[61] In recent years, the use of high-dose methylprednisolone has become controversial, largely based on the risk of serious adverse effects (e.g., gastric bleeding, wound infection, venous thrombosis, and steroid myopathy) versus what is perceived to be a modest neurologic benefit.[62] Other neuroprotective agents, including monosialoganglioside sodium (GM-1 ganglioside), naloxone, and tirilazad, have been tested in multicenter clinical trials, but primary end points have not been achieved.[62] Recent investigations are exploring the effects of early cooling strategies (i.e., mild and moderate hypothermia) on recovery outcomes in persons with spinal cord injury.[63]

Types and Classification of Spinal Cord Injury

Alterations in body function that result from SCI depend on the level of injury and the amount of cord involvement. *Tetraplegia,* sometimes referred to as *quadriplegia,* is the impairment or loss of motor or sensory function (or both) after damage to neural structures in the cervical segments of the spinal cord.[18,64] It results in impairment of function in the arms, trunk, legs, and pelvic organs (see Fig. 36-4). *Paraplegia* refers to impairment or loss of motor or sensory function (or both) from damage of neural elements in the spinal canal in the thoracic, lumbar, or sacral segments of the spinal cord. With paraplegia, arm functioning is spared, but depending on the level of injury, functioning of the trunk, legs, and pelvic organs may be impaired. Paraplegia includes conus medullaris and cauda equina injuries (discussed later).

Further definitions of SCI describe the extent of neurologic damage as *complete* or *incomplete*[64] (Chart 36-1). Complete cord injuries can result from severance of the cord, disruption of nerve fibers although they remain intact, or interruption of blood supply to that segment, resulting in complete destruction of neural tissue and UMN or LMN paralysis. With complete injuries, no motor or

CHART 36-1 American Spinal Injury Association (ASIA) Impairment Scale

A = Complete: No motor or sensory function is preserved in sacral segments S4–S5.
B = Incomplete: Sensory but not motor function is preserved below the neurologic level and includes sacral segments S4–S5.
C = Incomplete: Motor function is preserved below the neurologic level, and more that half of the key muscles below the neurologic level have a muscle grade less than 3.
D = Incomplete: Motor function is preserved below the neurologic level, and at least half of the key muscles below the level of injury have a muscle grade of 3 or more.
E = Normal: Motor and sensory functions are normal.

Muscle grading: (0) total paralysis; (2) active movement, full range of motion, gravity eliminated; (3) active movement, full range of motion, against gravity; (4) active movement, full range of motion, against gravity and provides some resistance; (5) active movement, full range of motion, against gravity and provides normal resistance

Developed from the American Spinal Injury Association. (2002). *International standards for neurological classification of SCI, revised 2002.* Chicago: American Spinal Cord Injury Association.

sensory function is preserved in sacral segments S4 to S6. Incomplete SCI implies there is some residual motor or sensory function below the level of injury. The prognosis for return of function is better in an incomplete injury because of preservation of axonal function. Incomplete injuries may manifest in a variety of patterns, but can be organized into certain patterns or "syndromes" that occur more frequently and reflect the predominant area of the cord that is involved. Types of incomplete lesions include the central cord syndrome, anterior cord syndrome, Brown-Séquard syndrome, and conus medullaris syndrome.

Central Cord Syndrome. A condition called *central cord syndrome* occurs when injury is predominantly in the central gray or white matter of the cord (Fig. 36-15).[18] Because the corticospinal tract fibers are organized with those controlling the arms located more centrally and those controlling the legs located more laterally, some external axonal transmission may remain intact. Motor function of the upper extremities is affected, but the lower extremities may not be affected or may be affected to a lesser degree, with some sparing of sacral sensation. Bowel, bladder, and sexual functions usually are affected to various degrees, and this may parallel the degree of lower extremity involvement. This syndrome occurs almost exclusively in the cervical cord, rendering the lesion a UMN lesion with spastic paralysis. Central cord damage is more frequent in elderly persons with narrowing or stenotic changes in the spinal canal that are related to arthritis. Damage also may occur in persons with congenital stenosis.

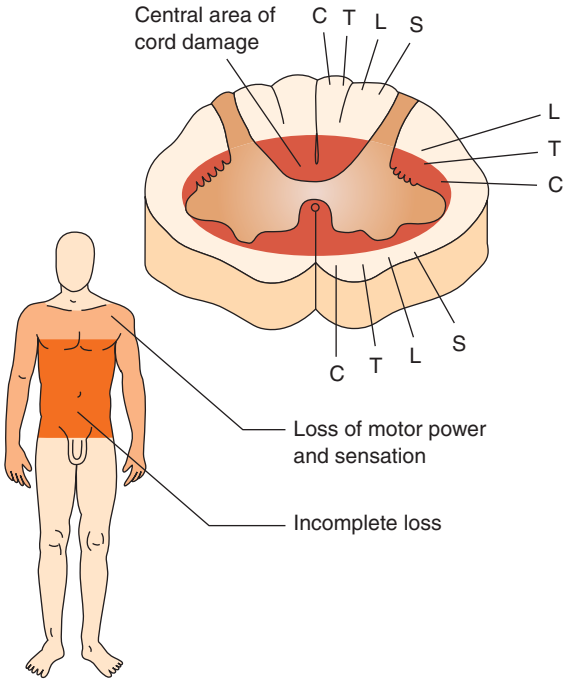


FIGURE 36-15. Central cord syndrome. A cross-section of the cord shows central damage and the associated motor and sensory loss. C, cervical; L, lumbar; S, sacral; T, thoracic. (From Kitt S., Kaiser J. [1990]. *Emergency nursing: A physiological and clinical perspective.* Philadelphia: W.B. Saunders.)

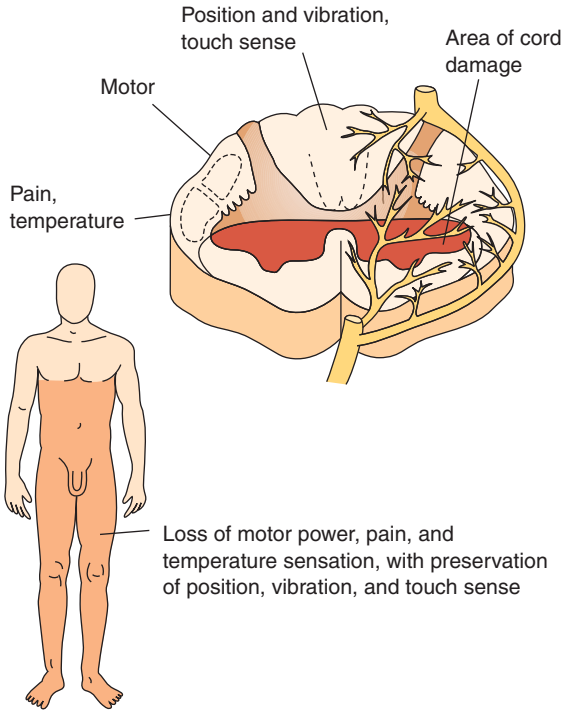


FIGURE 36-16. Anterior cord syndrome. Cord damage and associated motor and sensory loss are illustrated. (From Kitt S., Kaiser J. [1990]. *Emergency nursing: A physiological and clinical perspective.* Philadelphia: W.B. Saunders.)

Anterior Cord Syndrome. Anterior cord syndrome usually is caused by damage from infarction of the anterior spinal artery, resulting in damage to the anterior two thirds of the cord[18] (Fig. 36-16). The deficits include loss of motor function provided by the corticospinal tracts and loss of pain and temperature sensations from damage to the lateral spinothalamic tracts. The posterior one third of the cord is relatively unaffected, preserving the dorsal column axons that convey position, vibration, and touch sensations.

Brown-Séquard Syndrome. A condition called *Brown-Séquard syndrome* results from damage to a hemisection of the anterior and posterior cord[18] (Fig. 36-17). The effect is a loss of voluntary motor function from the corticospinal tract, proprioception loss from the ipsilateral side of the body, and contralateral loss of pain and temperature sensations from the lateral spinothalamic tracts for all levels below the lesion.

Conus Medullaris Syndrome. The conus medullaris syndrome involves damage to the conus medullaris or the sacral cord (i.e., conus) and lumbar nerve roots in the neural canal.[18] Functional deficits resulting from this type of injury usually result in flaccid bowel and bladder and altered sexual function. Sacral segments occasionally show preserved reflexes if only the conus is affected. Motor function in the legs and feet may be impaired

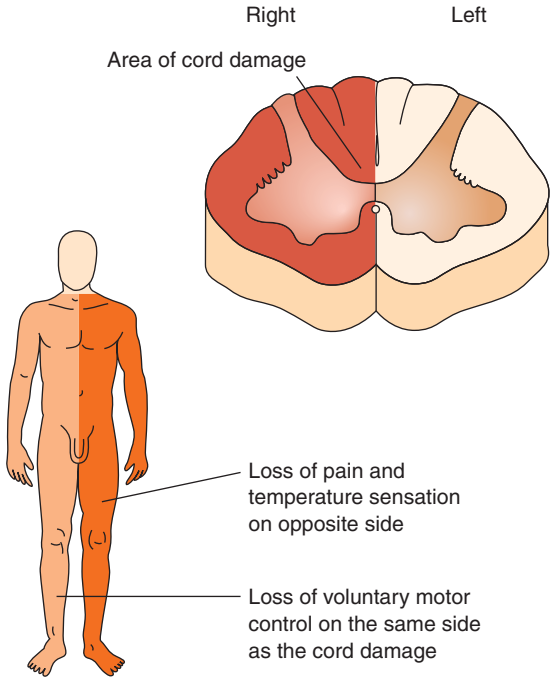


FIGURE 36-17. Brown-Séquard syndrome. Cord damage and associated motor and sensory loss are illustrated. (From Kitt S., Kaiser J. [1990]. *Emergency nursing: A physiological and clinical perspective.* Philadelphia: W.B. Saunders.)

without significant sensory impairment. Damage to the lumbosacral nerve roots in the spinal canal usually results in LMN and sensory neuron damage known as *cauda equina syndrome*. Functional deficits present as various patterns of asymmetric flaccid paralysis, sensory impairment, and pain.

Disruption of Somatosensory and Skeletal Muscle Function

Functional abilities after SCI are subject to various degrees of somatosensory and skeletal muscle function loss and altered reflex activity based on the level of cord injury and extent of cord damage (Table 36-2).

Motor and Somatosensory Function. Skeletal muscle function in cervical injuries ranges from complete dependence to independence with or without assistive devices in activities of mobility and self-care. The functional levels of cervical injury are related to C5, C6, C7, or C8 innervation. At the C5 level, deltoid and biceps function is spared, allowing full head, neck, and diaphragm control with good shoulder strength and full elbow flexion. At the C6 level, wrist dorsiflexion by the wrist extensors is functional, allowing tenodesis, which is the natural bending inward and flexion of the fingers when the wrist is extended and bent backward. Tenodesis is a

TABLE 36-2 Functional Abilities by Level of Cord Injury

Injury Level	Segmental Sensorimotor Function	Dressing, Eating	Elimination	Mobility*
C1	Little or no sensation or control of head and neck; no diaphragm control; requires continuous ventilation	Dependent	Dependent	Limited. Voice-controlled or sip-n-puff electric wheelchair
C2–C3	Head and neck sensation; some neck control. Independent of mechanical ventilation for short periods	Dependent	Dependent	Same as for C1
C4	Good head and neck sensation and motor control; some shoulder elevation; diaphragm movement	Dependent; may be able to eat with adaptive sling	Dependent	Limited to voice-, mouth-, head-, chin-, or shoulder-controlled electric wheelchair
C5	Full head and neck control; shoulder strength; elbow flexion	Independent with assistance	Maximal assistance	Electric or modified manual wheelchair, needs transfer assistance
C6	Fully innervated shoulder; wrist extension or dorsiflexion	Independent or with minimal assistance	Independent or with minimal assistance	Independent in transfers and wheelchair
C7–C8	Full elbow extension; wrist plantar flexion; some finger control	Independent	Independent	Independent; manual wheelchair
T1–T5	Full hand and finger control; use of intercostal and thoracic muscles	Independent	Independent	Independent; manual wheelchair
T6–T10	Abdominal muscle control, partial to good balance with trunk muscles	Independent	Independent	Independent; manual wheelchair
T11–L5	Hip flexors, hip abductors (L1–3); knee extension (L2–4); knee flexion and ankle dorsiflexion (L4–5)	Independent	Independent	Short distance to full ambulation with assistance
S1–S5	Full leg, foot, and ankle control; innervation of perineal muscles for bowel, bladder, and sexual function (S2–4)	Independent	Normal to impaired bowel and bladder function	Ambulate independently with or without assistance

*Assistance refers to adaptive equipment, setup, or physical assistance.

key movement because it can be used to pick up objects when finger movement is absent. A functional C7 injury allows full elbow flexion and extension, wrist plantar flexion, and some finger control. At the C8 level, finger flexion is added.

Thoracic cord injuries (T1 to T12) allow full upper extremity control with limited to full control of intercostal and trunk muscles and balance. Injury at the T1 level allows full fine motor control of the fingers. Because of the lack of specific functional indicators at the thoracic levels, the level of injury usually is determined by sensory level testing.

Functional capacity in the L1 through L5 nerve innervations allows hip flexion, hip abduction (L1 to L3), movement of the knees (L2 to L5), and ankle dorsiflexion (L4 to L5). Sacral (S1 to S5) innervation allows for full leg, foot, and ankle control and innervation of perineal musculature for bowel, bladder, and sexual function.

Reflex Activity. Spinal cord reflexes are fully integrated in the spinal cord and can function independent of input from higher centers. Altered spinal reflex activity after SCI is essentially determined by the level of injury and whether UMNs or LMNs are affected. With UMN injuries at T12 and above, the cord reflexes remain intact, whereas communication pathways with higher centers have been interrupted. This results in spasticity of involved skeletal muscle groups and of smooth and skeletal muscles that control bowel, bladder, and sexual function. In LMN injuries at T12 or below, the reflex circuitry itself has been damaged at the level of the spinal cord or spinal nerve, resulting in a decrease or absence of reflex function. The LMN injuries cause flaccid paralysis of involved skeletal muscle groups and the smooth and skeletal muscles that control bowel, bladder, and sexual function. However, injuries near the T12 level may result in mixed UMN and LMN deficits (e.g., spastic paralysis of the bowel and bladder with flaccid muscle tone).

After the period of spinal shock in a UMN injury, isolated spinal reflex activity and muscle tone that are not under the control of higher centers return. This may result in hypertonia and spasticity of skeletal muscles below the level of injury.[18] These spastic movements are involuntary instead of voluntary, a distinction that needs to be explained to persons with SCI and their families. The antigravity muscles, the flexors of the arms and extensors of the legs, are predominantly affected. Spastic movements are usually heightened initially after injury, reaching a peak and then becoming stable in approximately 1.5 to 2 years.[18]

The stimuli for reflex muscle spasm arise from somatic and visceral afferent pathways that enter the cord below the level of injury. The most common of these stimuli are muscle stretching, bladder infections or stones, fistulas, bowel distention or impaction, pressure areas or irritation of the skin, and infections. Because the stimuli that precipitate spasms vary from person to person, careful assessment is necessary to identify the factors that precipitate spasm in each person. Passive range-of-motion exercises to stretch the spastic muscles help to prevent spasm induced by muscle stretching, such as occurs with a change in body position.

Spasticity in itself is not detrimental and may even facilitate maintenance of muscle tone to prevent muscle wasting, improve venous return, and aid in mobility. Spasms become detrimental when they impair safety; they also reduce the ability to make functional gains in mobility and activities of daily living. Spasms also may cause trauma to bones and tissues, leading to joint contractures and skin breakdown.

Respiratory Muscle Function. Ventilation requires movement of the expiratory and inspiratory muscles, all of which receive innervation from the spinal cord.[65] The main muscle of ventilation, the diaphragm, is innervated by segments C3 to C5 through the phrenic nerves. The intercostal muscles, which function in elevating the rib cage and are needed for coughing and deep breathing, are innervated by spinal segments T1 through T7. The major muscles of expiration are the abdominal muscles, which receive their innervation from levels T6 to T12.

Although the ability to inhale and exhale may be preserved at various levels of SCI, functional deficits in ventilation are most apparent in the quality of the breathing cycle and the ability to oxygenate tissues, eliminate carbon dioxide, and mobilize secretions. Cord injuries involving C1 to C3 result in a lack of respiratory effort, and affected patients require assisted ventilation. Although a C3 to C5 injury allows partial or full diaphragmatic function, ventilation is diminished because of the loss of intercostal muscle function, resulting in shallow breaths and a weak cough. Below the C5 level, as less intercostal and abdominal musculature is affected, the ability to take a deep breath and cough is less impaired. Maintenance therapy consists of muscle training to strengthen existing muscles for endurance and mobilization of secretions. The ability to speak is compromised with assisted ventilation, whether continuous or intermittent. Thus, ensuring adequate communication of needs is also essential.

Disruption of Autonomic Nervous System Function

In addition to its effects on skeletal muscle function, SCI interrupts autonomic nervous system function below the site of injury.[66] This includes sympathetic outflow from the thoracic and upper lumbar cord and parasympathetic outflow from the sacral cord. Because of their sites of exit from the CNS, the cranial nerves, such as the vagus, are unaffected. Depending on the level of injury, the spinal reflexes that control autonomic nervous system function are largely isolated from the rest of the CNS. Afferent sensory input that enters the spinal cord is unaffected, as is the efferent motor output from the cord. Lacking are the regulation and integration of reflex function by centers in the brain and brain stem. This results in a situation in which the autonomic reflexes below the level of injury are uncontrolled, whereas those above the level of injury function in a relatively controlled manner.

Sympathetic nervous system regulation of circulatory function and body temperature (i.e., thermoregulation)

presents some of the most severe problems in SCI. The higher the level of injury and the greater the surface area affected, the more profound are the effects on circulation and thermoregulation. Persons with injury at the T6 level or above experience problems in regulating vasomotor tone, whereas those with injuries below the T6 level usually have sufficient sympathetic function to maintain adequate vasomotor function. The level of injury and its corresponding problems may vary among persons, and some dysfunctional effects may be seen at levels below T6. With lower lumbar and sacral injuries, sympathetic function remains essentially unaltered.

Vasovagal Response. The vagus nerve (cranial nerve X), which is unaffected in SCI, normally exerts a continuous inhibitory effect on heart rate. Vagal stimulation that causes a marked bradycardia is called the *vasovagal response*. Visceral afferent input to the vagal centers in the brain stem of persons with tetraplegia or high-level paraplegia can produce marked bradycardia when unchecked by a dysfunctional sympathetic nervous system. Severe bradycardia and even asystole can result when the vasovagal response is elicited by deep endotracheal suctioning or rapid position change. Preventive measures, such as hyperoxygenation before, during, and after tracheal suctioning, are advised. Rapid position changes should be avoided or anticipated, and anticholinergic drugs should be immediately available to counteract severe episodes of bradycardia.

Autonomic Dysreflexia. Autonomic dysreflexia, also known as *autonomic hyperreflexia,* represents an acute episode of exaggerated sympathetic reflex responses that occur in persons with injuries at T6 and above, in which CNS control of spinal reflexes is lost (Fig. 36-18). It does not occur until spinal shock has resolved and autonomic

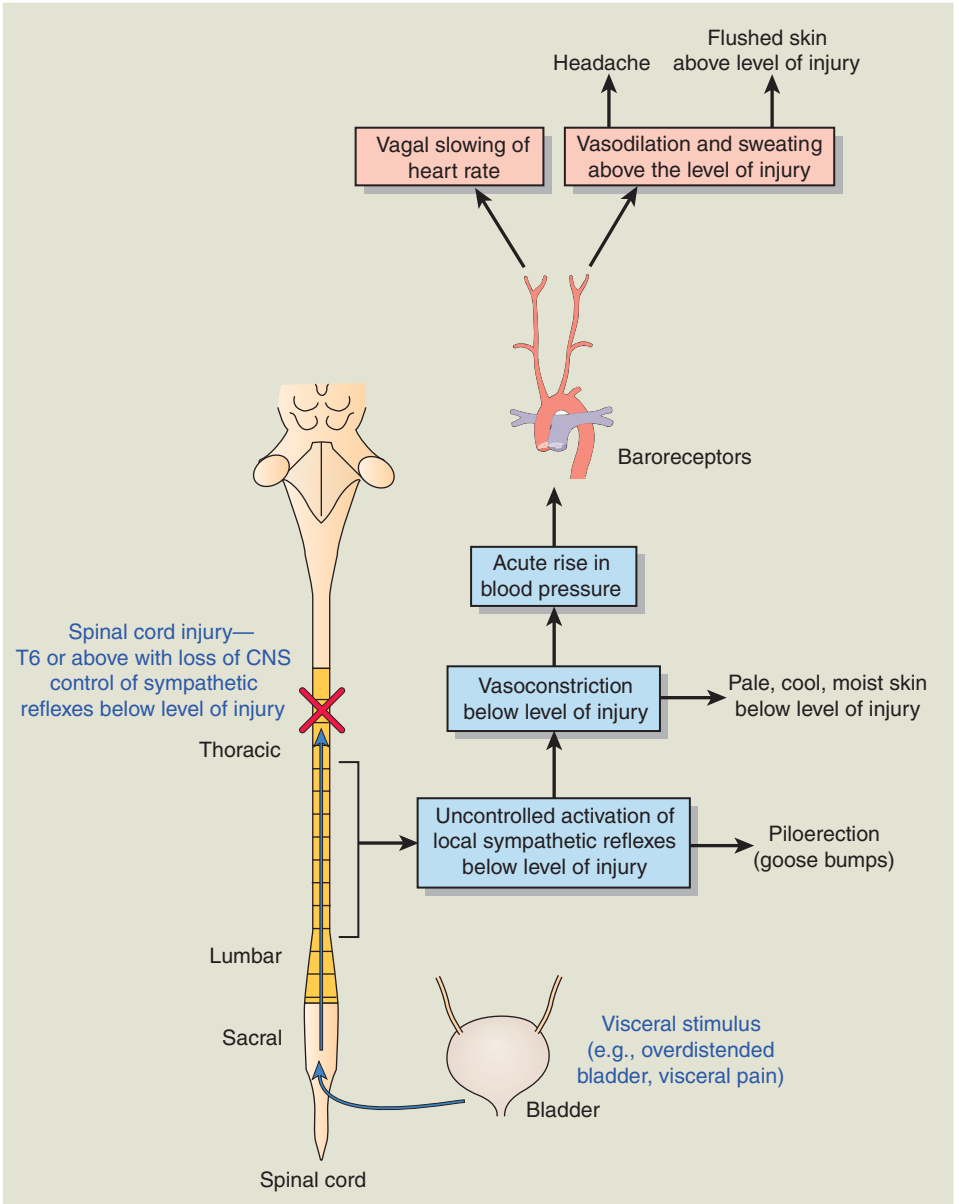


FIGURE 36-18. Mechanisms of autonomic dysreflexia.

reflexes return, most often within the first 6 months after injury. It is most unpredictable during the first year after injury, but can occur throughout the person's lifetime.

Autonomic dysreflexia is characterized by vasospasm, hypertension ranging from mild (20 mm Hg above baseline) to severe (as high as 240/120 mm Hg, or higher), skin pallor, and gooseflesh associated with the piloerector response.[67] Because baroreceptor function and parasympathetic control of heart rate travel by way of the cranial nerves, these responses remain intact. Continued hypertension produces a baroreflex-mediated vagal slowing of the heart rate to bradycardic levels. There is an accompanying baroreflex-mediated vasodilation, with flushed skin and profuse sweating above the level of injury, headache ranging from dull to severe and pounding, nasal stuffiness, and feelings of anxiety. A person may experience one, several, or all of the symptoms with each episode.

The stimuli initiating the dysreflexic response include visceral distention, such as a full bladder or rectum; stimulation of pain receptors, as occurs with pressure ulcers, dressing changes, and diagnostic or operative procedures; and visceral contractions, such as ejaculation, bladder spasms, or uterine contractions. In many cases, the dysreflexic response results from a full bladder.

Autonomic dysreflexia is a clinical emergency, and without prompt and adequate treatment, convulsions, loss of consciousness, and even death can occur. The major components of treatment include monitoring blood pressure while removing or correcting the initiating cause or stimulus. The person should be placed in an upright position, and all support hose or binders should be removed to promote venous pooling of blood and reduce venous return, thereby decreasing blood pressure. If the stimuli have been removed or the stimuli cannot be identified and the upright position is established, but the blood pressure remains elevated, drugs that block autonomic function are administered. Prevention of the type of stimuli that trigger the dysreflexic event is advocated.

Postural Hypotension. Postural, or orthostatic, hypotension usually occurs in persons with injuries at T4 to T6 and above and is related to the interruption of descending control of sympathetic outflow to blood vessels in the extremities and abdomen.[66] Pooling of blood, along with gravitational forces, impairs venous return to the heart, and there is a subsequent decrease in cardiac output when the person is placed in an upright position. The signs of orthostatic hypotension include dizziness, pallor, excessive sweating above the level of the lesion, complaints of blurred vision, and possibly fainting. Postural hypotension usually is prevented by slow changes in position and measures to promote venous return.

Disruption of Bladder, Bowel, and Sexual Function

Among the most devastating consequences of SCI is the loss of bowel, bladder, and sexual function.[68] Loss of bladder function results from disruption of neural pathways between the bladder and the reflex voiding center at the S2 to S4 level (i.e., a LMN lesion) or between the reflex voiding center and higher brain centers for communication and coordinated sphincter control (i.e., a UMN lesion). Persons with UMN lesions or spastic bladders lack awareness of bladder filling (i.e., storage) and voluntary control of voiding (i.e., evacuation). In LMN lesions or flaccid bladder dysfunction, lack of awareness of bladder filling and lack of bladder tone render the person unable to void voluntarily or involuntarily (see Chapter 27).

Bowel elimination is a coordinated function involving the enteric nervous system, the autonomic nervous system, and the CNS. Persons with SCI above S2 to S4 develop spastic functioning of the defecation reflex and loss of voluntary control of the external anal sphincter. Damage to the cord at the S2 to S4 level causes flaccid functioning of the defecation reflex and loss of anal sphincter tone. Even though the enteric nervous system innervation of the bowel remains intact, without the defecation reflex, peristaltic movements are ineffective in evacuating stool.

Sexual function, like bladder and bowel control, is mediated by the S2 to S4 segments of the spinal cord.[18] The genital sexual response in SCI, which is manifested by an erection in men and vaginal lubrication in women, may be initiated by mental or touch stimuli, depending on the level of injury. The T11 to L2 cord segments have been identified as the mental-stimulus, or psychogenic, sexual response area, where autonomic nerve pathways in communication with the forebrain leave the cord and innervate the genitalia. The S2 to S4 cord segments have been identified as the sexual-touch reflex center. In T10 or higher injuries, reflex sexual response to genital touch may occur freely. However, a sexual response to mental stimuli (T11 to L2) does not occur because of the spinal lesion blocking the communication pathway. In an injury at T12 or below, the sexual reflex center may be damaged, and there may be no response to touch.

In men, the lack of erectile ability or inability to experience penile sensations or orgasm is not a reliable indicator of fertility, which should be evaluated by an expert. In women, fertility is normally reestablished with the return of menses, which usually occurs at about 3 months to 5 months after injury. There are hazards to pregnancy, labor, and use of birth control devices relative to SCI that require the services of knowledgeable health care providers.

Disruption of Other Functions

Temperature Regulation. The central mechanisms for thermoregulation are located in the hypothalamus. In response to cold, the hypothalamus stimulates vasoconstrictor responses in peripheral blood vessels, particularly those of the skin. This results in decreased loss of body heat. Heat production results from increased metabolism, voluntary activity, or shivering. To reduce heat, hypothalamus-stimulated mechanisms produce vasodilation of skin blood vessels to dissipate heat and sweating to increase evaporative heat losses.

After SCI, the communication between the thermoregulatory centers in the hypothalamus and the sympathetic effector responses below the level of injury is

disrupted; the ability to control blood vessel responses that conserve or dissipate heat is lost, as are the abilities to sweat and shiver. Higher levels of injury tend to produce greater disturbances in thermoregulation. In tetraplegia and high paraplegia, there are few defenses against changes in the environmental temperature, and body temperature tends to assume the temperature of the external environment, a condition known as *poikilothermy*. Persons with lower-level injuries have various degrees of thermoregulation. Disturbances in thermoregulation are chronic and may cause continual loss of body heat. Treatment consists of education in the adjustment of clothing and awareness of how environmental temperatures affect the person's ability to accommodate to these changes.

Deep Vein Thrombosis and Edema. Persons with SCI are at high risk for development of deep vein thrombosis (DVT) and pulmonary embolism, particularly during the first 2 to 3 weeks after injury.[69] The high risk for DVT in patients with acute SCI is due to immobility, decreased vasomotor tone below the level of injury, and hypercoagulability and stasis of blood flow. Prevention strategies include the use of low–molecular-weight heparin, thigh-high graduated compression stockings, sequential compression boots, and early mobilization.[18] Electrical stimulation applied to the lower limbs has been reported to provide some benefit by achieving muscular contraction and improving venous flow. Local pain, a common symptom of DVT, is often absent because of sensory deficits. Thus, a regular schedule of visual inspection for local signs of DVT (e.g., swelling) is important. Testing of persons at high risk for DVT includes plethysmography and duplex ultrasonography.

Edema is also a common problem in persons with SCI. The development of edema is related to decreased peripheral vascular resistance, decreased muscle tone in the paralyzed limbs, and immobility that causes increased venous pressure and abnormal pooling of blood in the abdomen, lower limbs, and upper extremities. Edema in the dependent body parts usually is relieved by positioning to minimize gravitational forces or by using compression devices (e.g., support stockings, binders) that encourage venous return.

Skin Integrity. The entire surface of the skin is innervated by cranial or spinal nerves organized into dermatomes that show cutaneous distribution. The CNS and autonomic nervous system also play a vital role in skin function. The sympathetic nervous system, through control of vasomotor and sweat gland activity, influences the health of the skin by providing adequate circulation, excretion of body fluids, and temperature regulation. The lack of sensory warning mechanisms and voluntary motor ability below the level of injury, coupled with circulatory changes, places the spinal cord–injured person at major risk for disruption of skin integrity (see Chapter 46). Significant factors associated with disruption of skin integrity are pressure, shearing forces, and localized trauma and irritation. Relieving pressure, allowing adequate circulation to the skin, and skin inspection are primary ways of maintaining skin integrity. Of all the complications after SCI, skin breakdown is the most preventable.

Future Directions in Repair of the Injured Spinal Cord

There is a continued effort to determine new and innovative strategies for repairing the injured spinal cord.[70,71] At present, these strategies focus on promoting the regrowth of interrupted nerve fiber tracts, using nerve growth–stimulating factors or molecules that suppress inhibitors of neuronal extension; bridging spinal cord lesions with scaffolds that are impregnated with nerve growth factors, which promote axon growth and reduce the barriers caused by scar tissue; repairing damaged myelin and restoring nerve fiber conductivity in the lesion area; and enhancing CNS plasticity by promoting compensatory growth of spared, intact nerve fibers above and below the level of injury. Although these strategies may not allow for complete repair of the spinal cord so as to recreate what was present before the injury, even small successes may be useful for someone with SCI. For a person with an injury in the cervical region, "a return of function over even one spinal segment would improve the quality of life, while return to function over three or four segments would transform it."[71]

In summary, UMN lesions are those involving neurons completely contained in the CNS. Amyotrophic lateral sclerosis is a progressive and devastating neurologic disorder that selectively affects motor function. It affects LMNs in the spinal cord as well as UMNs in the brain stem and cerebral cortex. Multiple sclerosis is a slowly progressive demyelinating disease of the CNS. The most common symptoms are paresthesias, optic neuritis, and motor weakness. The disease is usually characterized by exacerbations and remissions. Initially, near-normal function returns between exacerbations.

Spinal cord injury (SCI) is a disabling neurologic condition most commonly caused by motor vehicle accidents, falls, and sports injuries. Dysfunctions of the nervous system after SCI consist of various degrees of sensorimotor loss and altered reflex activity based on the level of injury and extent of cord damage. Depending on the level of injury, the physical problems of SCI include spinal shock; ventilation and communication problems; autonomic nervous system dysfunction that predisposes to the vasovagal response, autonomic hyperreflexia, impaired body temperature regulation, and postural hypotension; impaired muscle pump and venous innervation leading to edema of dependent areas of the body and risk for deep vein thrombosis; altered sensorimotor integrity that contributes to uncontrolled muscle spasms, altered pain responses, and threats to skin integrity; alterations in bowel and bladder elimination; and impaired sexual function.

REVIEW EXERCISES

1. A 32-year-old woman presents with complaints of "drooping eyelids," difficulty chewing and swallowing, and weakness of her arms and legs that is less severe in the morning but becomes worse as the day progresses. She complains that climbing stairs and lifting objects are becoming increasingly difficult. Clinical examination confirms weakness of the eyelid and jaw muscles. She is told that she may have myasthenia gravis and is scheduled for testing using the short-acting acetylcholinesterase inhibitor edrophonium (Tensilon).

A. Explain the pathogenesis of this woman's symptoms as it relates to myasthenia gravis.
B. Explain how information from the administration of the acetylcholinesterase inhibitor edrophonium can be used to assist in the diagnosis of the disorder.

2. A 20-year-old man suffered spinal cord injury at the C2 to C3 level as the result of a motorcycle accident.

A. Explain the effects of this man's injury on ventilation and communication; sensorimotor function; autonomic nervous system function; bowel, bladder, and sexual function; and temperature regulation.
B. Autonomic dysreflexia, which is a threat to persons with spinal cord injuries at T6 or above, is manifested by hypertension, often to extreme levels, and bradycardia; constriction of skin vessels below the level of injury; and severe headache and nasal stuffiness. Explain the origin of the elevated blood pressure and bradycardia. The condition does not occur until spinal shock has resolved, and usually occurs only in persons with injuries at T6 and above. Explain.

REFERENCES

1. Jones G.M. (2000). Posture. In Kandel E.R., Schwartz J.H., Jessell T.M. (Eds.), *Principles of neural science* (4th ed., pp. 816–831). New York: McGraw-Hill.
2. Chez C., Krakauer J. (2000). The organization of movement. In Kandel E.R., Schwartz J.H., Jessell T.M. (Eds.), *Principles of neural science* (4th ed., pp. 653–672). New York: McGraw-Hill.
3. Guyton A., Hall J.E. (2006). *Medical physiology* (11th ed., pp. 85–91, 673–684, 685–692, 698–713). Philadelphia: Elsevier Saunders.
4. Penfield W., Rasmussen T. (1950). *The cerebral cortex of man.* New York: Macmillan.
5. Pearson K., Gordon J. (2000). Spinal reflexes. In Kandel E.R., Schwartz J.H., Jessell T.M. (Eds.), *Principles of neural science* (4th ed., pp. 713–735). New York: McGraw-Hill.
6. Bickley L.S., Szilagyi P.G. (2003). *Bates' guide to physical examination and history taking* (8th ed., pp. 571–592). Philadelphia: Lippincott Williams & Wilkins.
7. Rowland L.P. (2000). Diseases of the motor unit. In Kandel E.R., Schwartz J.H., Jessell T.M. (Eds.), *Principles of neural science* (4th ed., pp. 695–710). New York: McGraw-Hill.
8. Anthony D.P., Frosch M.P., DeGirolami U. (2010). Peripheral nerve and skeletal muscle. In Kumar V., Abbas A.K., Fausto N. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1257–1277). Philadelphia: Saunders Elsevier.
9. Kenyon L.C., Curtis M.T. (2008). Skeletal muscle. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1153–1170). Philadelphia: Lippincott Williams & Wilkins.
10. Sarnat H.B. (2007). Muscular dystrophies. In Behrman R.E., Kliegman R.M., Jenson H.B. et al. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 2540–2544). Philadelphia: Saunders Elsevier.
11. Deconinck N., Dan B. (2007). Pathophysiology of Duchenne muscular dystrophy: Current hypothesis. *Pediatric Neurology* 36, 1–7.
12. Horowitz B.Z. (2005). Botulinum toxin. *Critical Care Clinics* 21, 825–839.
13. Katzung B.G. (2007). *Basic and clinical pharmacology* (10th ed., pp. 92–102, 439, 442–456). New York: Lange Medical Books/McGraw-Hill.
14. Meriggioli M.N., Sanders D.B. (2009). Autoimmune myasthenia gravis: emerging clinical and biologic heterogeneity. *Lancet Neurology* 8, 475–490.
15. Thanvi B.R. (2004). Update on myasthenia gravis. *Post Medicine Journal* 80, 690–700.
16. Drachman D.B. (2006). Myasthenia gravis and other diseases of the neuromuscular junction. In Hauser S.L. (Ed.), *Harrison's neurology in clinical medicine* (pp. 527–536). New York: McGraw-Hill.
17. Trojanowski J.Q., Kenyon L. (2008). The nervous system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1211–1213, 1221–1224, 1238–1239). Philadelphia: Lippincott Williams & Wilkins.
18. Hickey J.V. (2008). *Neurological and neurosurgical nursing* (5th ed., pp. 410–453, 460–485, 702–703, 716–719). Philadelphia: Lippincott-Raven.
19. Viera A.J. (2003). Management of carpal tunnel syndrome. *American Family Physician* 68, 265–272.
20. Katz J.N., Simmons B.P. (2002). Carpal tunnel syndrome. *New England Journal of Medicine* 346, 1807–1812.
21. Hauser S.L., Asbury A.K. (2006). Guillain-Barré syndrome and other immune-mediated neuropathies. In Hauser S.L. (Ed.), *Harrison's neurology in clinical medicine* (pp. 517–526). New York: McGraw-Hill.
22. Doom P.A. (2008). Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. *Lancet Neurology* 7, 939–950.
23. Kuwabara S. (2004). Guillain-Barré syndrome. *Drugs* 64, 597–610.
24. Newswanger D.L., Warren C.R. (2004). Guillain-Barré syndrome. *American Family Physician* 69, 2405–2410.
25. McCamey K.M., Evans P. (2007). Low back pain. *Primary Care Clinics in Office Practice* 34, 71–82.
26. Deyo R.A., Weinstein J.N. (2001). Low back pain. *New England Journal of Medicine* 344, 363–370.
27. Harwood M.I., Smith B.J. (2005). Low back pain: A primary care approach. *Clinics in Family Practice* 7, 279–303.
28. Devereaux M. (2009). Low back pain. *Medical Clinics of North America* 93, 477–601.
29. Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 497–534). Philadelphia: Lippincott Williams & Wilkins.
30. Winters M.E., Kluetz P., Ziberstein J. (2006). Back pain emergencies. *Medical Clinics of North America* 90, 505–523.

31. Ghez C. (2000). The cerebellum. In Kandel E.R., Schwartz J.H., Jessell T.M. (Eds.), *Principles of neural science* (4th ed., pp. 832–852). New York. McGraw-Hill.
32. DeLong M.R. (2000). The basal ganglia. In Kandel E.R., Schwartz J.H., Jessell T.M. (Eds.), *Principles of neural science* (4th ed., pp. 853–867). New York: McGraw-Hill.
33. Rao S.S., Hofmann L.A., Shakil A. (2006). Parkinson's disease: Diagnosis and treatment. *American Family Physician* 74, 2046–2055.
34. Samil A., Nutt J.G., Ransom B.R. (2004). Parkinson's disease. *Lancet* 363, 1783–1793.
35. Parkinson J. (1817). *An essay on the shaking palsy.* London: Sherwood, Nelley & Jones.
36. Youdim M.B.H., Riederer P. (1997). Understanding Parkinson disease. *Scientific American* 276, 52–59.
37. Frosch M.P., Anthony D.C., De Girolami U. (2010). The central nervous system. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1309–1325). Philadelphia: Saunders Elsevier.
38. Trojanowski J.Q., Kenyon L. (2008). The nervous system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1211–1213, 1221–1224). Philadelphia: Lippincott Williams & Wilkins.
39. Klein C., Schlossmacher M.G. (2007). Parkinson disease, 10 years after its genetic revolution: Multiple clues to a complex disorder. *Neurology* 69, 2093–2104.
40. Pandya M., Kubu C.S., Giroux M.L. (2008). Parkinson disease: Not just a movement disorder. *Cleveland Clinic Journal of Medicine* 75(12), 856–864.
41. DeLong M., Juncos J.L. (2006). Parkinson's disease and other movement disorders. In Hauser S.L. (Ed.), *Harrison's neurology in clinical medicine* (pp. 295–314). New York: McGraw-Hill.
42. National Institute of Neurological Disorders and Stroke. (2007). *Deep brain stimulation for Parkinson's disease.* [Online] Available: http://www.ninds.nih.gov/disorders/deep_brain_stimulation/deep_brain_stimulation.htm. Accessed November 22, 2009.
43. Shoesmith C.L., Strong M.J. (2006). Amyotrophic lateral sclerosis. *Canadian Family Physician* 52, 1563–1569.
44. Rowland L.P., Shneider N.A. (2001). Amyotrophic lateral sclerosis. *New England Journal of Medicine* 344, 1688–1700.
45. Radunovic' A., Mitsumoto H., Leigh P.N. (2007). Clinical care of patients with amyotrophic lateral sclerosis. *Neurology: Lancet* 6, 913–925.
46. Noseworthy J.H., Lucchinetti C., Rodriguez M., et al. (2000). Multiple sclerosis. *New England Journal of Medicine* 343, 938–952.
47. Frohman E. (2003). Multiple sclerosis. *Medical Clinics of North America* 87, 867–897.
48. Hauser S.L., Goodin D.S. (2006). Multiple sclerosis and other demyelinating diseases. In Hauser S.L. (Ed.), *Harrison's neurology in clinical medicine* (pp. 405–422). New York: McGraw-Hill.
49. Peterson J.W., Trapp B.D. (2005). Neuropathobiology of multiple sclerosis. *Neurologic Clinics* 23, 107–129.
50. Frohman E.M., Racke M.K., Raine C.E. (2006). Multiple sclerosis—the plaque and its pathogenesis. *New England Journal of Medicine* 354(9), 942–955.
51. Calabresi P.A. (2004). Diagnosis and management of multiple sclerosis. *American Family Physician* 70, 1935–1944.
52. Lubin D.D. (2005). Clinical features and diagnosis of multiple sclerosis. *Neurologic Clinics* 23, 1–15.
53. Neuhaus O., Kieseier B.L., Hartung H.P. (2007). Immunosuppressive agents in multiple sclerosis. *Neurotherapeutics* 4, 654–660.
54. National Spinal Cord Injury Statistical Center. (2007). *Spinal cord injury: Facts and figures at a glance. Birmingham: University of Alabama.* [Online] Available: https://www.nscisc.uab.edu//public_content/facts_figures_2009.aspx. Accessed November 23, 2009.
55. McDonald J.W. (2002). Spinal cord injury. *Lancet* 359, 417–425.
56. Dobkin B.H., Havton L.A. (2004). Basic advances and new avenues in therapy of spinal cord injury. *Annual Review of Medicine* 55, 255–282.
57. Branco F., Cardenas D.D., Svircev J.N. (2007). Spinal cord injury: A comprehensive review. *Physical Medicine and Rehabilitation Clinics of North America* 18, 651–679.
58. Buckley D.A., Guanci M.K. (1999). Spinal cord trauma. *Nursing Clinics of North America* 34, 661–687.
59. Chiles B.W., Cooper P.R. (1996). Acute spinal cord injury. *New England Journal of Medicine* 334, 514–520.
60. Atkinson P.P., Atkinson J.L.D. (1996). Spinal shock. *Mayo Clinic Proceedings* 71, 384–389.
61. Bracken M.B., Shepard M.J., Collins W.F., et al. (1997). Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: Results of the Third National Acute Spinal Cord Injury Study. *Journal of the American Medical Association* 277, 1597–1604.
62. Hall E.D., Springer J.E. (2004). Neuroprotection and acute spinal cord injury: A reappraisal. *Neurotherapeutics* 1, 80–110.
63. Dietrich W.D. (2009). Therapeutic hypothermia in spinal cord injury. *Critical Care Medicine* 37(7), S238–S243.
64. American Spinal Injury Association. (2002). *International standards for neurological classification of SCI, revised 2002.* Chicago: American Spinal Injury Association.
65. Zimmer M.B., Nantwi K., Goshgarian H.G. (2007). Effect of spinal cord injury on the respiratory system: Basic research and current clinical treatment options. *Journal of Spinal Cord Medicine* 30, 319–330.
66. Garstang S.V., Miller-Smith S.A. (2007). Autonomic nervous system dysfunction after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America* 18, 275–296.
67. Blackner J. (2003). Rehabilitation medicine: Autonomic dysreflexia. *Canadian Medical Association Journal* 169, 931–935.
68. Benevento B.T., Sipski M.L. (2002). Neurogenic bladder, neurogenic bowel, and sexual dysfunction in people with spinal cord injury. *Physical Therapy* 62, 601–612.
69. Aito S., Pieri A., Marcelli F., et al. (2002). Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. *Spinal Cord* 40, 300–303.
70. Schwab M.E. (2002). Repairing the injured spinal cord. *Science* 295, 1029–1031.
71. Fawcett J. (2002). Repair of spinal cord injuries: Where are we, where are we going? *Spinal Cord* 40, 615–623.

Mechanisms and Manifestations of Brain Injury
Mechanisms of Brain Injury
Hypoxic and Ischemic Injury
Excitatory Amino Acid Injury
Cerebral Edema
Increased Intracranial Pressure, Herniation, and Hydrocephalus
Mechanisms of Increased Intracranial Pressure
Brain Herniation
Hydrocephalus
Traumatic Brain Injury
Types of Injury
Hematomas
Manifestations of Diffuse Brain Injury
Consciousness
Other Manifestations of Deteriorating Brain Function
Cerebrovascular Disease
The Cerebral Circulation
Regulation of Cerebral Blood Flow
Stroke (Brain Attack)
Ischemic Stroke
Hemorrhagic Stroke
Acute Stroke Management
Poststroke Management and Deficits
Aneurysmal Subarachnoid Hemorrhage
Arteriovenous Malformations
Infections and Brain Tumors
Infections
Meningitis
Encephalitis
Brain Tumors
Types of Tumors
Clinical Features
Seizure Disorders
Provoked and Unprovoked Seizures
Classification
Partial Seizures
Generalized Seizures
Unclassified Seizures
Diagnosis and Treatment
Diagnosis
Pharmacologic Treatment
Surgical Therapy
Generalized Convulsive Status Epilepticus
Disorders of Memory and Cognition
Dementia
Alzheimer Disease
Other Types of Dementia

Chapter 37

Disorders of Brain Function

Anatomically and functionally, the brain is the most complex structure in the body. It controls our ability to think, our awareness of things around us, and our interactions with the outside world. Signals to and from various parts of the body are controlled by very specific areas in the brain. Therefore, the brain is much more vulnerable to focal lesions that in other organs might produce no significant effects. For example, an isolated renal infarct would not be expected to have a significant effect on kidney function, whereas an infarct of comparable size in a specific area of the brain could produce complete paralysis on one side of the body.[1]

Mechanisms and Manifestations of Brain Injury

The brain is protected from external forces by the rigid confines of the skull and the cushioning afforded by the cerebrospinal fluid (CSF). The metabolic stability required by its electrically active cells is maintained by a number of regulatory mechanisms, including the blood-brain barrier and autoregulatory mechanisms that ensure its blood supply.

Mechanisms of Brain Injury

Injury to brain tissue can result from a number of conditions, including ischemia, trauma, infections, tumors, and degenerative processes. Brain damage resulting from these disorders involves several common pathways, including hypoxia and ischemia, the effects of excitatory amino acid injury, and cerebral edema. In many cases, the mechanisms of injury are interrelated.

Hypoxic and Ischemic Injury

The brain relies on the ability of the cerebral circulation to deliver sufficient oxygen for its energy needs. Although the brain makes up only 2% of the body weight, it receives one sixth of the resting cardiac output and accounts for 20% of the body's oxygen consumption.[1,2] By definition, *hypoxia* denotes a deprivation of oxygen with maintained blood flow, whereas *ischemia* represents

a situation of greatly reduced or interrupted blood flow. The cellular effects of hypoxia and ischemia are quite different, and the brain tends to have different sensitivities to the two conditions. Hypoxia interferes with the delivery of oxygen, while ischemia interferes with the delivery of oxygen and glucose as well as the removal of metabolic wastes.

Hypoxia usually is seen in conditions such as exposure to reduced atmospheric pressure, carbon monoxide poisoning, severe anemia, and failure of the lungs to oxygenate the blood. Contrary to popular belief, hypoxia is fairly well tolerated, particularly in situations of chronic hypoxia. Neurons are capable of substantial anaerobic metabolism and are fairly tolerant of pure hypoxia; it commonly produces euphoria, listlessness, drowsiness, and impaired problem solving. Unconsciousness and convulsions may occur when hypoxia is sudden and severe. However, the effects of severe hypoxia (i.e., anoxia) on brain function seldom are seen because the condition rapidly leads to cardiac arrest and ischemia.

Ischemia is seen in conditions of low blood flow. Cerebral ischemia can be focal, as in a stroke due to cerebral artery occlusion, or global, as in cardiac arrest.[3] Cerebral arterial occlusion leads to focal ischemia, and if sustained, to infarction of brain tissue in the distribution of the affected vessel. The location of the infarct and extent of tissue damage that results is determined by modifying variables, of which collateral blood flow is the most important. The collateral perfusion may even provide sufficient substrates to the borders of the focal ischemic region to maintain a low level of metabolic activity, thereby preserving tissue integrity.

Global Ischemia. Global ischemia occurs when blood flow is inadequate to meet the metabolic needs of the entire brain.[3] The result is a spectrum of neurologic disorders reflecting diffuse brain dysfunction. Unconsciousness occurs within seconds of severe global ischemia, such as that resulting from cardiac arrest. If cerebral circulation is restored immediately, consciousness is regained quickly. The unique vulnerability of the brain is attributed to its limited tolerance of ischemia and its response to reperfusion. The metabolic depletion of energy associated with ischemia can result in inappropriate release of excitatory amino acid neurotransmitters, disrupted calcium homeostasis, free radical formation, mitochondrial injury, and activation of cell-death pathways.[1,4] Although the threshold for ischemic neuronal injury is unknown, there is a period during which neurons can survive if blood flow is reestablished. Unfortunately, brain injury may not be reversible if the duration of ischemia is such that the threshold of injury has been reached. Even after circulation has been reestablished, damage to blood vessels and changes in blood flow can prevent return of adequate tissue perfusion. This period of postischemic hypoperfusion is thought to be associated with mechanisms such as the level of desaturation of venous blood, capillary and venular clotting, or sludging of blood.

Within the brain, certain regions and cell populations are more susceptible than others to hypoxic-ischemic injury[5] (Fig. 37-1). Selective neuronal sensitivity to a lack of oxygen is most apparent in the Purkinje cells of the cerebellum and neurons in the Sommer sector of the hippocampus, where cell death occurs earliest after global ischemia. The anatomic arrangement of the cerebral blood vessels predisposes to two types of injury: watershed infarcts and laminar necrosis. Areas of the brain located at the border zones between the overlapping territories supplied by the major cerebral arteries, sometimes called the *watershed areas*, are extremely vulnerable to ischemia. During events such as severe hypotension, these distal territories undergo a profound lowering of blood flow, predisposing to ischemia and infarction of brain tissues. As a consequence, areas of the cortex that are supplied by the major cerebral arteries usually regain function on recovery of adequate blood flow; however, infarctions may occur in the watershed boundary strips, resulting in focal neurologic deficits.

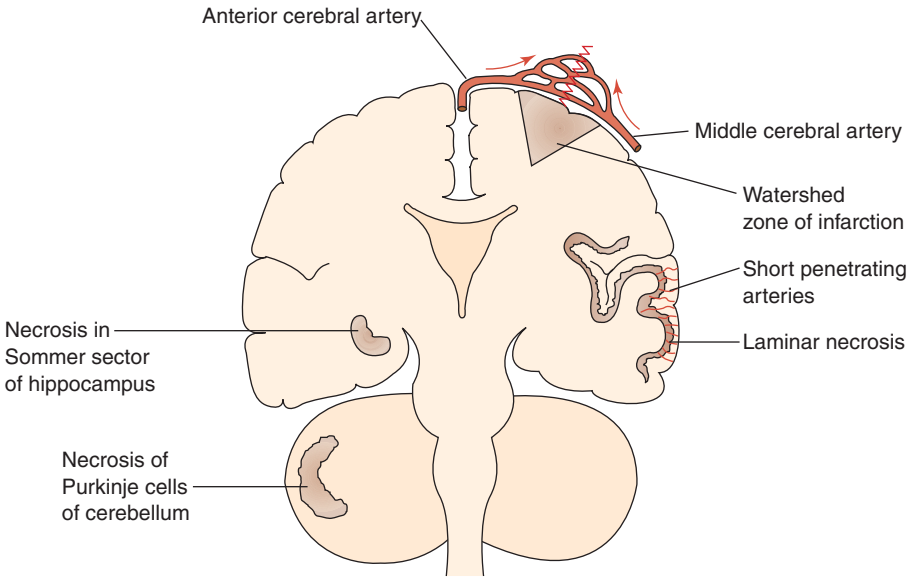


FIGURE 37-1. Consequences of global ischemia. A global insult induces lesions that reflect the vascular architecture (watershed infarcts, laminar necrosis) and the sensitivity of individual neuronal systems (pyramidal cells of the Sommer section, Purkinje cells). (Courtesy of Dmitri Karetnikov, artist.) (From Trojanowsi J.Q., Kenyon L. [2008]. The central nervous system. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1191]. Philadelphia: Lippincott Williams & Wilkins.)

Laminar necrosis refers to short, creeping segments of necrosis that occur within and parallel to the cerebral cortex, in areas supplied by the penetrating arteries. The gray matter of the cerebral cortex receives its major blood supply through short penetrating arteries that emerge at right angles from larger vessels in the pia mater and then form a cascade as they repeatedly branch, forming a rich capillary network. An abrupt loss of arterial blood pressure markedly diminishes flow through these capillary channels.

Treatment of global cerebral ischemia varies with the underlying cause (e.g., cardiac arrest, shock, asphyxia). General goals common to all causes are aimed at providing oxygen to the troubled brain and decreasing the metabolic needs of brain tissue during the nonflow state. Hemodynamic support aimed at restoring systemic and cerebral perfusion is required. Respiratory support including mechanical ventilation and supplemental oxygen may be indicated. Mild therapeutic hypothermia (i.e., 32°C to 34°C) for 12 to 24 hours is now recommended as an effective therapy for post–cardiac arrest syndrome.[4,6] Normovolemic hemodilution may be used to overcome sludging of cerebral blood flow during reperfusion. Because both hypoglycemia and hyperglycemia adversely affect the outcome in persons with global ischemia, control of blood glucose within a range of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) is appropriate.[4]

Excitatory Amino Acid Injury

In many neurologic disorders, injury to neurons may be caused by various mediators, including excitatory amino acids, catecholamines, free radicals, inflammatory cells, and intracellular proteases.[3] The earliest and most studied of these is the overstimulation of receptors for specific amino acids such as glutamate.[7,8] The neurologic conditions involved in excitotoxic injury range from acute insults due to conditions such as stroke, hypoglycemic injury, and trauma to chronic degenerative disorders such as Huntington disease and possibly Alzheimer dementia.

Many of the actions of glutamate are coupled with receptor-operated ion channels. One subtype in particular, the glutamate *N*-methyl-D-aspartate (NMDA) receptor, has been implicated in causing central nervous system (CNS) injury. This glutamate receptor subtype opens a large-diameter calcium channel that permits calcium ions to enter the cell. During prolonged ischemia, metabolic depletion of adenosine triphosphate (ATP) results in the inappropriate release of glutamate, initiating cell damage by allowing excessive influx of calcium ions. Excess intracellular calcium leads to a series of calcium-mediated processes called the *calcium cascade* (Fig. 37-2), which results in the release of intracellular enzymes that cause protein breakdown, free radical formation, lipid peroxidation, deoxyribonucleic acid (DNA) fragmentation, mitochondrial injury, nuclear breakdown, and eventually cell death.

The effects of acute glutamate toxicity may be reversible if the excess glutamate can be removed or if its effects can be blocked before the full cascade of events progresses. Various strategies that would protect viable brain cells from irreversible damage in the setting of excitotoxicity are currently under investigation. Pharmacologic strategies being explored include those that inhibit the synthesis or release of excitatory amino acid transmitters; block the NMDA receptors; prevent initiation of the calcium cascade; and block intracellular proteases, endonucleases, and lipases that are known to be cytotoxic.

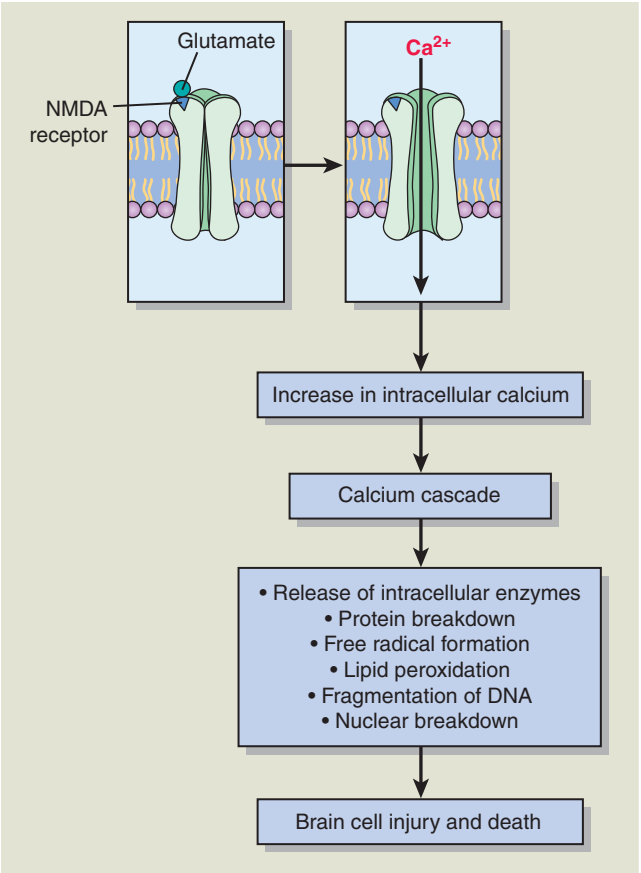


FIGURE 37-2. The role of the glutamate–*N*-methyl-D-aspartate (NMDA) receptor in brain cell injury.

Cerebral Edema

Cerebral edema, or brain swelling, is an increase in tissue volume secondary to abnormal fluid accumulation. There are two types of brain edema: vasogenic and cytotoxic.[1,9] Vasogenic edema occurs when integrity of the blood-brain barrier is disrupted, allowing fluid to escape into the extracellular fluid that surrounds brain cells. Cytotoxic edema involves the actual swelling of brain cells themselves.

Vasogenic Edema. Vasogenic edema occurs with conditions that impair the function of the blood-brain barrier and allow transfer of water and proteins from the vascular into the interstitial space. It occurs in conditions such as hemorrhage, brain injury, and infectious processes (e.g., meningitis). Vasogenic edema occurs primarily in the white matter of the brain, possibly because the white matter is more compliant than the gray matter.

Vasogenic edema can displace a cerebral hemisphere and can be responsible for various types of brain herniation. The functional manifestations of vasogenic edema include focal neurologic deficits, disturbances in consciousness, and severe intracranial hypertension.

Cytotoxic Edema. Cytotoxic edema involves an increase in intracellular fluid. It can result from hypo-osmotic states such as water intoxication or severe ischemia that impair the function of the sodium-potassium membrane pump. Ischemia also results in the inadequate removal of anaerobic metabolic end products such as lactic acid, producing extracellular acidosis. If blood flow is reduced to low levels for extended periods or to extremely low levels for a few minutes, cellular edema can cause the cell membrane to rupture, allowing the escape of intracellular contents into the surrounding extracellular fluid. This leads to damage of neighboring cells. The altered osmotic conditions result in water entry and cell swelling. Major changes in cerebral function, such as stupor and coma, occur with cytotoxic edema. The edema associated with ischemia may be severe enough to produce cerebral infarction with necrosis of brain tissue.

Increased Intracranial Pressure, Herniation, and Hydrocephalus

Intracranial pressure is, literally, the pressure inside the cranium. Increased intracranial pressure (ICP) is a common pathway for brain injury from different types of insults and agents. Excessive ICP can obstruct cerebral blood flow, destroy brain cells, displace brain tissue (as in herniation), and otherwise damage delicate brain structures.

Mechanisms of Increased Intracranial Pressure

The cranial cavity contains blood (approximately 10%), brain tissue (approximately 80%), and CSF (approximately 10%) in the rigid confines of a nonexpandable skull.[9] Each of these three volumes contributes to the ICP, which normally is maintained within a range of 0 to 15 mm Hg when measured in the lateral ventricles. The volumes of each of these components can vary slightly without causing marked changes in ICP. This is because small increases in the volume of one component can be compensated for by a decrease in the volume of one or both of the other two components.[10] This association is called the *Monro-Kellie hypothesis*.

Abnormal variation in intracranial volume with subsequent changes in ICP can be caused by a volume change in any of the three intracranial components. For example, an increase in tissue volume can result from a brain tumor, brain edema, or bleeding into brain tissue. An increase in blood volume develops when there is vasodilation of cerebral vessels or obstruction of venous outflow. Excess production, decreased absorption, or obstructed circulation of CSF affords the potential for an increase in the CSF component.

According to the modified Monro-Kellie hypothesis, reciprocal compensation occurs among the three intracranial compartments.[9] Of the three intracranial volumes, tissue volume is relatively restricted in its ability to undergo change; CSF and blood volume are best able to compensate for changes in ICP. Initial increases in ICP are buffered by a translocation of CSF to the spinal subarachnoid space and increased reabsorption of CSF. The compensatory ability of the blood compartment is limited by the small amount of blood that is in the cerebral circulation. The cerebral blood vessels contain less than 10% of the intracranial volume, most of which is contained in the low-pressure venous system. As the volume-buffering capacity of this compartment becomes exhausted, venous pressure increases, and cerebral blood volume and ICP rise. Also, cerebral blood flow is highly controlled by autoregulatory mechanisms, which affect its compensatory capacity. For example, conditions such as ischemia and an elevated partial pressure of carbon dioxide (PCO_2) in the blood produce a compensatory vasodilation of the cerebral blood vessels. A decrease in PCO_2 has the opposite effect; for this reason, hyperventilation, which results in a decrease in PCO_2 levels, is sometimes used in the treatment of ICP.

The impact of increases in blood, brain tissue, or CSF volumes on ICP varies among individuals and depends on the amount of increase, effectiveness of compensatory mechanisms, and compliance of brain tissue. *Compliance* represents the ratio of change in volume to the resulting change in pressure (compliance = change in volume/change in pressure).[9] In the case of intracranial volumes and pressure, an increase in intracranial volume will have little, or no, effect on ICP as long as compliance is high. Factors that influence compliance include the amount of volume increase, the time frame for accommodation, and the size of the intracranial compartments. For example, small volume increments over long periods of time can be accommodated more easily than a comparable amount introduced over a short time.

The cerebral perfusion pressure (CPP), which represents the difference between the mean arterial blood pressure (MABP) and the ICP (CPP = MABP – ICP), is the pressure perfusing the brain.[9,10] CPP is determined by the pressure gradient between the internal carotid artery and the subarachnoid veins. The MABP and ICP are monitored frequently in persons with brain conditions that increase ICP and impair brain perfusion. Normal CPP ranges from 70 to 100 mm Hg. In the laboratory, brain ischemia is not seen until the CPP falls below 40 mm Hg.[10] When the pressure in the cranial cavity approaches or exceeds the MABP, tissue perfusion becomes inadequate, cellular hypoxia results, and neuronal death may occur. The highly specialized cortical neurons are the most sensitive to oxygen deficit; a decrease in the level of consciousness is one of the earliest and most reliable signs of increased ICP. The continued cellular hypoxia leads to general neurologic deterioration; the level of consciousness may deteriorate from alertness through confusion, lethargy, obtundation, stupor, and coma.

One of the late reflexes seen with a marked increase in ICP is the CNS ischemic response, which is triggered by

ischemia of the vasomotor center in the brain stem. Neurons in the vasomotor center respond directly to ischemia by producing a marked increase in MABP in an attempt to increase CPP, sometimes to levels as high as 270 mm Hg, accompanied by a widening of the pulse pressure and reflex slowing of the heart rate. These three signs (i.e., hypertension, bradycardia, and widened pulse pressure), sometimes called the *Cushing reflex*, are important but late indicators of increased ICP.[11]

Brain Herniation

The brain is protected by the nonexpandable skull and two supporting septa, the falx cerebri and the tentorium cerebelli, which divide the intracranial cavity into fossae or compartments that normally protect against excessive movement.[1,9] The *falx cerebri* is a sickle-shaped septum that separates the two hemispheres. The *tentorium cerebelli* divides the cranial cavity into anterior and posterior fossae (Fig. 37-3A). This inflexible dural sheath extends posteriorly from the bony petrous ridges and anteriorly to the clinoid process, sloping downward and outward from its medial edge to attach laterally to the occipital bone. Extending posteriorly into the center of the tentorium is a large semicircular opening called the *incisura* or *tentorial notch*. The temporal lobe rests on the tentorial incisura, and the midbrain occupies the anterior portion of the tentorial notch. The cerebellum is closely opposed to the dorsum of the midbrain and fills the posterior part of the notch. Other important anatomic associations exist among the anterior cerebral, internal carotid, posterior communicating, and posterior and superior cerebellar arteries and the incisura (see Fig. 37-3B). The oculomotor nerve (cranial nerve [CN] III) emerges from the mediolateral surface of each peduncle just caudal to the tentorium.

Brain herniation represents a displacement of brain tissue under the falx cerebri or through the tentorial notch or incisura of the tentorium cerebelli. It occurs when an elevated ICP in one brain compartment causes displacement of the cerebral tissue toward an area of lower pressure. The different types of herniation syndromes are based on the area of the brain that has herniated and the structure under which it has been pushed. They commonly are divided into two broad categories, *supratentorial* and *infratentorial*, based on whether they are located above or below the tentorium.

Supratentorial Herniations. Progressive supratentorial lesions develop sequential clinical signs and symptoms of ocular, motor, and respiratory function. This pattern follows the predictable continuum of rostral-to-caudal failure that proceeds from the diencephalon to the midbrain, followed by the pons, and eventually medullary function. The pattern of deterioration is fairly predictable unless vascular or obstructive complications occur and exaggerate the condition.

There are two major types of supratentorial herniation: cingulate and transtentorial.[1,9] A *cingulate herniation* (see Fig. 37-3C [1]), which poses the less serious threat in terms of clinical outcomes, involves displacement of the cingulate gyrus and hemisphere beneath the sharp edges of the falx cerebri to the opposite side of the brain.[9] This displacement can compress local blood supply and cerebral tissue, causing edema and ischemia, which further increase the degree of ICP elevation. There may also be compression of branches of the anterior cerebral artery with unilateral or bilateral leg weakness.

Transtentorial herniations result in two distinct syndromes: a central syndrome and an uncal syndrome, which is the most common herniation syndrome.[9,12] Clinically, they display distinct patterns early in their course, but both merge in a similar pattern once they begin to involve the midbrain level and below. *Central transtentorial*

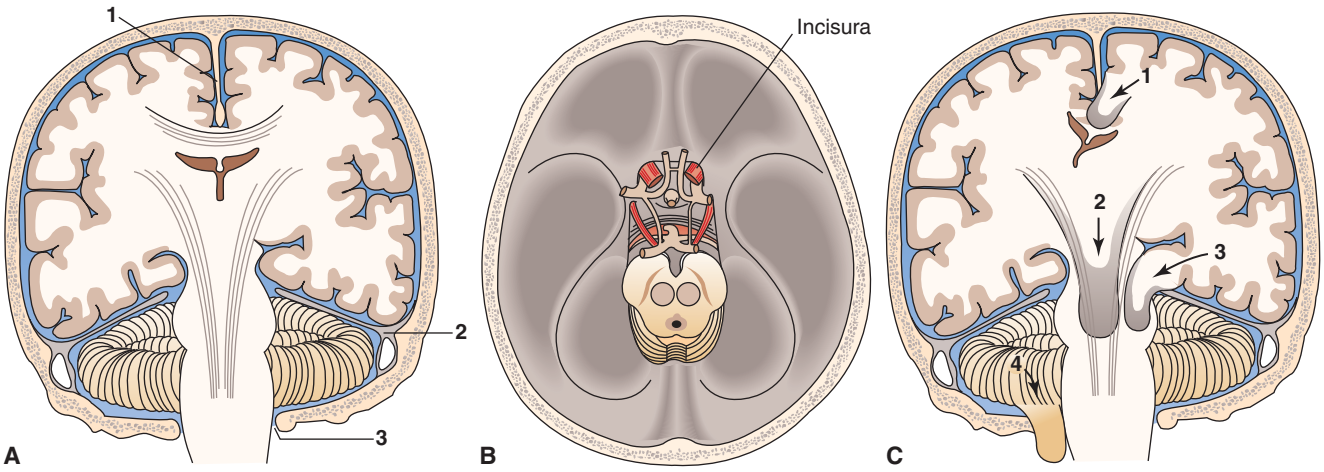


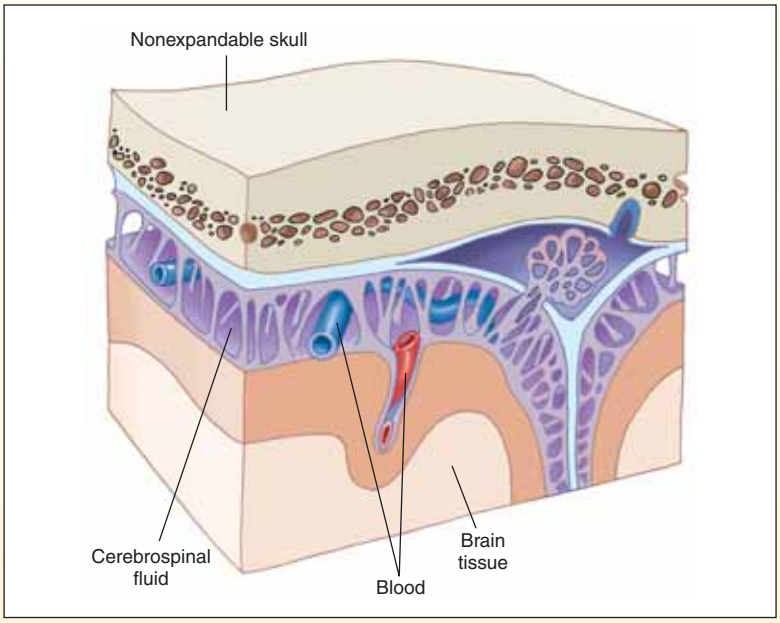
FIGURE 37-3. Supporting septa of the brain and patterns of herniation. **(A)** The falx cerebri [*1*], tentorium cerebelli [*2*], and foramen magnum [*3*]. **(B)** The location of the incisura or tentorial notch in relation to the cerebral arteries and oculomotor nerve. **(C)** Herniation of the cingulate gyrus under the falx cerebri [*1*], central or transtentorial herniation [*2*], uncal herniation of the temporal lobe into the tentorial notch [*3*], and infratentorial herniation of the cerebellar tonsils [*4*]. (Courtesy of Carole Russell Hilmer, C.M.I.)

UNDERSTANDING → Intracranial Pressure

The intracranial pressure (ICP) is the pressure within the intracranial cavity. It is determined by (1) the pressure-volume relationships among the brain tissue, cerebrospinal fluid (CSF), and blood in the intracranial cavity; (2) the Monro-Kellie hypothesis, which relates to reciprocal changes among the intracranial volumes; and (3) the compliance of the brain and its ability to buffer changes in intracranial volume.

1

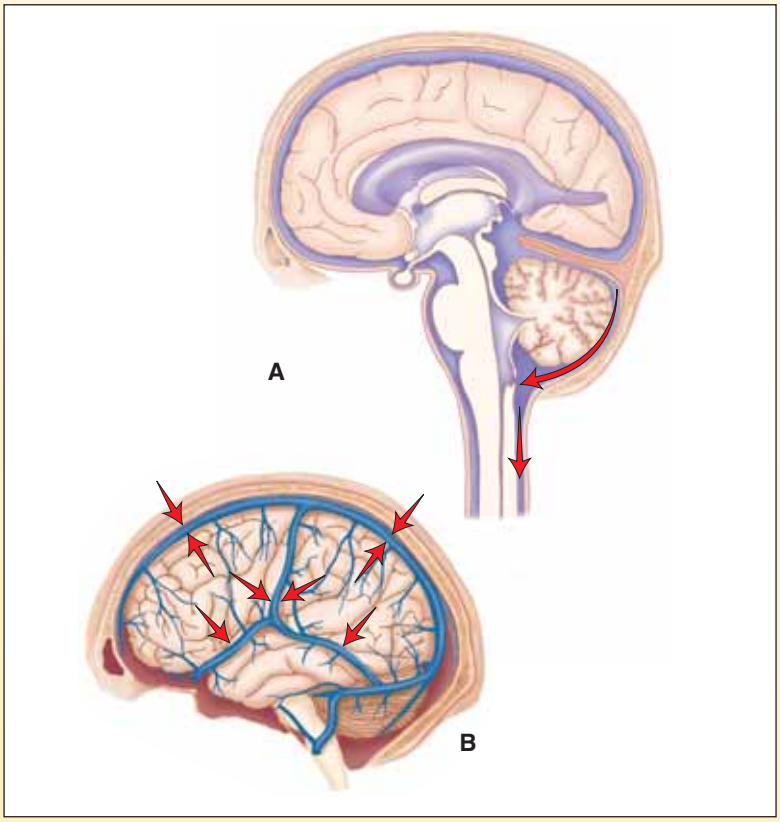
Intracranial Volumes and Pressure. The ICP represents the pressure exerted by the essentially incompressible tissue and fluid volumes of the three compartments contained within the rigid confines of the skull—the brain tissue and interstitial fluid (80%), the blood (10%), and the CSF (10%).



2

Monro-Kellie Hypothesis. Normally, a reciprocal relationship exists among the three intracranial volumes such that the ICP is maintained within normal limits. Because these volumes are practically incompressible, a change in one component must be balanced by an almost equal and opposite effect in one or both of the remaining components. This is known as the *Monro-Kellie hypothesis*.

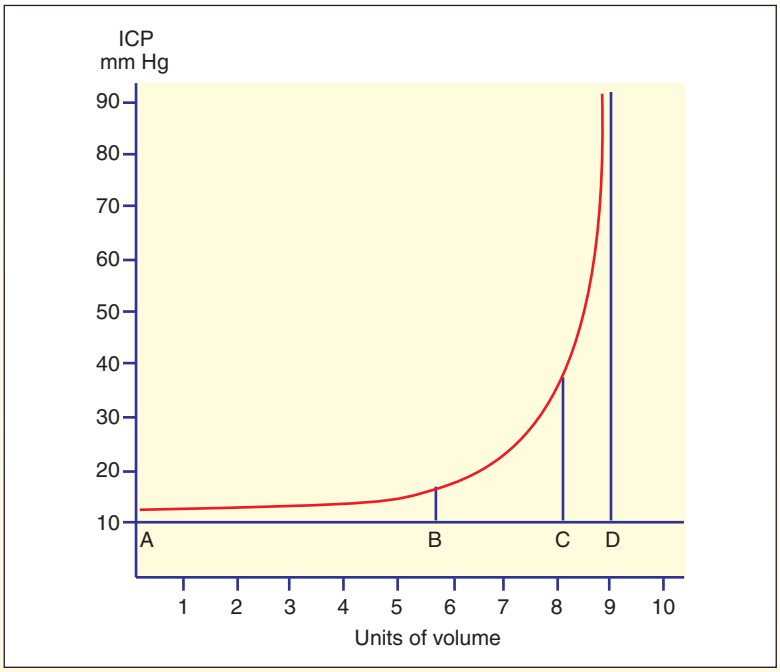
Of the three intracranial volumes, the fluid in the CSF compartment is the most easily displaced. The CSF (**A**) can be displaced from the ventricles and cerebral subarachnoid space to the spinal subarachnoid space, and it can also undergo increased absorption or decreased production. Because most of the blood in the cranial cavity is contained in the low-pressure venous system, venous compression (**B**) serves as a means of displacing blood volume.



3

Compliance and the Volume-Pressure Curve. Compliance, which refers to the ease with which a substance can be compressed or deformed, is a measure of the brain's ability to maintain its ICP during changes in intracranial volume. Compliance (C) represents the ratio of change (Δ) in volume (V) to change in pressure (P): $C = \Delta V/\Delta P$.

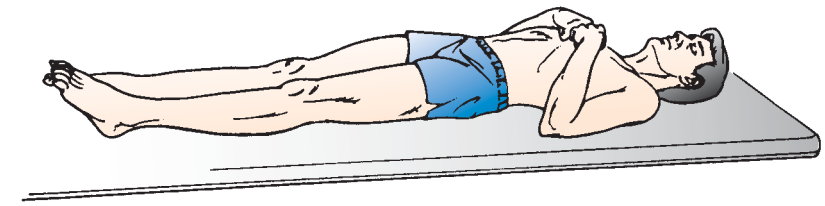
The dynamic effects of changes in intracranial volume and compliance on ICP can be illustrated on a graph with the volume represented on the horizontal axis and ICP on the vertical axis. The shape of the curve demonstrates the effect on ICP of adding volume to the intracranial cavity. From points A to B, the compensatory mechanisms are adequate, compliance is high, and the ICP remains relatively constant as volume is added to the intracranial cavity. At point B, the ICP is relatively normal, but the compensatory mechanisms have reached their limits, compliance is decreased, and ICP begins to rise with each change in volume. From points C to D, the compensatory mechanisms have been exceeded and ICP rises significantly with each increase in volume as compliance is lost.



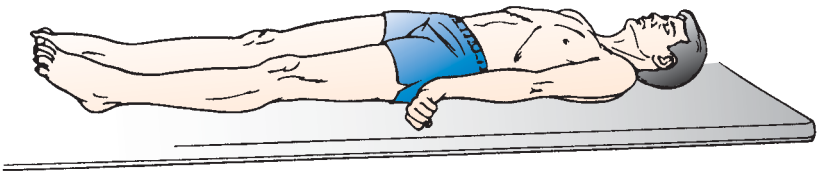
(From Hickey J.V. [2003]. *Neurological and neurosurgical nursing* [5th ed., p. 286]. Philadelphia. Lippincott Williams & Wilkins.)

herniations (see Fig. 37-3C [2]) involve the downward displacement of the cerebral hemispheres, basal ganglia, diencephalon, and midbrain through the tentorial incisura. Bilateral small, reactive pupils and drowsiness are heralding signs. The *uncal herniation syndrome* occurs when an expanding lesion pushes the medial aspect of the temporal lobe, which contains the uncus and hippocampal gyrus, through the incisura of the tentorium (see Fig 36-3C [3]). As a result, the diencephalon and midbrain are compressed and displaced laterally to the opposite side of the tentorium. The oculomotor nerve (CN III) and the posterior cerebral artery frequently are caught between the uncus and the tentorium. The oculomotor nerve controls pupillary constriction; entrapment of this nerve results in ipsilateral pupillary dilation, which usually is an early sign of uncal herniation. Consciousness may be unimpaired because the reticular activating system, which is responsible for wakefulness, has not yet been affected. As uncal herniations progress, there are changes in motor strength and coordination of voluntary movements because of compression of the descending motor pathways. It is not unusual for initial changes in motor function to occur ipsilateral to the side of the brain damage because of compression of the contralateral cerebral peduncles. Changes in consciousness and coma may follow due to compression of the midbrain against the opposite tentorial edge. Decerebrate posturing (Fig. 37-4B) may develop, followed by dilated, fixed pupils; flaccidity; and respiratory arrest.

Infratentorial Herniation. Infratentorial herniation results from increased pressure in the infratentorial compartment.[9] Herniation may occur superiorly (upward) through the tentorial incisura or inferiorly (downward)



A Flexor or decorticate posturing



B Extensor or decerebrate posturing

FIGURE 37-4. Abnormal posturing. **(A)** Decorticate rigidity. In decorticate rigidity, the upper arms are held at the sides, with elbows, wrists, and fingers flexed. The legs are extended and internally rotated. The feet are plantar flexed. **(B)** Decerebrate rigidity. In decerebrate rigidity, the jaws are clenched and neck extended. The arms are adducted and stiffly extended at the elbows with the forearms pronated, wrists and fingers flexed. (From Fuller J., Schaller-Ayers J. [1994]. *Health assessment: A nursing approach* [2nd ed.]. Philadelphia: J.B. Lippincott.)

through the foramen magnum. Upward displacement of brain tissue can cause blockage of the aqueduct of Sylvius and lead to hydrocephalus and coma. Downward herniation involves displacement of the midbrain through the tentorial notch or the cerebellar tonsils through the foramen magnum (Fig. 37-3C[4]). It often progresses rapidly and can cause death because it is likely to involve the lower brain stem centers that control vital cardiopulmonary functions.

In cases of preexisting ICP elevations, herniation may occur when the pressure is released from below, such as in a lumbar puncture. If the CSF pathway is blocked and fluid cannot leave the ventricles, the volume expands, and fluid is displaced downward through the tentorial notch. The result of this displacement is brain stem ischemia and hemorrhage extending from the diencephalon to the pons. If the lesion expands rapidly, displacement and obstruction occur quickly, leading to irreversible infarction and hemorrhage.

Hydrocephalus

Hydrocephalus represents a progressive enlargement of the ventricular system due to an abnormal increase in CSF volume (see Chapter 34, Fig. 34-21). It can result because of overproduction of CSF, impaired reabsorption of CSF, or obstruction of CSF flow in the ventricular system.

There are two types of hydrocephalus: noncommunicating and communicating.[1,9] *Noncommunicating* or *obstructive hydrocephalus* occurs when obstruction in the ventricular system prevents the CSF from reaching the arachnoid villi. CSF flow can be obstructed by congenital malformations, from tumors encroaching on the ventricular system, or by inflammation or hemorrhage. *Communicating hydrocephalus* is caused by impaired reabsorption of CSF from the arachnoid villi into the venous system. Decreased absorption can result from a block in the CSF pathway to the arachnoid villi or a failure of the villi to transfer the CSF to the venous system. It can occur if too few villi are formed, if postinfective (meningitis) scarring occludes them, or if the villi become obstructed with fragments of blood or infectious debris. Adenomas of the choroid plexus can cause an overproduction of CSF. This form of hydrocephalus is much less common than that resulting from decreased absorption of CSF.

Similar pathologic patterns occur with noncommunicating and communicating types of hydrocephalus. The cerebral hemispheres become enlarged, and the ventricular system beyond the point of obstruction is dilated. The sulci on the surface of the brain become effaced and shallow, and the white matter is reduced in volume. Computed tomographic (CT) and magnetic resonance imaging (MRI) scans are used to diagnose all types of hydrocephalus. The usual treatment is a shunting procedure, which provides an alternative route for return of CSF to the circulation.

Signs and symptoms of hydrocephalus vary greatly, depending on the rapidity of onset. When hydrocephalus develops in utero or before the cranial sutures have fused in infancy, the ventricles expand beyond the point of obstruction, the cranial sutures separate, the head expands, and there is bulging of the fontanels. Because the skull is able to expand, signs of increased ICP may be absent, and intelligence spared. However, seizures are not uncommon, and in severe cases, optic nerve atrophy leads to blindness. Weakness and uncoordinated movement are common. Surgical placement of a shunt allows for diversion of excess CSF fluid, preventing extreme enlargement of the head and neurologic deficits.

In adults and children in whom the cranial sutures have fused, head enlargement does not occur. Acute-onset hydrocephalus usually is marked by symptoms of increased ICP, including headache, vomiting, and papilledema or deviation in eye movements due to pressure on the cranial nerves. If the obstruction is not relieved, progression to herniation ensues (see previous discussion of herniation). Treatment includes surgical decompression and shunting.

An important type of communicating hydrocephalus that is seen in older adults is called *normal-pressure hydrocephalus*. In normal-pressure hydrocephalus, there is ventricular enlargement with compression of cerebral

tissue, but a normal CSF pressure. The signs and symptoms of normal-pressure hydrocephalus, which include memory changes, disturbances in gait, and urinary incontinence, usually have an insidious onset. The changes occur so slowly that they can be easily overlooked by the patient or his or her family or they may be attributed to the aging process in older persons.[9] The accepted treatment for normal-pressure hydrocephalus is a ventricular shunt.

Traumatic Brain Injury

The term *head injury* is used to describe all structural damage to the head and has become synonymous with *traumatic brain injury*.[13] The main causes of head injury are motor vehicle and bicycle crashes, pedestrian impacts, sports, falls, and assaults, with the most common cause of fatal head injuries being motor vehicle accidents.[14]

The physical forces associated with head injury may result in skull fractures, brain injury, and vascular damage, all three of which can coexist. Two thirds of skull fractures are accompanied by intracranial lesions, and the presence of skull fracture greatly increases the risk of an underlying subdural and/or epidural hemorrhage.[14] Skull fractures also provide pathways for the entry of bacteria (meningitis) or air (pneumocephalus) to the CSF and for leakage of CSF out of the dura. Skull fractures can also cause damage to the cranial nerves as they exit the cranial vault. The cranial nerves likely to be injured with head trauma include the olfactory (CN I), optic (CN II), oculomotor (CN III), and trochlear (CN IV); the first and second branches of the trigeminal (CN V); and the facial (CN VII) and auditory (CN VIII).[9]

Types of Injury

The effects of traumatic head injuries can be divided into two categories: primary or direct injuries, in which damage is caused by impact, and secondary injuries, in which damage results from the subsequent brain swelling, infection, or cerebral hypoxia.[9,14–17] The direct brain injuries include diffuse axonal injury and the focal lesions of lacerations, contusion, and hemorrhage. Secondary brain injuries are often diffuse or multifocal, including concussion, infection, and hypoxic brain injury. Although the skull and CSF provide protection for the brain, they also can contribute to trauma. When the mechanical forces inducing head injury cause bouncing of the brain in the closed confines of the rigid skull, a coup–contrecoup injury occurs. Because the brain floats freely in the CSF, blunt force to the head accelerates the brain within the skull, and then the brain decelerates abruptly upon hitting the inner skull surfaces[5,9] (Fig. 37-5). The direct contusion of the brain at the site of external force is referred to as a *coup* injury, whereas the rebound injury on the opposite side of the brain is the *contrecoup* injury. As the brain

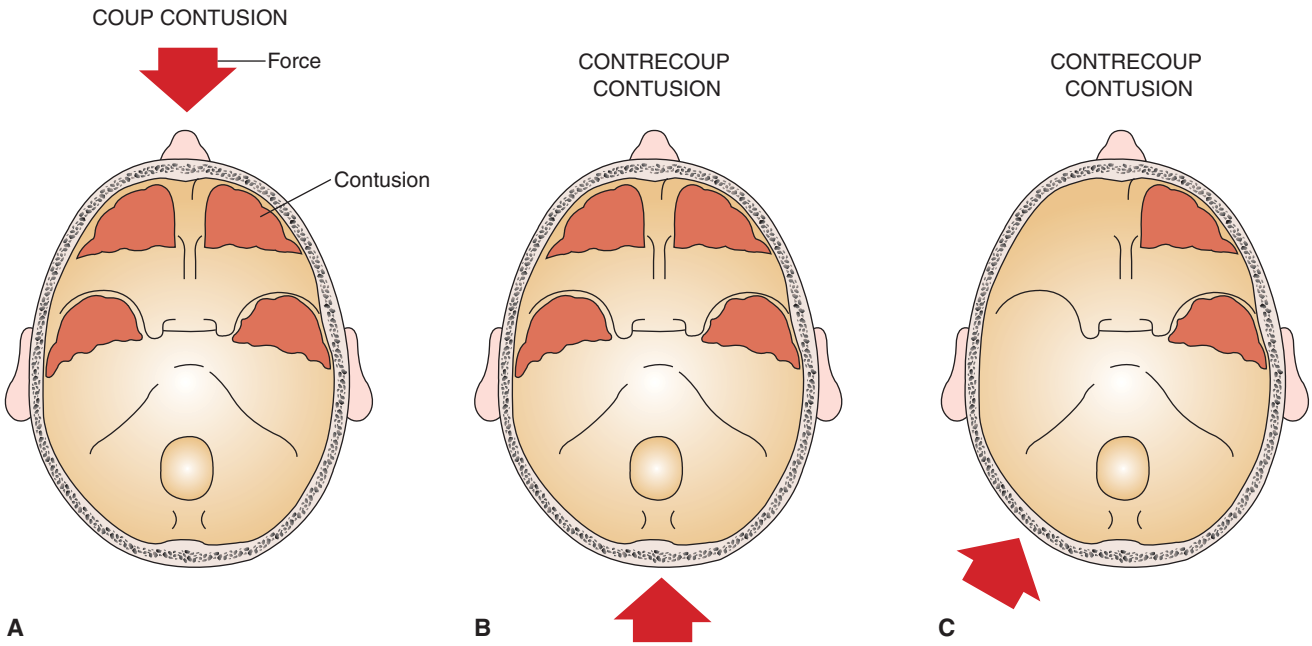


FIGURE 37-5. Mechanisms of cerebral contusion in coup–contrecoup injuries. **(A)** A focal area of cerebral injury (coup contusion) at the point of impact. The cerebral hemispheres float in the cerebrospinal fluid. **(B)** Rapid deceleration or, less commonly, acceleration causes the cortex to impact forcefully into the anterior or middle fossa, causing injury to the side of the brain opposite the site of injury (contrecoup contusion). **(C)** The position of a contrecoup contusion is determined by the direction of the force and the intracranial anatomy. (Courtesy of Dmitri Karetnikov, artist.) (From Trojanowski J.Q. [2005]. The central nervous system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 1430]. Philadelphia: Lippincott Williams & Wilkins.)

strikes the rough surface of the cranial vault, brain tissue, blood vessels, nerve tracts, and other structures are bruised and torn, resulting in contusions and hematomas.

Ischemia is considered the most common cause of secondary brain injury. It can result from the hypoxia and hypotension that occur during the resuscitation process or from the impairment of regulatory mechanisms by which cerebrovascular responses maintain an adequate blood flow and oxygen supply.[16,17] Insults that occur immediately after injury or in the course of resuscitation efforts are important determinants of the outcome from severe brain injury. More than 25% of patients with severe head injury sustain one or more secondary insults in the time between injury and resuscitation, indicating the need for improved airway management and circulatory status.[17] The significance of secondary injuries depends on the extent of damage caused by the primary injury. Certain secondary injuries have been discussed, such as increased ICP, cerebral edema, and brain herniation.

In *mild head injury*, there may be momentary loss of consciousness without demonstrable neurologic symptoms or residual damage, except for possible residual amnesia. Microscopic changes usually can be detected in the neurons and neuroglia within hours of injury, but brain imaging is negative. Concussion refers to an immediate and transient loss of consciousness accompanied by a brief period of amnesia after a blow to the head.[15,18] Although recovery usually takes place within 24 hours, mild symptoms, such as headache, irritability, insomnia, and poor concentration and memory, may persist for months. This is known as the *postconcussion syndrome*. The memory loss usually includes an interval of time preceding the injury (retrograde amnesia) and following the injury (anterograde amnesia). The duration of retrograde amnesia correlates with the severity of the brain injury. Because these cognitive complaints are vague and subjective, they sometimes are regarded as being of psychological origin. Postconcussion syndrome can have a significant effect on activities of daily living and return to employment. Persons with postconcussion syndrome may need cognitive retraining, medications, or psychological support.

In *moderate head injury*, many small hemorrhages and some swelling of brain tissue occur. These contusions often are distributed along the rough, irregular inner surface of the brain and are more likely to occur in the frontal or temporal lobes, resulting in cognitive and motor deficits. Moderate head injury is characterized by a period of unconsciousness and may be associated with focal manifestations such as hemiparesis, aphasia, and cranial nerve palsy. In this type of injury, the contusions often can be visualized on CT scan.

Severe head injury involves extensive mechanical and secondary damage to brain structures and deficits in arousal, usually coma. In severe head injury, the mechanical injury is instantaneous and irreversible, resulting from shearing and pressure forces that cause diffuse axonal injury, disruption of blood vessels, and tissue damage. It often is accompanied by severe neurologic deficits such as coma, hemiplegia, and all the other signs of elevated ICP. Contusions and intracerebral, subdural, epidural, and subarachnoid hemorrhages are often evident on CT scan. Severe head injuries often occur with injury to other parts of the body such as the extremities, chest, and abdomen, which often limits the examiner's ability to carefully assess the neurologic deficits.

Hematomas

Hematomas result from vascular injury and bleeding. Depending on the anatomic position of the ruptured vessel, bleeding can occur in any of several compartments, including the epidural, subdural, and subarachnoid spaces, or into the brain itself (intracerebral hematoma).

Epidural Hematoma. An epidural hematoma is one that develops between the inner bones of the skull and the dura (Fig. 37-6). It usually results from a tear in an artery, most often the middle meningeal, usually in association with a head injury in which the skull is fractured.[1,5,17] Because bleeding is arterial in origin, rapid expansion of the hematoma compresses the brain. Epidural hematoma is more common in a young person because the dura is less firmly attached to the skull surface than in an older person; as a consequence, the dura can be easily separated from the inner surface of the skull, allowing the hematoma to grow.

Typically, a person with an epidural hematoma presents with a history of head injury and a brief period of unconsciousness followed by a lucid period in which consciousness is regained, followed by rapid progression to

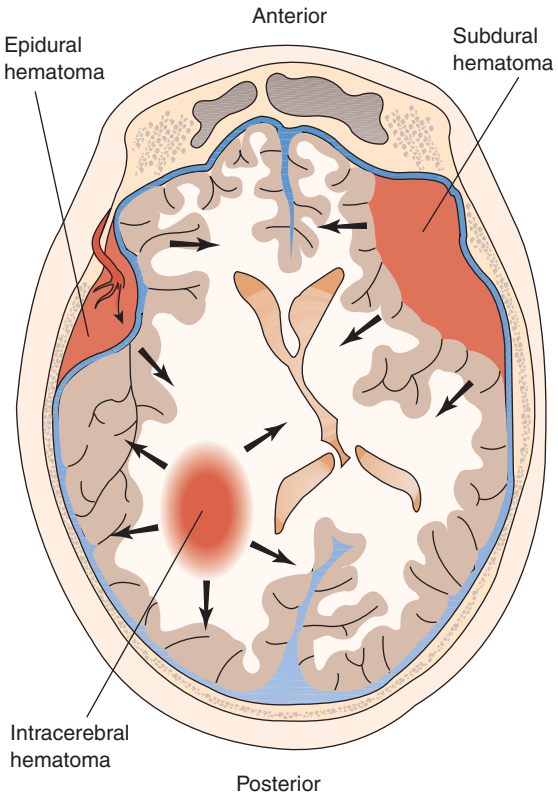


FIGURE 37-6. Location of epidural, subdural, and intracerebral hematomas.

unconsciousness. The lucid interval does not always occur, but when it does, it is of great diagnostic value. With rapidly developing unconsciousness, there are focal symptoms related to the area of the brain involved. These symptoms can include ipsilateral (same side) pupil dilation and contralateral (opposite side) hemiparesis from uncal herniation. If the hematoma is not removed, the condition progresses, with increased ICP, tentorial herniation, and death. However, prognosis is excellent if the hematoma is removed before loss of consciousness occurs.

Subdural Hematoma. A subdural hematoma develops in the area between the dura and the arachnoid (subdural space) and usually is the result of a tear in the small bridging veins that connect veins on the surface of the cortex to dural sinuses. The bridging veins pass from the pial vessels through the CSF-filled subarachnoid space, penetrate the arachnoid and the dura, and empty into the intradural sinuses.[1,5] These veins are readily snapped in head injury when the brain moves suddenly in relation to the cranium (Fig. 37-7). Bleeding can occur between the dura and arachnoid (i.e., subdural hematoma) or into the CSF-filled subarachnoid space (i.e., subarachnoid hematoma).

The venous source of bleeding in a subdural hematoma develops more slowly than the arterial bleeding in an epidural hematoma. Subdural hematomas are classified as acute, subacute, or chronic. This classification system is based on the approximate time before the appearance of symptoms. Symptoms of acute hematoma are seen within 24 hours of the injury, whereas subacute hematoma does not produce symptoms until 2 to 10 days after injury. Symptoms of chronic subdural hematoma may not arise until several weeks after the injury.

Acute subdural hematomas progress rapidly and have a high mortality rate because of the severe secondary injuries related to edema and increased ICP. The high mortality rate has been associated with uncontrolled ICP increase, loss of consciousness, decerebrate posturing (Fig. 37-4B), and delay in surgical removal of the hematoma. The clinical picture is similar to that of epidural hematoma, except that there usually is no lucid interval. By contrast, in subacute subdural hematoma, there may be a period of improvement in the level of consciousness and neurologic symptoms, only to be followed by deterioration if the hematoma is not removed.

Symptoms of chronic subdural hematoma develop weeks after a head injury, so much later that the person may not remember having had a head injury. Chronic subdural hematoma is more common in older persons because brain atrophy causes the brain to shrink away from the dura and stretch fragile bridging veins. These veins rupture, causing slow seepage of blood into the subdural space. Fibroblastic activity causes the hematoma to become encapsulated. The sanguineous fluid in this encapsulated area has high osmotic pressure and draws in fluid from the surrounding subarachnoid space; the mass expands, exerting pressure on the cranial contents. In some instances, the clinical picture is less defined, with the most prominent symptom being a decreasing level of consciousness indicated by drowsiness, confusion, headache, and apathy.

Traumatic Intracerebral Hematomas. Traumatic intracerebral hematomas may be single or multiple. They can occur in any lobe of the brain but are most common in the frontal or temporal lobes, related to the bony prominences on the inner skull surface (Fig. 37-8). They may occur in association with the severe motion that the brain undergoes during head injury, or a contusion can coalesce into a hematoma. Intracerebral hematomas occur more frequently in older persons and alcoholics, whose cerebral vessels are more friable.

The signs and symptoms produced by an intracerebral hematoma depend on its size and location in the brain. Signs of increased ICP can be manifested if the hematoma

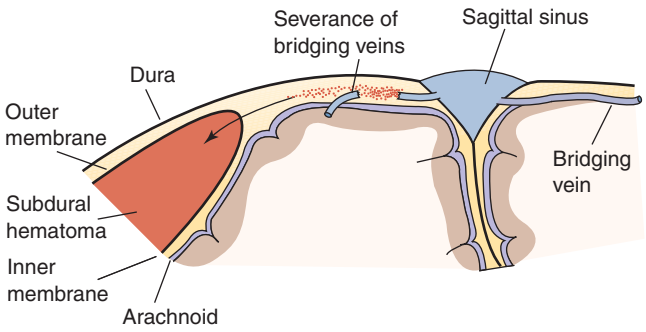


FIGURE 37-7. Mechanism of bleeding in subdural hematoma. (Courtesy of Dmitri Karetnikov, artist.) (From Trojanowski J.Q. [2005]. The central nervous system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 1430]. Philadelphia: Lippincott Williams & Wilkins.)

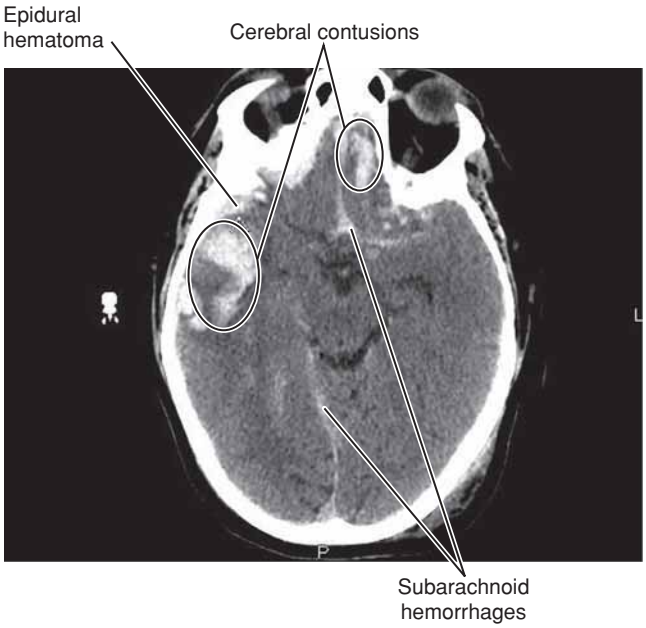


FIGURE 37-8. Computed tomography scan of brain in traumatic brain injury, showing hemorrhagic cerebral contusions in right temporal and bifrontal lobes, subarachnoid hemorrhages, and epidural hematoma.

is large and encroaching on vital structures. A hematoma in the temporal lobe can be dangerous because of the potential for lateral herniation.

Manifestations of Diffuse Brain Injury

Global or diffuse brain injury, whether due to head trauma, stroke, or other pathologic processes, is manifested by alterations in sensory, motor, and cognitive function and by changes in the level of consciousness. In contrast to a localized injury, which causes focal neurologic deficits without altered consciousness, global injury nearly always results in altered levels of consciousness, ranging from inattention to stupor or coma. Severe injury that seriously compromises brain function may result in brain death.

The cerebral hemispheres are the most susceptible to damage, and the most frequent sign of brain dysfunction is an altered level of consciousness and change in behavior. As the brain structures in the diencephalon, midbrain, pons, and medulla are sequentially affected, additional signs related to pupillary and eye movement reflexes, motor function, and respiration become evident (Table 37-1). Hemodynamic and respiratory instability are the last signs to occur because their regulatory centers are located low in the medulla.

In progressive brain deterioration, the person's neurologic capabilities appear to deteriorate in stepwise fashion. Similarly, as neurologic function returns, there usually is a stepwise progression to higher levels of consciousness. Deterioration of brain function from supratentorial lesions tends to follow a stepwise rostral-to-caudal progression, which is observed as the brain initially compensates for injury and subsequently decompensates with loss of autoregulation and cerebral perfusion. Infratentorial (brain stem) lesions may lead to an early, sometimes abrupt disturbance in consciousness without any orderly rostral to caudal progression of neurologic signs.

Consciousness

Consciousness is the state of awareness of self and the environment and of being able to become oriented to new stimuli.[19–21] It has traditionally been divided into two components: (1) arousal and wakefulness and (2) content and cognition. The content and cognition aspects of consciousness are determined by a functioning cerebral cortex. Arousal and wakefulness require the concurrent functioning of both cerebral hemispheres and an intact reticular activating system (RAS) in the brain stem.

The RAS is a diffuse, primitive system of interlacing nerve cells and fibers in the brain stem that receives input from multiple sensory pathways (Fig. 37-9). Anatomically, the RAS constitutes the central core of the brain stem, extending from the medulla through the pons to the midbrain, which is continuous caudally with the spinal cord and rostrally with the subthalamus, the hypothalamus, and the thalamus. Fibers from the reticular formation also project to the autonomic nervous system and motor systems. The hypothalamus plays a predominant role in maintaining homeostasis through integration of somatic, visceral, and endocrine functions. Inputs from the reticular formation, vestibulospinal projections, and other motor systems are integrated to provide a continuously adapting background of muscle tone and posture to facilitate voluntary motor actions. Reticular formation neurons that function in regulation of cardiovascular, respiratory, and other visceral functions are intermingled with those that maintain other reticular formation functions.

Ascending fibers of the reticular formation, known as the *ascending reticular activating system*, transmit activating information to all parts of the cerebral cortex. The

Brain Injury and Levels of Consciousness

- Consciousness is a global function that depends on a diffuse neural network that includes activity of the reticular activating system (RAS) and both cerebral hemispheres.
- Impaired consciousness implies diffuse brain injury to the RAS at any level (medulla through thalamus) or both cerebral hemispheres simultaneously.
- In contrast, local brain injury causes focal neurologic deficit but does not disrupt consciousness.

TABLE 37-1 Key Signs in Rostral-to-Caudal Progression of Brain Lesions

Level of Brain Injury	Key Clinical Signs
Diencephalon	Impaired consciousness; small, reactive pupils; intact oculocephalic reflex; decorticate posturing; Cheyne-Stokes respirations
Midbrain	Coma; fixed, midsize pupils; impaired oculocephalic reflex; neurogenic hyperventilation; decerebrate posturing
Pons	Coma; fixed, irregular pupils; dysconjugate gaze; impaired cold caloric stimulation; loss of corneal reflex; hemiparesis/quadriparesis; decerebrate posturing; apneustic respirations
Medulla	Coma; fixed pupils, flaccidity, loss of gag and cough reflexes, ataxic/apneic respirations

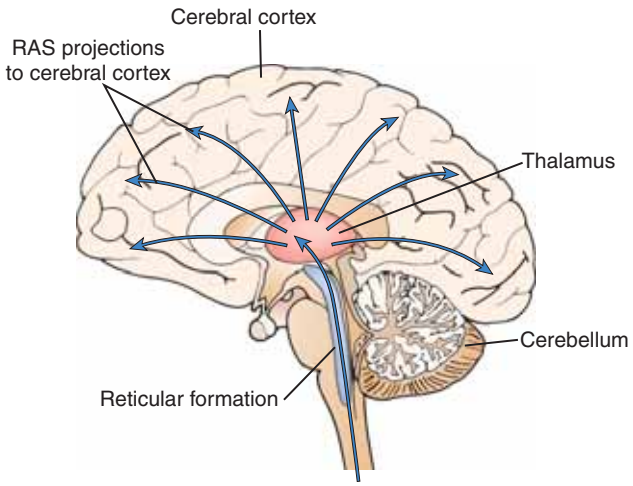


FIGURE 37-9. The reticular activating system (RAS). Ascending sensory tracts send axon collateral fibers to the reticular formation. These give rise to fibers synapsing in the nonspecific nuclei of the thalamus. From there, the nonspecific thalamic projections influence widespread areas of the cerebral cortex and limbic system.

flow of information in the ascending RAS activates the hypothalamic and limbic structures that regulate emotional and behavioral responses such as those that occur in response to pain and loud noises, and they exert facilitatory effects on cortical neurons. Without cortical activation, a person is less able to detect specific stimuli, and the level of consciousness is reduced.

The pathways for the ascending RAS travel from the medulla through the midbrain, such that lesions of the brain stem can interrupt RAS activity, leading to altered levels of consciousness and coma. Any deficit in level of consciousness, from mild confusion to stupor or coma, indicates injury to either the RAS or to both cerebral hemispheres concurrently. For example, consciousness may decline owing to severe systemic metabolic derangements that affect both hemispheres, or from head trauma causing shear injuries to white matter of both the RAS and the cerebral hemispheres. Brain injuries that affect a hemisphere unilaterally and also spare the RAS, such as cerebral infarction, usually do not impair consciousness.

Levels of Consciousness. Levels of consciousness reflect awareness and response to the environment. A fully conscious person is totally aware of his or her surroundings and able to react to stimuli in the environment.[19] Levels of consciousness exist on a continuum that includes consciousness, confusion, delirium, obtundation, stupor, and coma (Table 37-2).

The earliest signs of diminution in level of consciousness are inattention, mild confusion, disorientation, and blunted responsiveness. With further deterioration, the delirious person becomes markedly inattentive and variably lethargic or agitated. The person may progress to become obtunded and may respond only to vigorous or noxious stimuli.

Because of its simplicity of application, the Glasgow Coma Scale has gained almost universal acceptance as a method for assessing the level of consciousness in persons with brain injury[22,23] (Table 37-3). Numbered scores are given to responses of eye opening, verbal utterances, and motor responses. The total score is the sum of the best response in each category.

Other Manifestations of Deteriorating Brain Function

Additional elements in the initial neurologic evaluation of a person with brain injury include checking for abnormalities in the size of the pupils and their reaction to light, evidence of decorticate or decerebrate posturing, and altered patterns of respiration.

Pupillary Reflexes and Eye Movements. Although the pupils may initially respond briskly to light, they become unreactive and dilated as brain function deteriorates. A bilateral loss of the pupillary light response is indicative of lesions of the brain stem. A unilateral loss

TABLE 37-2 Descending Levels of Consciousness and Their Characteristics

Level of Consciousness	Characteristics
Confusion	Disturbance of consciousness characterized by impaired ability to think clearly, and to perceive, respond to, and remember current stimuli; also disorientation
Delirium	State of disturbed consciousness with motor restlessness, transient hallucinations, disorientation, and sometimes delusions
Obtundation	Disorder of decreased alertness with associated psychomotor retardation
Stupor	A state in which the person is not unconscious but exhibits little or no spontaneous activity
Coma	A state of being unarousable and unresponsive to external stimuli or internal needs; often determined by the Glasgow Coma Scale

Data from Bates D. (1993). The management of medical coma. *Journal of Neurology, Neurosurgery, and Psychiatry* 56, 590.

TABLE 37-3 The Glasgow Coma Scale

Test	Score*
Eye Opening (E)	
Spontaneous	4
To call	3
To pain	2
None	1
Motor Response (M)	
Obeys commands	6
Localizes pain	5
Normal flexion (withdrawal)	4
Abnormal flexion (decorticate)	3
Extension (decerebrate)	2
None (flaccid)	1
Verbal Response (V)	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
None	1

*GCS Score = E + M + V. Best possible score = 15; worst possible score = 3.

of the pupillary light response may be due to a lesion of the optic or oculomotor pathways. The oculocephalic reflex (doll's-head eye movement) can be used to determine whether the brain stem centers for eye movement are intact (Fig. 37-10). If the oculocephalic reflex is inconclusive, and if there are no contraindications, the oculovestibular test (i.e., cold caloric test, in which cold water is instilled into the ear canal) may be used to elicit nystagmus (see Chapter 38).

Decorticate and Decerebrate Posturing. With the early onset of unconsciousness, there is some combative and purposeful movement in response to pain. As coma progresses, noxious stimuli can initiate rigidity and abnormal postures if the motor tracts are interrupted at specific levels. These abnormal postures are classified as decorticate and decerebrate.[9] Decorticate (flexion) posturing is characterized by flexion of the arms, wrists, and fingers, with abduction of the upper extremities, internal rotation, and plantar flexion of the lower extremities (see Fig. 37-4A). Decorticate posturing results from lesions of the cerebral hemisphere or internal capsule. Decerebrate (extensor) posturing results from increased muscle excitability (see Fig. 37-4B). It is characterized by rigidity of the arms with palms of the hands turned away from the body and with stiffly extended legs and plantar flexion of the feet. This response occurs with rostral-to-caudal deterioration, when lesions of the diencephalon extend to involve the midbrain and upper brain stem. Both decerebrate and decorticate posturing are poor prognostic signs.

Respiratory Responses. Early respiratory changes include yawning and sighing, with progression to Cheyne-Stokes breathing, in which there is waxing and waning of respirations with variable periods of apnea. With progression of injury continuing to the midbrain, respirations change to neurogenic hyperventilation, in which the frequency of respirations may exceed 40 breaths per minute because of uninhibited stimulation of inspiratory and expiratory centers. With medullary involvement, respirations become ataxic (i.e., totally uncoordinated and irregular). Apnea may occur because of a lack of responsiveness to carbon dioxide stimulation. Complete ventilatory assistance is often required at this point.

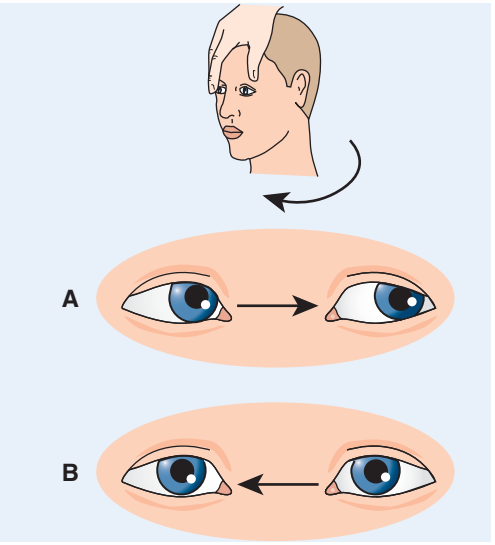


FIGURE 37-10. The *doll's-head eye response* demonstrates the always-present vestibular static reflexes without forebrain interference or suppression. Severe damage to the forebrain or to the brain stem rostral to the pons often results in loss of rostral control of these static vestibular reflexes. If the person's head is moved from side to side or up and down, the eyes will move in conjugate gaze to the opposite side **(A)**, much like those of a doll with counterweighted eyes. If the doll's-head phenomenon is observed, brain stem function at the level of the pons is considered intact (in a comatose person). In the unconscious person without intact brain stem function and vestibular static reflexes, the eyes stay in midposition (fixed) or turn in the same direction **(B)** as the head is turned.

In summary, many of the agents that cause brain damage do so through common pathways, including hypoxia or ischemia, accumulation of excitatory neurotransmitters, cerebral edema, and increased ICP. Deprivation of oxygen (i.e., hypoxia) or blood flow (i.e., ischemia) can have deleterious effects on the brain structures. Ischemia can be focal, as in stroke, or global. Global ischemia occurs when blood flow is inadequate to meet the metabolic needs of the entire brain, as in cardiac arrest. The term *excitotoxicity* has been coined for the final common pathway for neuronal cell injury and death associated with excessive activity of excitatory neurotransmitters, particularly glutamine.

Cerebral edema represents an increase in tissue volume secondary to abnormal fluid accumulation.

Vasogenic edema occurs when integrity of the blood-brain barrier is disrupted, allowing fluid to escape into the extracellular fluid that surrounds brain cells, whereas cytotoxic edema involves the swelling of brain cells. The ICP is the pressure exerted by the essentially incompressible tissue and fluid volumes of the three compartments contained within the rigid confines of the skull—brain tissue, blood, and CSF. Excessive ICP can obstruct cerebral blood flow, destroy brain cells, displace brain tissue as in herniation, and otherwise damage delicate brain structures. Hydrocephalus represents enlargement of the CSF compartment owing to an abnormal CSF volume. It can result from impaired reabsorption from the arachnoid villi into the venous system (communicating hydrocephalus) or from obstruction of the ventricular system (noncommunicating hydrocephalus), which prevents the CSF from reaching the arachnoid villi.

Head injury is the term used to describe injuries associated with skull fractures, brain injuries, and associated cerebral vascular injuries. The effects of traumatic head injuries can be divided into two categories: primary or secondary injuries. Primary injuries come from direct impact of the head and brain as an immediate result of the initial insult. The injuries may be focal (contusion or laceration) or diffuse (concussion and diffuse axonal injury). Hematomas result from vascular injury and bleeding. Depending on its location, the bleeding may result in an epidural hematoma, subdural hematoma, or intracerebral hematoma. Secondary injuries result from complicating processes that are initiated at the time of injury.

Deterioration of brain function is manifested by alterations in sensory and motor function and changes in the level of consciousness. Consciousness is a state of awareness of self and environment. It exists on a normal continuum from normal wakefulness and sleep to the pathologic continuum of stupor and coma. Any deficit in level of consciousness, from mild confusion to stupor or coma, indicates injury to either the ascending reticular activating system or to both cerebral hemispheres concurrently. In progressive brain injury, coma may follow a rostral-to-caudal progression with characteristic changes in levels of consciousness, breathing patterns, level of arousal and motor responses, and the pupillary light response and eye movements.

Cerebrovascular Disease

Cerebrovascular disease encompasses a number of disorders involving vessels in the cerebral circulation. These disorders include ischemic and hemorrhage stroke, aneurysmal subarachnoid hemorrhage, and arteriovenous malformations.

The Cerebral Circulation

The blood flow to the brain is supplied by the two internal carotid arteries anteriorly and the vertebral arteries posteriorly[24,25] (Fig. 37-11A). The internal carotid artery, a terminal branch of the common carotid artery, branches into several arteries—the ophthalmic, posterior communicating, anterior choroidal, anterior cerebral, and middle cerebral arteries (see Fig. 37-11B). Most of the arterial blood in the internal carotid arteries is distributed through the anterior and middle cerebral arteries. The anterior cerebral arteries supply the medial surface of the frontal and parietal lobes and the anterior half of the thalamus, the corpus striatum, part of the corpus callosum, and the anterior limb of the internal capsule. The genu and posterior limb of the internal capsule and medial globus pallidus are fed by the anterior choroidal branch of the internal carotid artery.

The middle cerebral artery passes laterally, supplying the lateral basal ganglia and the insula, and then emerges on the lateral cortical surface, supplying the inferior frontal gyrus, the motor and premotor frontal cortex concerned with delicate face and hand control (Fig. 37-12). It is the major vascular source for the language cortices (frontal and superior temporal), the primary and association auditory cortex (superior temporal gyrus), and the primary and association somesthetic cortex for the face and hand (postcentral gyrus, parietal). The middle cerebral artery is functionally a continuation of the internal carotid; emboli of the internal carotid most frequently become lodged in branches of the middle cerebral artery. The consequences of ischemia of these areas may be the most devastating, resulting in damage to the fine manipulative skills of the face and upper limbs and to receptive and expressive communication functions (e.g., aphasia).

The two vertebral arteries arise from the subclavian artery and enter the foramina in the transverse spinal processes at the level of the sixth cervical vertebra and continue upward through the foramina of the upper six vertebrae; they wind behind the atlas and enter the skull through the foramen magnum and unite to form the basilar artery, which then diverges to terminate in the posterior cerebral arteries. Branches of the basilar and vertebral arteries supply the medulla, pons, cerebellum, midbrain, and caudal part of the diencephalon. The posterior cerebral arteries supply the remaining occipital and inferior regions of the temporal lobes and the thalamus.

The distal branches of the internal carotid and vertebral arteries communicate at the base of the brain through the circle of Willis; this anastomosis of arteries can provide continued circulation if blood flow through one of the main vessels is disrupted (see Fig. 37-11B). For instance, occlusion of one middle cerebral artery may have limited consequences if the anterior and posterior communicating arteries are patent, allowing collateral flow from the ipsilateral posterior cerebral and opposite carotid arteries. Without collateral input, cessation of blood flow in cerebral arteries results in ischemic neural damage as metabolic needs of electrically active cells exceed nutrient supply.

The cerebral circulation is drained by two sets of veins that empty into the dural venous sinuses: the deep (great) cerebral venous system and the superficial venous system. In contrast to the superficial cerebral veins that travel through the pia mater on the surface of the cerebral

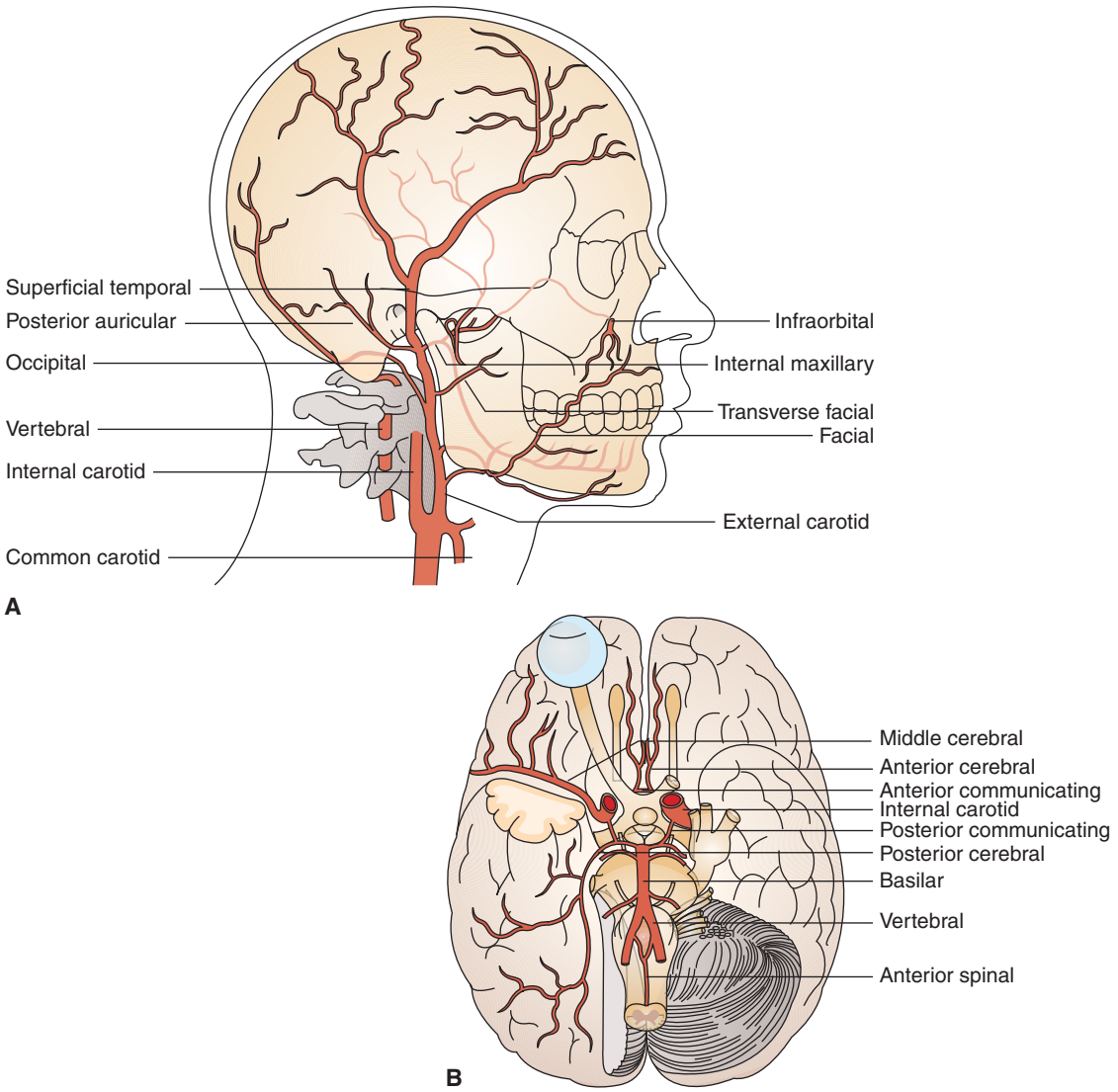


FIGURE 37-11. Cerebral circulation. **(A)** The internal carotid artery ascends to the base of the brain. The right vertebral artery is also shown as it ascends through the transverse foramina of the cervical vertebrae. **(B)** The cerebral arterial circle (circle of Willis).

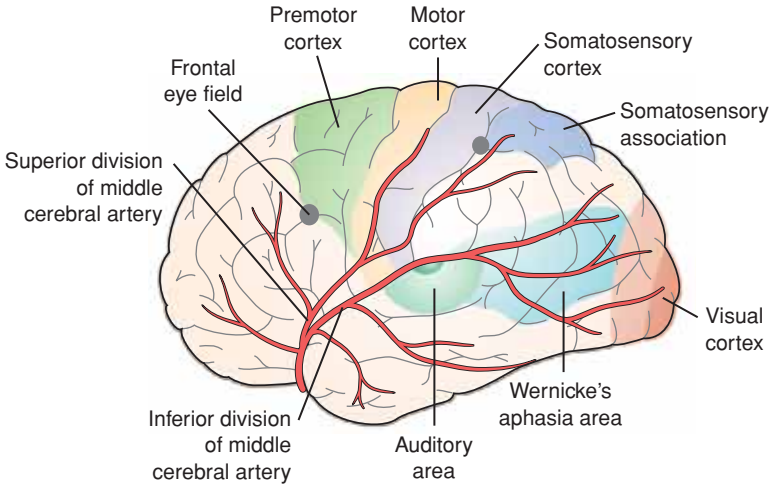


FIGURE 37-12. Lateral view of the cerebral hemisphere, showing areas of the cortex supplied by the superior and inferior divisions of the middle cerebral artery.

cortex, the deep venous system is well protected. These vessels connect directly to the sagittal sinuses in the falx cerebri by bridging veins. They travel through the CSF-filled subarachnoid space and penetrate the arachnoid and then the dura to reach the dural venous sinuses. This system of sinuses returns blood to the heart primarily through the internal jugular veins. The intracranial veins do not have valves. The direction of flow depends on gravity and pressures in the venous sinuses as compared with those of the extracranial veins. Increases in intrathoracic pressure, as can occur with coughing or performance of the Valsalva maneuver (i.e., exhaling against a closed glottis), produce a rise in central venous pressure that is reflected back into the internal jugular veins and then to the dural sinuses. This briefly raises the ICP.

Regulation of Cerebral Blood Flow

The blood flow to the brain is maintained at approximately 750 to 900 mL/minute or 15% of the resting cardiac output.[11] The regulation of blood flow to the brain is controlled largely by autoregulatory or local mechanisms that respond to the metabolic needs of the brain. Cerebral autoregulation has been classically defined as the ability of the brain to maintain constant cerebral blood flow despite changes in systemic arterial pressure. This allows the cerebral cortex to adjust cerebral blood flow locally to satisfy its metabolic needs. The autoregulation of cerebral blood flow is efficient within an MABP range of approximately 60 to 140 mm Hg.[11] Although total cerebral blood flow remains relatively stable throughout marked changes in cardiac output and arterial blood pressure, regional blood flow may vary markedly in response to local changes in metabolism. If blood pressure falls below 60 mm Hg, cerebral blood flow becomes severely compromised, and if it rises above the upper limit of autoregulation, blood flow increases rapidly and overstretches the cerebral vessels. In persons with hypertension, this autoregulatory range shifts to higher MABP levels.

At least three metabolic factors affect cerebral blood flow—an increase in carbon dioxide and hydrogen ion concentrations and an oxygen deficiency. Increased carbon dioxide provides a potent stimulus for vasodilation—a doubling of the PCO_2 in the blood results in a doubling of cerebral blood flow. Carbon dioxide is thought to increase cerebral blood flow by first combining with water to form carbonic acid, with subsequent dissociation into hydrogen ions, which then causes vasodilation of the cerebral vessels. Other substances, such as lactic acid and pyruvic acid, which increase the acidity of brain tissues, will produce a similar increase in cerebral blood flow. Except during periods of intense brain activity, the rate of oxygen utilization by the brain remains within a narrow range. If blood flow to the brain becomes insufficient to supply this needed amount of oxygen, the oxygen deficiency causes the cerebral vessels to dilate, returning cerebral blood flow to near normal.

The sympathetic nervous system also contributes to the control of blood flow in the large brain arteries and the arteries that penetrate into the brain substance.[11] Under normal physiologic conditions, local regulatory and autoregulatory mechanisms override the effects of sympathetic stimulation. However, when local mechanisms fail, sympathetic control of cerebral blood pressure becomes important. For example, when the arterial pressure rises to very high levels during strenuous exercise or in other conditions, the sympathetic nervous system constricts the large and intermediate-sized superficial blood vessels as a means of protecting the smaller, more easily damaged vessels. Sympathetic reflexes are believed to cause vasospasm in the intermediate and large arteries in some types of brain damage, such as that caused by rupture of a cerebral aneurysm.

Stroke (Brain Attack)

Stroke is the syndrome of acute focal neurologic deficit from a vascular disorder that injures brain tissue. Stroke remains one of the leading causes of mortality and morbidity in the United States. Each year, about 795,000 Americans are afflicted with stroke, and approximately 20% of these persons die; many survivors are left with at least some degree of neurologic impairment.[26] The term *brain attack* has been promoted to raise awareness that time-dependent tissue damage occurs and that rapid emergency treatment is necessary, similar to that with heart attack.

There are two main types of strokes: ischemic and hemorrhagic. Ischemic strokes are caused by an interruption of blood flow in a cerebral vessel and are the most common type of stroke, accounting for about 87% of all strokes.[26] The less common hemorrhagic strokes are caused by bleeding into brain tissue. This type of stroke usually is from a blood vessel rupture caused by hypertension, aneurysm, arteriovenous malformation, head injury, or blood dyscrasias and has a much higher fatality rate than ischemic strokes.

Among the major risk factors for ischemic stroke are age, gender, race, family history, hypertension, cigarette smoking, diabetes mellitus, asymptomatic carotid stenosis, sickle cell disease, hyperlipidemia, and atrial fibrillation[26,27] (Table 37-4). The incidence of stroke increases

TABLE 37-4 Modifiable and Unmodifiable Risk Factors for Stroke

Modifiable Factors	Unmodifiable Factors
• Hypertension	• Age
• Hyperlipidemia	• Gender
• Smoking	• Race
• Diabetes	• Heredity
• Heart disease	
Atrial fibrillation	
Wall motion defects	
• Carotid artery disease	
• Coagulation disorders	
• Obesity/inactivity	
• Heavy alcohol use	
• Cocaine use	

Stroke/Brain Attack

- Stroke is an acute focal neurologic deficit due to a disturbance in the blood vessels supplying the brain. It can be due to ischemia caused by thrombi or emboli that interrupt blood flow or rupture of a blood vessel with bleeding into brain tissue.
- The term *brain attack* as a description for stroke is intended to alert people to the need for immediate treatment at the first sign of a stroke.
- During the evolution of an ischemic stroke, there usually is a central core of dead or dying cells surrounded by an ischemic band of minimally perfused cells called a *penumbra*. Whether the cells of the penumbra continue to survive depends on the successful timely return of adequate circulation.
- The realization that there is a window of opportunity during which ischemic but viable brain tissue can be salvaged has led to the use of thrombolytic agents in the early treatment of ischemic stroke.

with age, with men's stroke incidence rates being greater than women's at younger ages, but not at older ages. Because women live longer than men, more women die of stroke each year. African Americans have almost twice the risk of first-ever strokes as whites. Blood pressure is a powerful determinant of stroke risk. Individuals with a blood pressure less than 120/80 mm Hg have about half the lifetime risk of stroke compared with persons with hypertension. Heart disease, particularly atrial fibrillation and other conditions that predispose to clot formation on the wall of the heart or valve leaflets, or to paradoxical embolism through right-to-left shunting, predisposes to cardioembolic stroke. Polycythemia, sickle cell disease (during sickle cell crisis), and blood disorders predispose to clot formation in the cerebral vessels.

Other, less well-documented risk factors include obesity, physical inactivity, alcohol and drug abuse, hypercoagulability disorders, hormone replacement therapy, and oral contraceptive use.[26–28] Clinical trial data indicate that estrogen plus progestin, as well as estrogen alone, increase stroke risk in postmenopausal, generally healthy women, and provide no protection for women with established heart disease. Although extensively used in the past, the use of hormone therapy is no longer recommended (see Chapter 40). Heavy alcohol consumption can lead to hypertension, hypercoagulability of blood, reduction of cerebral blood flow, and greater likelihood of atrial fibrillation. Cocaine use causes both ischemic and hemorrhagic strokes by inducing vasospasm, enhanced platelet activity, and increased blood pressure, heart rate, body temperature, and metabolic rate. Cocaine stroke victims range in age from newborn (i.e., from maternal cocaine use) to elderly.[29]

Ischemic Stroke

Ischemic strokes are caused by cerebrovascular obstruction by thrombosis or emboli (Fig. 37-13). Various methods have been used to classify ischemic cerebrovascular disease. A common classification system identifies the five main mechanisms of stroke as stroke subtypes and their frequency: 20% large artery atherosclerotic disease (both thrombosis and arterial emboli); 25% small vessel or penetrating artery disease (so-called lacunar stroke); 20% cardiogenic embolism; 30% cryptogenic stroke (undetermined cause); and 5% other, unusual causes[28] (i.e., migraine, vessel dissection, coagulopathy).

Ischemic Penumbra in Evolving Stroke. During the evolution of a stroke, there usually is a central core of dead or dying cells, surrounded by an ischemic band or area of minimally perfused cells called the *penumbra* ("halo"). Brain cells of the penumbra receive marginal blood flow, and their metabolic activities are impaired; although the area undergoes an "electrical failure," the

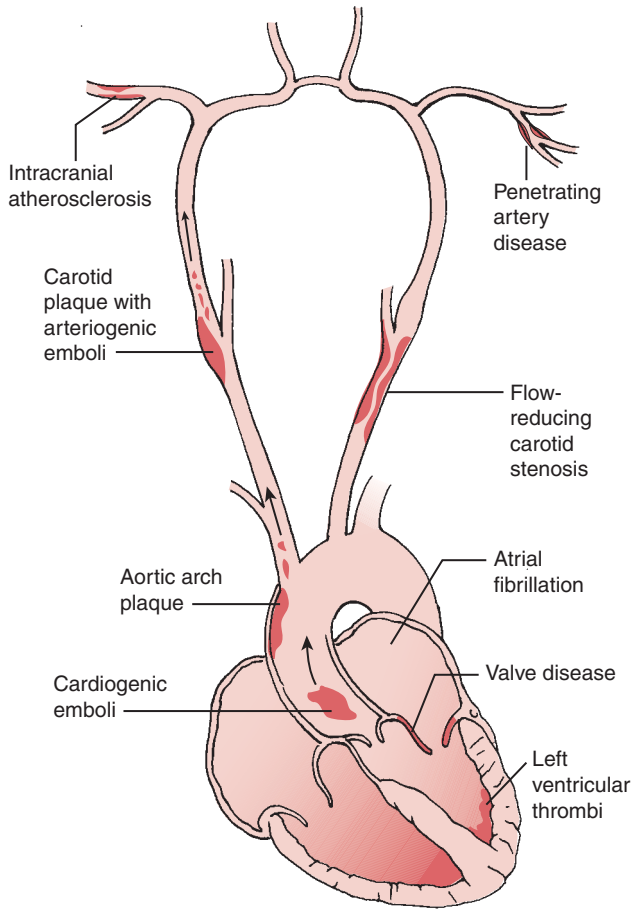


FIGURE 37-13. The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke. (From Albers G.W., Easton D., Sacco R.L., et al. [1999]. Antithrombotic and thrombotic therapy for ischemic stroke. *Chest* 114[5], 684S.)

structural integrity of the brain cells is maintained.[25,30] Whether the cells of the penumbra continue to survive depends on the successful timely return of adequate circulation, the volume of toxic products released by the neighboring dying cells, the degree of cerebral edema, and alterations in local blood flow. If the toxic products result in additional death of cells in the penumbra, the core of dead or dying tissue enlarges, and the volume of surrounding ischemic tissue increases.

Transient Ischemic Attacks. Transient ischemic attacks (TIAs) are brief episodes of neurologic dysfunction resulting from focal cerebral ischemia not associated with infarction.[31,32] A TIA or "ministroke" is equivalent to "brain angina" and reflects a temporary disturbance in cerebral blood flow, which reverses before infarction occurs, analogous to angina in relation to heart attack. The traditional definition of TIAs as a neurologic deficit resolving within 24 hours was developed before the mechanisms of ischemic cell damage and the penumbra were known and before the newer, more advanced methods of neuroimaging became available. A more accurate definition now is a deficit lasting less than 1 hour, and it may best be described as a zone of penumbra without central infarction.[31] The causes of TIAs are the same as those of ischemic stroke and include atherosclerotic disease of cerebral vessels and emboli. TIAs are important because they may provide warning of impending stroke. In fact, the risk for stroke after a TIA is 15% within 3 months.[31] Diagnosis of TIA before a stroke may permit surgical or medical intervention that prevents an eventual stroke and the associated neurologic deficits.

Large Vessel (Thrombotic) Stroke. Thrombi are the most common cause of ischemic strokes, usually occurring in atherosclerotic blood vessels. In the cerebral circulation, atherosclerotic plaques are found most commonly at arterial bifurcations. Common sites of plaque formation include larger vessels of the brain, notably the origins of the internal carotid and vertebral arteries, and junctions of the basilar and vertebral arteries. Cerebral infarction can result from an acute local thrombosis and occlusion at the site of chronic atherosclerosis, with or without embolization of the plaque material distally, or from critical perfusion failure distal to a stenosis (watershed). These infarcts often affect the cortex, causing aphasia or neglect, visual field defects, or transient monocular blindness (amaurosis fugax). In most cases of stroke, a single cerebral artery and its territories are affected. Usually, thrombotic strokes are seen in older persons and frequently are accompanied by evidence of atherosclerotic heart or peripheral arterial disease. The thrombotic stroke is not associated with activity and may occur in a person at rest.

Small Vessel Stroke (Lacunar Infarct). Lacunar infarcts are small (<15 mm wide) to very small infarcts located in the deep, noncortical parts of the brain or in the brain stem.[1] They are found in the territory of single deep penetrating arteries supplying the internal capsule, basal ganglia, or brain stem. They result from occlusion of the smaller penetrating branches of large cerebral arteries, commonly the middle cerebral and posterior cerebral arteries. In the process of healing, lacunar infarcts leave behind small cavities, or *lacunae* ("lakes"). They are thought to result from arteriolar sclerosis, commonly in the settings of chronic hypertension or diabetes. Because of their size and location, lacunar infarcts usually do not cause cortical deficits such as aphasia or apraxia. Instead, they produce classic recognizable "lacunar syndromes" such as pure motor hemiplegia, pure sensory hemiplegia, and dysarthria with the clumsy hand syndrome. Because CT scans are not sensitive enough to detect these tiny infarcts, diagnosis used to depend on clinical features alone. The use of MRI has allowed frequent visualization of small vessel infarcts and is obligatory to confirm such a lesion.

Cardiogenic Embolic Stroke. An embolic stroke is caused by a moving blood clot that travels from its origin to the brain. It usually affects the larger proximal cerebral vessels, often lodging at bifurcations. The most frequent site of embolic strokes is the middle cerebral artery, reflecting the large territory of this vessel and its position as the terminus of the carotid artery. Although most cerebral emboli originate from a thrombus in the left heart, they also may originate in an atherosclerotic plaque in the carotid arteries. The embolus travels quickly to the brain and becomes lodged in a smaller artery through which it cannot pass. Embolic stroke usually has a sudden onset with immediate maximum deficit.

Various cardiac conditions predispose to formation of emboli that produce embolic stroke, including rheumatic heart disease, atrial fibrillation, recent myocardial infarction, ventricular aneurysm, and bacterial endocarditis. More recently, the use of transesophageal echocardiography, which better images the interatrial septum, has implicated a patent foramen ovale as a source for paradoxical venous emboli to the arterial system. Advances in the diagnosis and treatment of heart disease can be expected to alter favorably the incidence of embolic stroke.

Hemorrhagic Stroke

The most frequently fatal stroke is a spontaneous hemorrhage into the brain substance resulting in an intracerebral hemorrhage.[33,34] With rupture of a blood vessel, hemorrhage into the brain tissue occurs, resulting in a focal hematoma and sometimes intraventricular hemorrhage, edema, compression of the brain contents, or spasm of the adjacent blood vessels. The most common predisposing factors are advancing age and hypertension. Other causes of hemorrhage are aneurysm, trauma, erosion of the vessels by tumors, arteriovenous malformations, blood coagulation disorders, vasculitis, and drugs. A cerebral hemorrhage occurs suddenly, usually when the person is active. Vomiting commonly occurs at the onset, and headache often occurs. Focal symptoms depend on which vessel is involved. In the most common situation, hemorrhage into the basal ganglia results in contralateral hemiplegia, with initial flaccidity progressing to spasticity. The hemorrhage and resultant edema exert great pressure

on the brain substance, and the clinical course progresses rapidly to coma and frequently to death.

Treatment of hemorrhagic stroke focuses on management of the increased arterial pressure and intracranial pressure and prevention of recurrent hemorrhage. Recombinant factor VII is available and has been approved for treating bleeding in persons with hemophilia who have antibodies to factor VIII and IX (see Chapter 12). It is also being studied for use in early treatment of hemorrhagic stroke due to other causes.[34]

Acute Stroke Management

The specific manifestations of stroke or TIA are determined by the cerebral artery that is affected, by the area of brain tissue that is supplied by that vessel, and by the adequacy of the collateral circulation.[9,25] Symptoms of stroke/TIA always are sudden in onset and focal, and usually are one-sided. The most common symptom is weakness of the face and arm, sometimes also of the leg. Other frequent stroke symptoms are unilateral numbness, vision loss in one eye (amaurosis fugax) or to one side (hemianopia), language disturbance (aphasia), slurred speech (dysarthria), and sudden, unexplained imbalance or ataxia. In the event of TIA, symptoms rapidly resolve spontaneously, usually within minutes, although the underlying mechanisms are the same as for stroke. The specific stroke signs depend on the specific vascular territory compromised (Table 37-5). As a generalization, carotid ischemia causes monocular visual loss or aphasia (dominant hemisphere) or hemineglect (nondominant hemisphere), contralateral sensory or motor loss, or other discrete cortical signs such as apraxia and agnosia. Vertebrobasilar ischemia induces ataxia, diplopia, hemianopia, vertigo, cranial nerve deficits, contralateral hemiplegia, sensory deficits (either contralateral or crossed, i.e., contralateral body and ipsilateral face), and arousal defects. Discrete subsets of these vascular syndromes usually occur, depending on which branches of the involved artery are blocked.

Diagnosis. Accurate diagnosis of acute stroke, based on a complete history and thorough physical and neurologic examination, should aim to determine the presence of hemorrhage or ischemia, identify the stroke or TIA mechanism (i.e., large vessel or small vessel atherothrombotic, cardioembolic, hemorrhagic, other or cryptogenic), characterize the severity of clinical deficits, and unmask the presence of risk factors.[25,35–37] A careful history, including documentation of previous TIAs, the time of onset and pattern and rapidity of system progression, the specific focal symptoms (to determine the likely vascular territory), and any coexisting diseases, can help to determine the type of stroke that is involved.

CT scans and MRI have become essential brain imaging tools in diagnosing stroke, differentiating cerebral hemorrhage from ischemia, and excluding intracranial lesions that mimic stroke clinically. CT scans are a necessary screening tool in the acute setting for rapid identification of hemorrhage, but are insensitive to ischemia within 24 hours and to any brain stem or small infarcts. MRI is superior for imaging ischemic lesions in all territories and differentiating other nonstroke pathologic processes (e.g., tumors, contusion, infection). Newer

TABLE 37-5 Signs and Symptoms of Stroke by Involved Cerebral Artery

Cerebral Artery	Brain Area Involved	Signs and Symptoms*
Anterior cerebral	Infarction of the medial aspect of one frontal lobe if lesion is distal to communicating artery; bilateral frontal infarction if flow in other anterior cerebral artery is inadequate	Paralysis of contralateral foot or leg; impaired gait; paresis of contralateral arm; contralateral sensory loss over toes, foot, and leg; problems making decisions or performing acts voluntarily; lack of spontaneity, easily distracted; slowness of thought; aphasia depends on the hemisphere involved; urinary incontinence; cognitive and affective disorders
Middle cerebral	Massive infarction of most of lateral hemisphere and deeper structures of the frontal, parietal, and temporal lobes; internal capsule; basal ganglia	Contralateral hemiplegia (face and arm); contralateral sensory impairment; aphasia; homonymous hemianopia; altered consciousness (confusion to coma); inability to turn eyes toward paralyzed side; denial of paralyzed side or limb (hemiattention); possible acalculia, alexia, finger agnosia, and left–right confusion; vasomotor paresis and instability
Posterior cerebral	Occipital lobe; anterior and medial portion of temporal lobe	Homonymous hemianopia and other visual defects such as color blindness, loss of central vision, and visual hallucinations; memory deficits, perseveration (repeated performance of same verbal or motor response)
	Thalamus involvement	Loss of all sensory modalities; spontaneous pain; intentional tremor; mild hemiparesis; aphasia
Basilar and vertebral	Cerebral peduncle involvement	Oculomotor nerve palsy with contralateral hemiplegia
	Cerebellum and brain stem	Visual disturbance such as diplopia, dystaxia, vertigo, dysphagia, dysphonia

*Depend on hemisphere involved and adequacy of collaterals.

MRI techniques such as perfusion- and diffusion-weighted imaging (DWI) can reveal cerebral ischemia immediately after onset and identify areas of potentially reversible damage (i.e., penumbra).

Vascular imaging is accomplished with CT angiography (CTA), magnetic resonance angiography (MRA), catheter-based "conventional" arteriography, and ultrasonography. All except ultrasonography can demonstrate the site of vascular abnormality (intracranial and extracranial) and afford visualization of most intracranial vascular areas. MRA is noninvasive and most widely available, but less sensitive and specific than CTA or catheter angiography. CTA is exquisitely detailed for a noninvasive technique, but is limited in availability and requires iodinated contrast, which is nephrotoxic. Catheter angiography remains the gold standard in sensitivity and allows visualization of dynamic patterns of collateral flow, but is invasive and requires significant contrast doses. CTA and MRA have largely replaced angiography as a screening tool for vascular lesions. Ultrasonographic techniques allow quick bedside assessment of the carotid bifurcation (duplex ultrasonography) or of flow velocities in the cerebral circulation (transcranial Doppler).

Treatment. Treatment of acute ischemic stroke has changed markedly since the early 1990s, with an emphasis on salvaging brain tissue, preventing secondary stroke, and minimizing long-term disability. The care of patients with stroke has shifted away from the "nearest hospital" to stroke centers that have been certified by some external agency, most commonly the state or joint commission.[38,39] Certification establishes that a hospital can manage stroke patients with appropriate care throughout the continuum, from emergency treatments, through the inpatient stay, and into the rehabilitation phase. With this advancement, the medical and lay communities acknowledge that care of the patient with stroke requires specialized personnel and resources to minimize the devastating effects from stroke, the leading cause of adult disability in the United States.

Stroke care begins with emergency treatments aimed at reversing the evolving ischemic brain injury. The realization that there is a window of opportunity during which ischemic but viable brain tissue can be salvaged has led to the use of reperfusion techniques and neuroprotective strategies in the early treatment of ischemic stroke.[25,35–39] Although the results of emergent treatment of hemorrhagic stroke have been less dramatic, continued efforts to reduce disability have been promising.

Reperfusion techniques include thrombolytic therapy (administered either intravenously or intra-arterially), catheter-directed mechanical clot disruption, and augmentation of CPP during acute stroke. The first and only agent approved by the U.S. Food and Drug Administration (FDA) for treatment of acute ischemic stroke is tissue plasminogen activator (tPA), which was approved in 1996.[40] A subcommittee of the Stroke Council of the American Heart Association has developed guidelines for the use of tPA for acute stroke.[35] These guidelines recommend that in persons with suspected stroke, the diagnosis of hemorrhagic stroke be excluded through the use of CT scanning before administration of thrombolytic therapy, which must be administered within 3 hours of onset of symptoms. Generally, although patient selection is more stringent for these invasive methods, patients can be treated past the 3-hour time window with intravenous tPA.[41] The major risk of treatment with thrombolytic agents is intracranial hemorrhage of the infarcted brain. A number of conditions, including therapeutic levels of oral anticoagulant medications, a history of gastrointestinal or urinary tract bleeding in the previous 21 days, prior stroke or head injury within 3 months, major surgery within the past 14 days, and a blood pressure greater than 185/110 mm Hg, are considered contraindications to intravenous thrombolytic therapy.[35]

Emerging experimental treatments for ischemic stroke are being increasingly used as alternative methods of reperfusion beyond intravenous thrombolysis. New catheter-based methods allow recanalization of a directly visualized cerebral clot with intra-arterial techniques. The interventional specialist might mechanically disrupt the clot, deliver the thrombolytic drug intra-arterially at the clot surface, or urgently stent intracranial vessels to restore flow. However, these methods require an experienced interventional angiography team and extensive institutional infrastructure, and thus remain limited to tertiary care centers. Other experimental treatments include neuroprotection with drugs that limit the calcium cascade (see Fig. 37-2) and treatments such as hypothermia that decrease brain metabolic demands in the setting of ischemia. All are being actively tested in clinical trials.

Poststroke Management and Deficits

Poststroke treatment is aimed at preventing recurrent stroke and medical complications while promoting the fullest possible recovery of function.[42] The risk of stroke recurrence is highest in the first week after a stroke or TIA, so the early implementation of antiplatelet agents in most cases, or warfarin (an anticoagulant) in cardioembolic stroke, is imperative. Long-term stroke recurrence is most effectively prevented with aggressive reduction of risk factors, primarily hypertension, diabetes, smoking, and hyperlipidemia. In cases of carotid territory stroke with carotid stenosis, revascularization with surgery or stenting should be considered. Early hospital care also requires careful prevention of aspiration, deep vein thrombosis, and falls. Recovery is maximized with early and aggressive rehabilitation efforts that include all members of the rehabilitation team—physician, nurse, speech therapist, physical therapist, and occupational therapist—and the family.

Poststroke Motor Deficits. Poststroke motor deficits are most common, followed by deficits of language, sensation, and cognition. After a stroke affecting the corticospinal tract such as the motor cortex, posterior limb of the internal capsule, basis pontis, or medullary pyramids, there is profound weakness on the contralateral side (hemiparesis; see Chapter 36, Fig. 36-4). Involvement at the level of the motor cortex is most often in the territory of the middle cerebral artery, usually with a sparing of

the leg, which is supplied by the anterior cerebral artery. Subcortical lesions of the corticospinal tracts cause equal weakness of the face, arm, and leg. Within 6 to 8 weeks, the initial weakness and flaccidity are replaced by hyperreflexia and spasticity. Spasticity involves an increase in the tone of affected muscles and usually an element of weakness. The flexor muscles usually are more strongly affected in the upper extremities and the extensor muscles more strongly affected in the lower extremities. There is a tendency toward foot drop; outward rotation and circumduction of the leg with gait; flexion at the wrist, elbow, and fingers; lower facial paresis; slurred speech; an upgoing toe to plantar stimulation (Babinski sign); and dependent edema in the affected extremities. A slight corticospinal lesion may be indicated only by clumsiness in carrying out fine coordinated movements rather than obvious weakness. Passive range-of-motion exercises help to maintain joint function and to prevent edema, shoulder subluxation (i.e., incomplete dislocation), and muscle atrophy, and may help to reestablish motor patterns. If no voluntary movement or movement on command appears within a few months, significant function usually will not return to that extremity.

Poststroke Dysarthria and Aphasia. Two key aspects of verbal communication are speech and language. Speech involves the mechanical act of articulating language, the "motor act" of verbal expression, whereas language involves the written or spoken use of symbolic formulations, such as words or numbers. *Dysarthria* is a disorder of speech, which manifests as the imperfect articulation of speech sounds or changes in voice pitch or quality. It results from a stroke affecting the muscles of the pharynx, palate, tongue, lips, or mouth and does not relate to the content of speech. A person with dysarthria may demonstrate slurred speech while still retaining language ability, or may have a concurrent language problem as well. *Aphasia* is a general term that encompasses varying degrees of inability to comprehend, integrate, and express language. Aphasia may be localized to the dominant cerebral cortex or thalamus, usually the left side in 95% of people who are right handed and 70% of people who are left handed. In children, language dominance can readily shift to the unaffected hemisphere, resulting in more transient language deficits after stroke. A stroke in the territory of the middle cerebral artery is the most common aphasia-producing stroke.

Aphasia can be categorized as receptive or expressive, or as fluent or nonfluent. Receptive or fluent speech requires little or no effort, is intelligible, and is of increased quantity. The term *fluent* refers only to the ease and rate of verbal output, and does not relate to the content of speech or the ability of the person to comprehend what is being said. Verbal utterances are often paraphrasic, meaning that letters, syllables, or whole words are substituted for the target words. There are three categories of fluent aphasia: Wernicke, anomic, and conductive aphasia. *Wernicke aphasia* is characterized by an inability to comprehend the speech of others or to comprehend written material. Lesions of the posterior superior temporal or lower parietal lobe (areas 22 and 39) are associated with receptive or *fluent aphasia*. *Anomic aphasia* is speech that is nearly normal except for a difficulty with finding singular words. Conductive aphasia is manifest as impaired repetition and speech riddled with letter substitutions, despite good comprehension and fluency. *Conductive aphasia* (i.e., disconnection syndrome) results from destruction of the fiber system under the insula that connects the Wernicke and Broca areas.

Expressive or *nonfluent aphasia* is characterized by an inability to easily communicate spontaneously or translate thoughts or ideas into meaningful speech or writing. Speech production is limited, effortful, and halting and often may be poorly articulated because of a concurrent dysarthria. The person may be able, with difficulty, to utter or write two or three words, especially those with an emotional overlay. Comprehension is normal, and the person seems to be fully aware of his or her deficits but is unable to correct them. This often leads to frustration, anger, and depression. Expressive, nonfluent aphasia is associated with lesions of the Broca area at the dominant inferior frontal lobe cortex (areas 44 and 45).

Poststroke Cognitive and Other Deficits. Stroke can also cause cognitive, sensory, visual, and behavioral deficits. One distinct cognitive syndrome is that of hemineglect or hemi-inattention. Usually caused by strokes affecting the nondominant (right) hemisphere, hemineglect is the inability to attend to and react to stimuli coming from the contralateral (left) side of space. Affected persons may not visually track, orient, or reach to the neglected side. They may neglect to use the limbs on that side, despite normal motor function, and may not shave, wash, or comb that side. Such persons are unaware of this deficit, which is another form of their neglect (*anosognosia*). Other cognitive deficits include impaired ability to carry out previously learned motor activities despite normal sensory and motor function (*apraxia*), impaired recognition with normal sensory function (*agnosia*), memory loss, behavioral syndromes, and depression. Sensory deficits affect the body contralateral to the lesion and can manifest as numbness, tingling paresthesias, or distorted sensations such as dysesthesia and neuropathic pain. Visual disturbances from stroke are diverse, but most common are hemianopia from a lesion of the optic radiations between the lateral geniculate body and the temporal or occipital lobes, and monocular blindness from occlusion of the ipsilateral central retinal artery, a branch of the internal carotid artery.

Aneurysmal Subarachnoid Hemorrhage

An aneurysm is a bulge at the site of a localized weakness in the muscular wall of an arterial vessel. Most cerebral aneurysms are small saccular aneurysms called *berry aneurysms*. They usually occur in the anterior circulation and are found at bifurcations and other junctions of vessels such as those in the circle of Willis (Fig. 37-14). They are thought to arise from a congenital defect in the media of the involved vessels. Their incidence is higher in

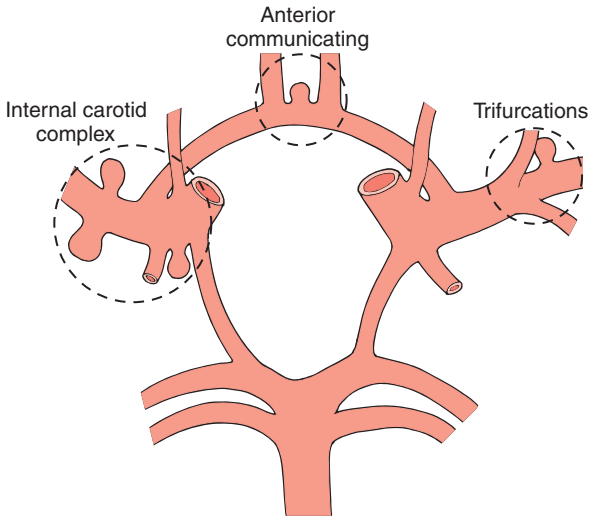


FIGURE 37-14. Common sites of berry aneurysms.

persons with certain disorders, including polycystic kidney disease, fibromuscular dysplasia, coarctation of the aorta, and arteriovenous malformations of the brain.[1,5] Other causes of cerebral aneurysms are atherosclerosis, hypertension, and bacterial infections.

Aneurysmal subarachnoid hemorrhage represents bleeding into the subarachnoid space caused by a ruptured cerebral aneurysm. Bleeding into the subarachnoid space can extend well beyond the site of origin, flooding the basal cistern, ventricles, and spinal subarachnoid space. The incidence of rupture increases with age, occurring most commonly between 40 and 60 years of age.[43] The probability of rupture increases with the size of the aneurysm; aneurysms larger than 10 mm in diameter have a 50% chance of bleeding per year.[1] Of the various environmental factors that may predispose to aneurysmal subarachnoid hemorrhage, cigarette smoking, hypertension, and excessive alcohol intake appear to constitute the greatest threat.[43] Rupture may occur at any time, but often occurs with acute increases in ICP, such as with straining at stool. The mortality rate for subarachnoid hemorrhage is high (33% to 50%), with the majority of deaths occurring within the first few days of hemorrhage.[43]

The signs and symptoms of cerebral aneurysms can be divided into two phases: those presenting before rupture and those presenting after rupture. Most small aneurysms are asymptomatic; intact aneurysms frequently are found at autopsy as an incidental finding. Large aneurysms may cause chronic headache, neurologic deficits, or both.[43,44] Persons with subarachnoid hemorrhage often have a history of atypical headaches occurring days to weeks before the onset of hemorrhage, suggesting the presence of a small leak. These headaches are characterized by sudden onset and often are accompanied by nausea, vomiting, and dizziness. Persons with these symptoms may be mistakenly diagnosed as having tension or migraine headaches.

The onset of subarachnoid aneurysmal rupture often is heralded by a sudden and severe headache, described as "the worst headache of my life."[43] If the bleeding is severe, the headache may be accompanied by collapse and loss of consciousness. Vomiting may accompany the presenting symptoms. Other manifestations include signs of meningeal irritation such as nuchal rigidity (neck stiffness) and photophobia (light intolerance); cranial nerve deficits, especially CN II, and sometimes CN III and CN IV (diplopia and blurred vision); stroke syndromes (focal motor and sensory deficits); cerebral edema and increased ICP; and pituitary dysfunction (diabetes insipidus and hyponatremia). Hypertension, a frequent finding, and cardiac arrhythmias result from massive release of catecholamines triggered by the subarachnoid hemorrhage.

The diagnosis of subarachnoid hemorrhage and intracranial aneurysms is made by clinical presentation, CT scan, lumbar puncture, and angiography.[43,44] Lumbar puncture may reveal the presence of blood in the CSF, whereas CT may demonstrate the location and extent of subarachnoid blood. To identify the aneurysm at the source of bleeding, conventional angiography, MRA, and helical (spiral) CTA are used. Conventional catheter angiography is the definitive diagnostic tool for detecting the aneurysm.

The course of treatment after aneurysm rupture depends on the extent of neurologic deficit. The best outcomes are achieved when the aneurysm can be secured early and prevention of complications initiated.[44] Persons with mild to no neurologic deficits may undergo cerebral arteriography and early surgery, usually within 24 to 72 hours. Surgery involves craniotomy and inserting a specially designed silver clip that is tightened around the neck of the aneurysm. This procedure offers protection from rebleeding and may permit removal of the hematoma. The use of endovascular techniques such as balloon embolization and platinum coil electrothrombosis is emerging as an alternative to surgery, particularly in surgically inaccessible aneurysms or poor surgical candidates. Some persons with subarachnoid hemorrhage are managed medically for 10 days or more in an attempt to improve their clinical status before surgery.

The complications of aneurysmal rupture include rebleeding, vasospasm with cerebral ischemia, hydrocephalus, hypothalamic dysfunction, and seizure activity. Rebleeding and vasospasm are the most serious and most difficult to treat. Rebleeding, which usually occurs on the first day after the initial rupture, results in further and usually catastrophic neurologic deficits.

Cerebral vasospasm is a dreaded complication of aneurysmal rupture. The condition is difficult to treat and is associated with a high incidence of morbidity and mortality. Usually, the condition develops within 3 to 10 days (peak, 7 days) after aneurysm rupture and involves a focal narrowing of the cerebral artery or arteries that can be visualized on arteriography or by transcranial Doppler. The neurologic status gradually deteriorates as blood supply to the brain in the region of the spasm is decreased; this usually can be differentiated from the rapid deterioration seen in rebleeding. Vasospasm is treated by attempting to maintain adequate CPP through the use of vasoactive drugs or administration of large amounts of intravenous fluids to increase intravascular

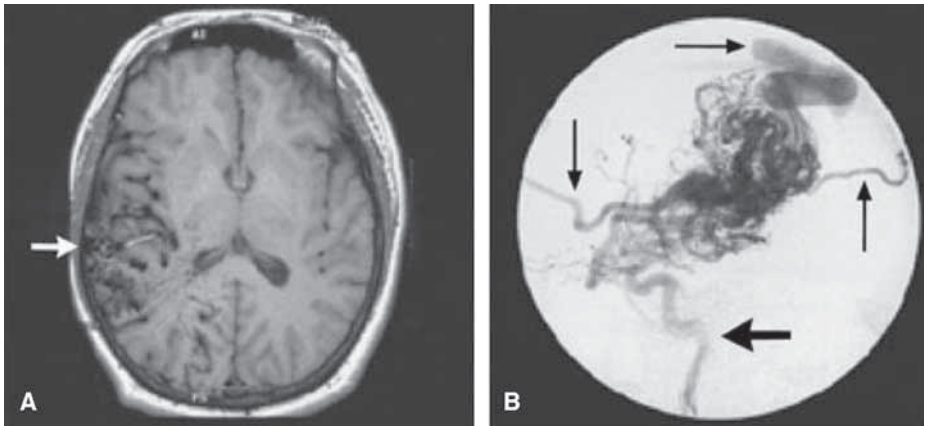


FIGURE 37-15. **(A)** Computed tomography scan of an arteriovenous malformation in the right parietal region of the brain (*arrow*). **(B)** Angiographic study of the internal carotid artery delineating the malformation in the middle cerebral artery distribution (*large arrow*), with draining veins (*small arrows*) to the superior sagittal sinus. (From Vermillion J.M., Harris F.S. [2004]. Hemispheric arteriovenous malformation. *New England Journal of Medicine* 350[17], e15.)

volume and produce hemodilution. There is risk for rebleeding from this therapy. Early surgery may provide some protection from vasospasm. Endovascular techniques, including balloon dilation, have been developed to treat spasmodic arterial segments mechanically. Nimodipine, a drug that blocks calcium channels and selectively acts on cerebral blood vessels, may be used to prevent or treat vasospasm.

Another complication of aneurysm rupture is the development of hydrocephalus. It is caused by plugging of the arachnoid villi with products from lysis of blood in the subarachnoid space. Hydrocephalus is diagnosed by serial CT scans showing increasing size of the ventricles and by the clinical signs of increased ICP. Hydrocephalus may respond to osmotic diuretics, but if neurologic deterioration is significant, surgical placement of a shunt is indicated.

Arteriovenous Malformations

Arteriovenous malformations are a complex tangle of abnormal arteries and veins linked by one or more fistulas[45,46] (Fig. 37-15). These vascular networks lack a capillary bed, and the small arteries have a deficient muscularis layer. Arteriovenous malformations are thought to arise from failure in development of the capillary network in the embryonic brain. As the child's brain grows, the malformation acquires additional arterial contributions that enlarge to form a tangled collection of thin-walled vessels that shunt blood directly from the arterial to the venous circulation. Arteriovenous malformations typically present before 40 years of age and affect men and women equally. Rupture of vessels in the malformation causing hemorrhagic stroke accounts for approximately 2% of all strokes.[46]

The hemodynamic effects of arteriovenous malformations are twofold. First, blood is shunted from the high-pressure arterial system to the low-pressure venous system without the buffering advantage of the capillary network. The draining venous channels are exposed to high levels of pressure, predisposing them to rupture and hemorrhage. Second, the elevated arterial and venous pressures divert blood away from the surrounding tissue, impairing tissue perfusion. Clinically, this is evidenced by slowly progressive neurologic deficits. The major clinical manifestations of arteriovenous malformations are intracerebral and subarachnoid hemorrhage, seizures, headache, and progressive neurologic deficits. Headaches often are severe, and persons with the disorder may describe them as throbbing and synchronous with their heartbeat. Other, focal symptoms depend on the location of the lesion and include visual symptoms (i.e., diplopia and hemianopia), hemiparesis, mental deterioration, and speech deficits.

Definitive diagnosis often is obtained through cerebral angiography. Treatment methods include surgical excision, endovascular occlusion, and radiation therapy.[46] Because of the nature of the malformation, each of these methods is accompanied by some risk for complications. If the arteriovenous malformation is accessible, surgical excision usually is the treatment of choice. Endovascular treatment involves the insertion of microcatheters into the cerebral circulation for delivery of embolic materials (e.g., microballoons, sclerosing agents, microcoils, or quick-drying glue) into the arteriovenous malformation vessels.[47] Radiation therapy (also known as *radiosurgery*) may involve the use of a gamma knife, proton beam, or linear accelerator.

In summary, a stroke, or brain attack, is an acute focal neurologic deficit caused by a vascular disorder that injures brain tissue. It is a leading cause of death in the United States and a major cause of disability. There are two main types of stroke: ischemic and hemorrhagic. Ischemic stroke, which is the most common type, is caused by cerebrovascular obstruction by a thrombus or embolus. Hemorrhagic stroke, which is associated with greater morbidity and mortality, is caused by the rupture of a blood vessel and bleeding into the brain. The acute manifestations of stroke depend on the location of the blood vessel that is involved and can include motor, sensory, language, speech, and cognitive disorders. Early diagnosis and treatment with thrombolytic therapy have improved the outlook for many persons with ischemic stroke.

A subarachnoid hemorrhage involves bleeding into the subarachnoid space. Most subarachnoid hemorrhages are the result of a ruptured cerebral aneurysm. Presenting symptoms include headache, nuchal rigidity, photophobia, and nausea. Complications include rebleeding, vasospasm, and hydrocephalus. Arteriovenous malformations are congenital abnormal communications between arterial and venous channels that result from failure in the development of the capillary network in the embryonic brain. The vessels in the arteriovenous malformations may enlarge to form a space-occupying lesion, become weak and predispose to bleeding, and divert blood away from other parts of the brain; they can cause brain hemorrhage, seizures, headache, and other neurologic deficits.

Infections and Brain Tumors

Infections

Infections of the CNS may be classified according to the structure involved—meninges (meningitis), parenchymal brain tissue (encephalitis), spinal cord (myelitis), or brain and spinal cord (encephalomyelitis). They also may be classified by the type of invading organism: bacterial, viral, or other. In general, the pathogen enters the CNS through the bloodstream by crossing the blood-brain barrier or by direct invasion through skull fracture, or, rarely, by contamination during surgery or lumbar puncture.

Meningitis

Meningitis is an inflammation of the pia mater, the arachnoid, and the CSF-filled subarachnoid space. Inflammation spreads rapidly because of CSF circulation around the brain and spinal cord. The inflammation usually is caused by an infection, but chemical meningitis can occur. There are two types of acute infectious meningitis: acute purulent meningitis (usually bacterial) and acute lymphocytic (usually viral) meningitis.[1] Factors responsible for the severity of meningitis include virulence factors of the pathogen, host factors, brain edema, and the presence of permanent neurologic sequelae.

Bacterial Meningitis. Most cases of bacterial meningitis are caused by *Streptococcus pneumoniae* (the pneumococcus) or *Neisseria meningitidis* (the meningococcus), except in neonates (infected most by group B streptococci).[1,5,48,49] *Haemophilus influenzae* infection was a leading cause of meningitis in decades past, but its incidence has declined dramatically during recent years because of vaccination against *H. influenza*. Epidemics of meningococcal meningitis occur in settings such as colleges and the military, where young people reside in close contact. Other pathogens in adults are gram-negative bacilli and *Listeria monocytogenes*. The very young and the very old are at highest risk for pneumococcal meningitis. Risk factors associated with contracting meningitis include head trauma with basilar skull fractures, otitis media, sinusitis or mastoiditis, neurosurgery, dermal sinus tracts, systemic sepsis, or immunocompromise.

In the pathophysiologic process of bacterial meningitis, the bacterial organisms replicate and undergo lysis in the CSF, releasing endotoxins or cell wall fragments. These substances initiate the release of inflammatory mediators, which set off a complex sequence of events permitting pathogens, neutrophils, and albumin to move across the capillary wall into the CSF. As the pathogens enter the subarachnoid space, they cause inflammation, characterized by a cloudy, purulent exudate. Thrombophlebitis of the bridging veins and dural sinuses or obliteration of arterioles by inflammation may develop, causing vascular congestion and infarction in the surrounding tissues. Ultimately, the meninges thicken and adhesions form. These adhesions may impinge on the cranial nerves, giving rise to cranial nerve palsies, or may impair the outflow of CSF, causing hydrocephalus.

The most common symptoms of acute bacterial meningitis are sudden onset of headache, fever, and stiffness of the neck (nuchal rigidity), sometimes accompanied by nausea, vomiting, photophobia, and altered mental status.[48,50] Other signs include seizures, cranial nerve palsies, and focal cerebral signs. Meningococcal meningitis is characterized by a petechial rash with palpable purpura in most people. These petechiae vary in size from pinhead to large ecchymoses or even areas of skin gangrene, often associated with rapid onset of hypotension, acute adrenal hemorrhage (the Waterhouse-Friderichsen syndrome), and multiple organ failure. Persons infected with *H. influenzae* or *S. pneumoniae* may present with difficulty in arousal and seizures, whereas those with *N. meningitidis* infection may present with delirium or coma. Cranial nerve damage (especially CN VIII, with resulting deafness) and hydrocephalus may occur as complications of pyogenic meningitis.

Diagnosis of bacterial meningitis is based on the history and physical examination, along with laboratory data. Two assessment techniques can help determine whether meningeal irritation is present. The *Kernig sign* is resistance to extension of the knee while the person is lying with the hip flexed at a right angle. The *Brudzinski sign* is elicited when flexion of the neck induces flexion of the hip and knee. These postures reflect resistance to the painful stretching of the inflamed meninges from the lumbar level to the head. Lumbar puncture findings, which are necessary for accurate diagnosis, include a cloudy and purulent CSF under increased pressure. Bacteria can be seen on smears and can easily be cultured with appropriate media. Occasionally, previous antibiotic use limits culture sensitivities, in which case latex agglutination or polymerase chain reaction (PCR) testing for *N. meningitidis, H. influenzae,* and *Listeria* species can be used. Because complications associated with lumbar puncture include life-threatening cerebral herniation, at-risk patients (i.e., those who are immunocompromised, had a seizure within a week, have papilledema, or have specific neurologic abnormalities) should have a CT scan before undergoing the procedure.

Treatment includes urgent antibiotics while diagnostic testing ensues.[49–51] Delay in initiation of antimicrobial

therapy, most frequently because of performance of medical imaging before performance of lumbar puncture or transfer to another medical facility, can result in poor outcomes.[49,50] Initial choice of antibiotics includes broad-spectrum coverage with a third-generation cephalosporin, vancomycin, and sometimes ampicillin. Further adjustment of antibiotics is driven by results of CSF cultures. Effective antibiotics produce rapid lysis of the pathogen, which produces inflammatory mediators that have the potential for exacerbating the abnormalities of the blood-brain barrier. To suppress this pathologic inflammation, adjunctive corticosteroid therapy is increasingly administered with or just before the first dose of antibiotics in patients of all ages.[49,50]

Persons who have been exposed to someone with meningococcal meningitis should be treated prophylactically with antibiotics.[49] A quadrivalent polysaccharide–protein conjugate vaccine is now available to protect against meningococcal meningitis. The vaccine is recommended for all persons aged 11 to 18 years and for persons 19 to 55 years who are at increased risk for meningococcal disease (e.g., military recruits, college students living in dormitories, microbiologists who are routinely exposed to *N. meningitides*, and persons with complement deficiencies or anatomic or functional asplenia).[52]

Viral Meningitis. Viral meningitis manifests in much the same way as bacterial meningitis, but the course is less severe and the CSF findings are markedly different. There are lymphocytes in the fluid rather than polymorphonuclear cells, the protein content is only moderately elevated, and the sugar content usually is normal. The acute viral meningitides are self-limited and usually require only symptomatic treatment, except for herpes simplex virus (HSV) type 2, which responds to intravenous acyclovir. Viral meningitis can be caused by many different viruses, most often enteroviruses, including coxsackievirus, poliovirus, and echovirus. Others include Epstein-Barr virus, mumps virus, HSV, and West Nile virus. Although often the virus cannot be identified, newer assays are emerging that allow in some circumstances for rapid identification of viral ribonucleic acid (RNA) in CSF.

Encephalitis

Encephalitis represents a generalized infection of the parenchyma of the brain or spinal cord. It usually is caused by a virus, but it also may be caused by bacteria, fungi, and other organisms. The nervous system is subject to invasion by many viruses, such as arbovirus, poliovirus, and rabies virus. The mode of transmission may be the bite of a mosquito (arbovirus), a rabid animal (rabies virus), or ingestion (poliovirus). Common causes of encephalitis in the United States are HSV and West Nile virus. Less frequent causes of encephalitis are toxic substances such as ingested lead and vaccines for measles and mumps. Encephalitis caused by human immunodeficiency virus (HIV) infection is discussed in Chapter 16.

The pathologic picture of encephalitis includes local necrotizing hemorrhage, which ultimately becomes generalized, with prominent edema. There is progressive degeneration of nerve cell bodies. The histologic picture, although rather general, may demonstrate some specific characteristics. For example, the poliovirus selectively destroys the cells of the anterior horn of the spinal cord.

Like meningitis, encephalitis is characterized by fever, headache, and nuchal rigidity, but more often patients also experience neurologic disturbances, such as lethargy, disorientation, seizures, focal paralysis, delirium, and coma. Diagnosis of encephalitis is made by clinical history and presenting symptoms, in addition to traditional CSF studies.

Brain Tumors

Primary brain tumors account for 2% of all cancers in the United States.[5,53] Metastasis to the brain from other sites is even more common. One estimate suggests that more than 100,000 people per year die with symptomatic intracranial metastasis.[54] In children, primary brain tumors are second only to leukemia as a cause of death from cancer, with 2200 primary brain tumors being diagnosed each year.[55] The mortality rate among this age group approaches 45%.[55]

The etiology of brain tumors is largely unknown. Several CNS tumors are associated with rare genetic conditions, most commonly the autosomal dominant disorder neurofibromatosis 1 (see Chapter 6). Although a large number of studies have examined the relationship between environmental and occupational factors, only high-dose radiation has been shown to be a proven risk factor.[53,55] Irradiation given to treat intracranial and extracranial cancers, including prophylactic irradiation for leukemia, increases the incidence of brain tumors.

Types of Tumors

The term *brain tumor* refers to a collection of intracranial neoplasms, each with its own histology, site of origin, prognosis, and treatment.[1,5,9] For most neoplasms, the term *malignant* is used to describe the tumor's lack of cell differentiation, its invasive nature, and its ability to metastasize. However, the terms *benign* and *malignant* do not apply to brain tumors in the same sense as they do to tumors in other parts of the body. In the brain, even a well-differentiated and histologically benign tumor may grow and cause death because of its location. Also, tumors in the brain are rarely benign because surgery rarely cures. Most histologically benign tumors infiltrate the normal brain tissue, preventing total resection and allowing for tumor recurrence. Furthermore, brain tumors seldom metastasize, except within the CNS itself.

Brain tumors can be divided into three basic types: primary intracranial tumors of neuroepithelial tissue (e.g., neuroglia, neurons), primary intracranial tumors that originate in the cranial cavity but are not derived from the brain tissue itself (e.g., meninges, primary CNS lymphoma, pituitary gland tumors [discussed in Chapter 32]), and metastatic tumors.[5] Collectively, neurogliomas of astrocytic origin are the most common type of primary

brain tumor in adults, and medulloblastomas the most common type in children. Whatever the type, brain tumors commonly present with symptoms related to a disruption in neuronal activity (seizures), signs of increased ICP (progressive headache, nausea and vomiting, drowsiness, visual abnormalities), focal motor or sensory deficits, and cognitive dysfunction.[56,57]

Neuroglial Tumors. Neuroglial tumors, which are the most common form of primary brain tumors, derive from astrocytes, oligodendrocytes, and ependymal cells.[1,5,58] Gliomas are divided into four grades: grades I and II are low-grade tumors, whereas grade III and IV are high-grade tumors.

Astrocyte tumors are generally divided into two categories: infiltrating astrocytomas and noninfiltrating astrocytomas. Infiltrating astrocytomas account for 80% of adult primary brain tumors.[1] They occur most commonly in the fourth through the sixth decade. Although they usually are found in the cerebral hemispheres, they also can occur in the cerebellum, brain stem, or spinal cord. The most common presenting signs and symptoms are seizures, headaches, and focal neurologic deficits related to the location of the tumor. Infiltrating astrocytomas are characterized by a spectrum of histologic differentiation that includes diffuse astrocytomas (grade II); anaplastic astrocytomas (grade III); and the least differentiated and most aggressive, glioblastomas (grade IV).[1] The grade I designation is reserved for the noninfiltrating pilocytic astrocytomas, which are distinguished from other astrocytomas by their cellular appearance and their benign behavior. Typically, they occur in children and young adults and usually are located in the cerebellum, but they also can be found in the floor and walls of the third ventricle, in the optic chiasm and nerves, and occasionally in the cerebral hemispheres. These tumors grow slowly and, in the cerebellum particularly, may be treated by resection.

Oligodendrogliomas are tumors of the oligodendrocytes or their precursors.[1] They represent approximately 5% to 15% of neuroglial tumors and are most common in the fourth and fifth decades of life. The tumors are found mostly in the cerebral hemispheres, with a predilection for white matter. The prognosis of persons with oligodendrogliomas is less predictable than for persons with infiltrating astrocytomas. It depends on the histologic grade of the tumor, its location, and, more recently, recognition of molecular features that can be linked to chemosensitivity.[54] The oligodendroglial tumors are prone to spontaneous hemorrhage owing to their delicate vasculature.

Ependymomas are derived from the single layer of epithelium that lines the ventricles and spinal canal. Although they can occur at any age, they are most likely to occur in the first two decades of life and most frequently affect the fourth ventricle; they constitute 5% to 10% of brain tumors in this age group.[1] In adults, the spinal cord is the most common location. The clinical features depend on the location of the neoplasm. Intracranial tumors are often associated with hydrocephalus and evidence of increased ICP.

Medulloblastoma. Tumors of neuronal origin (e.g., medulloblastoma) usually occur during infancy and childhood.[55,59] This is in accord with the principle that a cell must be capable of replication to undergo neoplastic transformation. Medulloblastoma is thought to originate from a primitive cell type in the cerebellum, arising from one of two cerebellar germinal zones: the ventricular zone that forms the outermost boundary or the external germinal layer that lines the outside of the cerebellum.

Medulloblastomas have a bimodal distribution, peaking at 3 to 4 years and then again between 8 and 9 years of age.[59] About 10% to 15% of cases are diagnosed in infancy.[59] Children usually present with signs and symptoms of increased ICP (i.e., headache, nausea, vomiting, mental status changes, hypertension) and cerebellar dysfunction (i.e., ataxia, balance problems, movement disorders). The tumor is highly malignant, and the prognosis for untreated children is dismal. However, the tumor is highly radiosensitive; with total excision and irradiation, the 5-year survival rate may be as high as 75%.

Meningiomas. Meningiomas develop from the meningothelial cells of the arachnoid and are outside the brain. They usually have their onset in the middle or later years of life and constitute approximately 20% of primary brain tumors in this age group.[1] Meningiomas are slow-growing, well-circumscribed, and often highly vascular tumors. They usually are benign, and complete removal is possible if the tumor does not involve vital structures.

Primary Central Nervous System Lymphomas. Primary CNS lymphoma has increased in incidence by a factor of 10 in the past two decades.[1,5] These deep, periventricular, and diffuse tumors are especially common in immunocompromised persons, including those with acquired immunodeficiency syndrome (AIDS) and immunosuppression after transplantation.

Most primary brain lymphomas are of B-cell origin. Overall primary lymphomas of the CNS are highly aggressive, and recurrence is common despite treatment. Behavioral and cognitive changes, which are the most common presenting symptoms, occur in about 65% of patients; hemiparesis, aphasia, and visual field deficits in about 50%; and seizures in 15% to 20%.[54]

Metastatic Tumors. Metastatic tumors, mostly carcinomas, affect approximately 20% to 40% of persons with cancer.[60] The five most common primary sites are the lung, breast, skin (melanoma), kidney, and gastrointestinal tract.[1,60] Within the brain there is regional selectivity for growth metastasis from the different primary types of cancer: melanoma is more typically found in the frontal and temporal lobes, breast cancer in the cerebellum and basal ganglia, and non–small cell lung cancer in the occipital lobe. Thus, it appears that tumor-specific interactions with brain physiology mediate the establishment and proliferation of brain metastasis. Recent investigations have begun to elucidate the mechanisms of such molecular mechanisms. For women with breast cancer, hormone receptor and human epidermal growth factor receptor-2 (HER2)/neu status is predictive of brain metastasis risk.[60]

Clinically evident brain metastases present with signs of increased ICP, mental status changes, seizures, and focal neurologic deficits. Management of persons with CNS metastasis consists of symptomatic and definitive therapies. The mainstays of symptomatic control are corticosteroids for tumor-related edema, antiepileptic drugs for seizure control, and multidisciplinary interventions aimed at minimizing neurologic disability.[60]

Clinical Features

The clinical manifestations of brain tumors depend on the size and location of the tumor. General signs and symptoms include headache, nausea, vomiting, mental changes, papilledema, visual disturbances (e.g., diplopia), alterations in sensory and motor function, and seizures.[9,56,57] Because the volume of the intracranial cavity is fixed, brain tumors cause a generalized increase in ICP when they reach sufficient size or produce edema. Cerebral edema usually is of the vasogenic type, which develops around the tumors and is characterized by an increased extracellular fluid volume. The edema is thought to result from increased permeability of tumor capillary endothelial cells. Tumors can also obstruct the flow of CSF in the ventricular cavities and produce hydrocephalic dilation of the proximal ventricles and atrophy of the cerebral hemispheres. With very slow-growing tumors, complete compensation of ventricular volumes can occur, but with rapidly growing tumors, increased ICP is an early sign.

The brain itself is insensitive to pain. The headache that accompanies brain tumors results from compression or distortion of pain-sensitive dural or vascular structures. It may be felt on the same side of the head as the tumor, but more commonly is diffuse. In the early stages, the headache is mild and occurs in the morning on awakening and improves with head elevation. The headache becomes more constant as the tumor enlarges and often is worsened by coughing, bending, or sudden movements of the head.

Vomiting occurs with or without nausea, may be projectile, and is a common symptom of increased ICP and brain stem compression. Direct stimulation of the vomiting center, which is located in the medulla, may contribute to the vomiting that occurs with brain tumors. The vomiting is often associated with headache. Papilledema (edema of the optic disk) results from increased ICP and obstruction of the CSF pathways. It is associated with decreased visual acuity, diplopia, and deficits in the visual fields. Visual defects associated with papilledema often are the reason that persons with brain tumor seek medical care.

Personality and mental changes such as depression are common with brain tumors. Persons with brain tumors often are irritable initially and later become quiet and apathetic. They may become forgetful, seem preoccupied, and appear to be psychologically depressed. Because of the mental changes, a psychiatric consultation may be sought before a diagnosis of brain tumor is made.

Focal signs and symptoms are determined by the location of the tumor. Tumors arising in the frontal lobe may grow to a large size, increase the ICP, and cause signs of generalized brain dysfunction before focal signs are recognized. Tumors that impinge on the visual system cause visual loss or visual field defects long before generalized signs develop. Certain areas of the brain have a relatively low threshold for seizure activity. Temporal lobe tumors often produce seizures as their first symptom. Hallucinations of smell or hearing and déjà vu phenomena are common focal manifestations of temporal lobe tumors. Brain stem tumors commonly produce upper and lower motor neuron signs, such as weakness of facial muscles and ocular palsies that occur with or without involvement of sensory or long motor tracts. Cerebellar tumors often cause ataxia of gait.

Diagnosis and Treatment. The diagnosis of brain tumors rests mainly on MRI.[54,56,57] Gadolinium-enhanced MRI is the test of choice for identifying and localizing the presence and extent of tumor involvement. CT scans may fail to reveal certain mass lesions such as low-grade tumors or posterior fossa masses. Diagnostic maneuvers that suggest a possible tumor and indicate the need for MRI include physical and neurologic examinations, visual field and funduscopic examination, and sometimes electroencephalography (EEG). Approximately 75% of persons with a brain tumor have an abnormal EEG, which can indicate an underlying structural lesion warranting MRI. Cerebral angiography can be used to visualize the tumor's vascular supply, information that is important when planning surgery. MRI may be supplemented with positron emission tomography to better characterize the metabolic properties of the tumor, useful in planning treatment.[54] MRA and CTA can be used to distinguish vascular masses from tumors.

The three general methods for treatment of brain tumors are surgery, irradiation, and chemotherapy. Surgery is part of the initial management of virtually all brain tumors; it establishes the diagnosis and achieves tumor removal in many cases. The development of microsurgical neuroanatomy, the operating microscope, and advanced stereotactic and ultrasonographic technology; the fusion of imaging systems with resection techniques; and the intraoperative monitoring of evoked potentials or the EEG have improved the effectiveness of surgical resection. However, the degree of removal may be limited by the location of the tumor and its invasiveness. Stereotactic surgery uses three-dimensional coordinates and CT and MRI to localize a brain lesion precisely. Ultrasonographic technology has been used for localizing and removing tumors. The ultrasonic aspirator, which combines a vibrating head with suction, permits atraumatic removal of tumors from cranial nerves and important cortical areas. Intraoperative monitoring of evoked potentials is an important adjunct to some types of surgery. For example, evoked potentials can be used to monitor auditory, visual, speech, or motor responses during surgery done under local anesthesia.

Most malignant brain tumors respond to external irradiation. Irradiation can increase longevity and sometimes can allay symptoms when tumors recur. The treatment

dose depends on the tumor's histologic type, radioresponsiveness, and anatomic site and on the level of tolerance of the surrounding tissue. A newer technique called *gamma knife* combines stereotactic localization of tumor with radiosurgery, allowing delivery of high-dose radiation to deep tumors while sparing surrounding brain. Radiation therapy is avoided in children younger than 2 years of age because of the long-term effects, which include developmental delay, panhypopituitarism, and secondary tumors. The use of chemotherapy for brain tumors is somewhat limited by the blood-brain barrier. Chemotherapeutic agents can be administered intravenously, intra-arterially, intrathecally (i.e., into the spinal canal), as wafers impregnated with a drug and implanted into the tumor at the time of surgery, or intraventricularly.

In summary, infections of the CNS may be classified according to the structures involved—the meninges (meningitis) or brain parenchyma (encephalitis)—and the type of organism causing the infection (bacteria or virus). The damage caused by infection may predispose to hydrocephalus, seizures, or other neurologic defects.

Brain tumors account for 2% of all aggressive neoplasms and are the second most common type of cancer in children. Brain tumors can be divided into primary intracranial tumors of neuroepithelial tissue (e.g., neuroglia, neurons), primary intracranial tumors that originate in the skull cavity but are not derived from the brain tissue itself (e.g., meninges, primary CNS lymphoma, pituitary gland tumors), and metastatic tumors. Neuroglial tumors, the most common type of brain tumors, are broadly classified into astrocytomas, oligodendrogliomas, and ependymomas. Metastatic tumors, mostly carcinomas, affect approximately 20% to 40% of persons with cancer, with cancers of the lung, breast, skin (melanoma), kidney, and gastrointestinal tract being the common site of the primary cancer. The clinical manifestations of brain tumor depend on the size and location of the tumor. Focal disturbances result from brain compression, tumor infiltration, disturbances in blood flow, and cerebral edema. General signs and symptoms include headache, nausea, vomiting, mental changes, papilledema, visual disturbances, alterations in motor and sensory function, and seizures. Diagnostic tests include physical examination, visual field testing and funduscopic examination, CT scans, MRI studies, skull x-ray films, brain scans, EEG, and cerebral angiography. Treatment includes surgery, irradiation, and chemotherapy.

Seizure Disorders

A seizure represents an abrupt and temporary alteration in cerebral activity resulting in changes in electrical discharge from neurons in the cerebral cortex.[9,61] A seizure is a discrete clinical event with associated signs and symptoms that vary according to the site of neuronal discharge in the brain. Manifestations of seizure generally include sensory, motor, autonomic, or psychic phenomena. A convulsion refers to the specific type of a motor seizure involving the entire body. Seizure activity is the most common disorder encountered in pediatric neurology, and among adults its incidence is exceeded only by cerebrovascular disorders. In most persons, the first seizure episode occurs before 20 years of age.[62] After 20 years of age, a seizure is caused most often by a structural change, trauma, tumor, or stroke.

A seizure is not a disease but a symptom of underlying CNS dysfunction. Seizures may occur during almost all serious illnesses or injuries affecting the brain, including metabolic derangements, infections, tumors, drug abuse, vascular lesions, congenital deformities, and brain injury. *Epilepsy* is characterized by recurrent seizures that are not provoked by other illnesses or circumstances.[63–65]

Seizures

- Seizures are paroxysmal motor, sensory, or cognitive manifestations of spontaneous, abnormally synchronous electrical discharges from collections of neurons in the cerebral cortex.
- Seizures are thought to result directly or indirectly from changes in excitability of single neurons or groups of neurons.
- The site of seizure generation and the extent to which the abnormal neural activity is conducted to other areas of the brain determine the type and manifestations of the seizure activity.
- Partial seizures originate in a small group of neurons in one hemisphere with secondary spread of seizure activity to other parts of the brain. Simple partial seizures usually are confined to one hemisphere and do not involve loss of consciousness. Complex partial seizures begin in a localized area, spread to both hemispheres, and involve impairment of consciousness.
- Generalized seizures show simultaneous disruption of normal brain activity in both hemispheres from the onset. They include unconsciousness and varying bilateral degrees of symmetric motor responses with evidence of localization to one hemisphere. Absence seizures are generalized nonconvulsive seizure events that are expressed mainly by brief periods of unconsciousness. Tonic-clonic seizures involve unconsciousness along with both tonic and clonic muscle contractions.

Provoked and Unprovoked Seizures

Many theories have been proposed to explain the cause of the abnormal brain electrical activity that occurs with seizures. Seizures may be caused by alterations in cell membrane permeability or distribution of ions across the neuronal cell membranes.[63] Another cause may be decreased inhibition of cortical or thalamic neuronal activity or structural changes that alter the excitability of neurons. Neurotransmitter imbalances such as an acetylcholine excess or γ-aminobutyric acid (GABA, an inhibitory neurotransmitter) deficiency have also been proposed as causes. Certain epilepsy syndromes have been linked to specific genetic mutations causing ion channel defects.

Clinically, seizures may be categorized as unprovoked (primary or idiopathic) or provoked (secondary or acute symptomatic).[9,61] Unprovoked or idiopathic seizures are those for which no identifiable cause can be determined, and are thought to be genetic. Most unprovoked seizures occur in the setting of an epileptic syndrome. These patients usually require chronic administration of antiepileptic medications to limit seizure recurrences. Provoked or symptomatic seizures include febrile seizures, seizures precipitated by systemic metabolic conditions, and those that follow a primary insult to the CNS. Most provoked seizures are best prevented by treatment of the underlying cause. For example, the most common subgroup is that of febrile seizures in children.[62] In susceptible children, a high fever, usually over 104°F, will provoke a generalized seizure. Treatment includes aggressive use of antipyretics to prevent seizures during a febrile illness. Transient systemic metabolic disturbances may precipitate seizures. Examples include electrolyte imbalances, hypoglycemia, hypoxia, hypocalcemia, uremia, alkalosis, and rapid withdrawal of sedative drugs. Specific CNS injuries such as toxemia of pregnancy, water intoxication, meningitis, trauma, cerebral hemorrhage and stroke, and brain tumors may precipitate a seizure. In all cases of provoked seizures, treatment of the immediate underlying cause often results in their resolution.

Classification

The International Classification of Epileptic Seizures determines seizure type by clinical symptoms and EEG activity. It divides seizures into two broad categories: partial seizures, in which the seizure begins in a specific or focal area of one cerebral hemisphere, and generalized seizures, which begin simultaneously in both cerebral hemispheres[66,67] (Chart 37-1). Further classification of epileptic syndromes characterizes the underlying diseases that cause the seizures, and divides seizures into idiopathic (suspected to be genetic), symptomatic (resulting from some CNS injury), and cryptogenic (presumed to be symptomatic of some unidentified cause). The system also has categories for seizures of undetermined origin such as neonatal seizures and a category of special syndromes such as febrile seizures.

CHART 37-1 Classification of Epileptic Seizures

Partial Seizures

Simple partial seizures (no impairment of consciousness)
- With motor symptoms
- With sensory symptoms
- With autonomic signs
- With psychic symptoms

Complex partial seizures (impairment of consciousness)
- Simple partial onset followed by impaired consciousness
- Impairment of consciousness at onset

Partial seizures evolving to secondarily generalized seizures
- Simple partial leading to generalized seizures
- Complex partial leading to generalized seizures

Unclassified Seizures

Classification not possible because of inadequate or incomplete data

Generalized Seizures

Absence seizures (typical or atypical)
Atonic seizures
Myoclonic seizures
Clonic seizures
Tonic
Tonic-clonic seizures

Adapted from Commission on Classification and Terminology of the International League Against Epilepsy. (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 22, 489.

Partial Seizures

Partial or focal seizures are the most common type of seizure among newly diagnosed cases in all groups older than 10 years of age. Partial seizures can be subdivided into three major groups: simple partial (consciousness is not impaired), complex partial (impairment of consciousness), and secondarily generalized partial seizures. These categories are based primarily on current neurophysiologic theories related to seizure propagation and the extent of involvement of the brain's hemispheres.

Simple Partial Seizures. Simple partial seizures usually involve only one hemisphere and are not accompanied by loss of consciousness or responsiveness. These seizures also have been referred to as elementary partial seizures, partial seizures with elementary symptoms, or focal seizures. Simple partial seizures are classified according to motor signs, sensory symptoms, autonomic manifestations, and psychic symptoms.[66]

The observed clinical signs and symptoms depend on the area of the brain where the abnormal neuronal discharge is taking place. If the motor area of the brain is involved, the earliest symptom is motor movement corresponding to the location of onset on the contralateral

side of the body. The motor movement may remain localized or may spread to other cortical areas, with sequential involvement of body parts in an epileptic-type "march," known as a *Jacksonian seizure*. If the sensory portion of the brain is involved, there may be no observable clinical manifestations. Sensory symptoms correlating with the location of seizure activity on the contralateral side of the brain may involve somatic sensory disturbance (e.g., tingling and crawling sensations) or special sensory disturbance (i.e., visual, auditory, gustatory, or olfactory phenomena). When abnormal cortical discharge stimulates the autonomic nervous system, flushing, tachycardia, diaphoresis, hypotension or hypertension, or pupillary changes may be evident.

The term *prodrome* or *aura* traditionally has meant a stereotyped warning sign of impending seizure activity described by the affected person. The aura actually represents a simple partial seizure, reflecting only a small area of abnormal electrical activity in the brain. Simple partial seizures may progress to complex partial seizures or generalized tonic-clonic seizures that result in unconsciousness. Most patients perceive the aura as a warning sign of impending complex partial seizures or other generalized seizures.

Complex Partial Seizures. Complex partial seizures involve impairment of consciousness and often arise from the temporal lobe. The seizure begins in a localized area of the brain but may progress rapidly to involve both hemispheres. These seizures are sometimes referred to as *psychomotor seizures,* reflecting their typical manifestations.

Complex partial seizures often are accompanied by automatisms. Automatisms are repetitive, nonpurposeful activities such as lip smacking, grimacing, patting, or rubbing clothing. Confusion during the postictal state (after a seizure) is common. Hallucinations and illusional experiences such as déjà vu (familiarity with unfamiliar events or environments) or jamais vu (unfamiliarity with a known environment) have been reported. There may be overwhelming fear, uncontrolled forced thinking or a flood of ideas, and feelings of detachment and depersonalization. A person with a complex partial seizure disorder sometimes is misdiagnosed as having a psychiatric disorder.

Secondarily Generalized Partial Seizures. These seizures are focal at onset but then become generalized as the neuronal discharge spreads, involving deeper structures of the brain, such as the thalamus or the reticular formation. Discharges spread to both hemispheres, resulting in progression to tonic-clonic seizure activity. These seizures may start as simple or complex partial seizures and may be preceded by an aura. The aura, often a stereotyped peculiar sensation that precedes the seizure, is the result of partial seizure activity. A history of an aura is clinically useful to identify the seizure as partial and not generalized in onset. However, absence of an aura does not reliably exclude a focal onset because many partial seizures generalize too rapidly to generate an aura.

Generalized Seizures

Generalized-onset seizures are the most common type in young children. These seizures are classified as primary or generalized when clinical signs, symptoms, and supporting EEG changes indicate involvement of both hemispheres at onset. The clinical symptoms include unconsciousness and involve varying bilateral degrees of symmetric motor responses without evidence of localization to one hemisphere.

These seizures are divided into four broad categories: absence seizures (typical and atypical), atonic (akinetic) seizures, myoclonic seizures, and major motor seizures, characterized by tonic, clonic, or tonic-clonic activity.[62,67]

Absence Seizures. Absence seizures are generalized, nonconvulsive epileptic events and are expressed mainly as disturbances in consciousness. Formerly referred to as *petit mal seizures,* absence seizures typically occur only in children and cease in adulthood or evolve to generalized motor seizures. Children may present with a history of school failure that predates the first evidence of seizure episodes. Although typical absence seizures have been characterized as a blank stare, motionlessness, and unresponsiveness, motion occurs in many cases of absence seizures. This motion takes the form of automatisms such as lip smacking, mild clonic motion (usually in the eyelids), increased or decreased postural tone, and autonomic phenomena. There often is a brief loss of contact with the environment. The seizure usually lasts only a few seconds, and then the child is able to resume normal activity immediately. The manifestations often are so subtle that they may pass unnoticed. Because automatisms and unresponsiveness are common to complex partial seizures, the latter often are mistakenly labeled as "petit mal" seizures.

Atypical absence seizures are similar to typical absence seizures except for greater alterations in muscle tone and less abrupt onset and cessation. In practice, it is difficult to distinguish typical from atypical absence seizures without the benefit of supporting EEG findings. However, it is important to distinguish between complex partial and absence seizures because the drugs of choice for treatment are different. Medications that are effective for partial seizures may increase the frequency of absence seizures.

Atonic Seizures. In akinetic or atonic seizures, there is a sudden, split-second loss of muscle tone leading to slackening of the jaw, drooping of the limbs, or falling to the ground. These seizures also are known as *drop attacks*.

Myoclonic Seizures. Myoclonic seizures involve brief involuntary muscle contractions induced by stimuli of cerebral origin. A myoclonic seizure involves bilateral jerking of muscles, generalized or confined to the face, trunk, or one or more extremities. Tonic seizures are characterized by a rigid, violent contraction of the muscles, fixing the limbs in a strained position. Clonic

seizures consist of repeated contractions and relaxations of the major muscle groups.

Tonic-Clonic Seizures. Tonic-clonic seizures, formerly called *grand mal seizures,* are the most common major motor seizure. Frequently, a person has a vague warning (probably a simple partial seizure) and experiences a sharp tonic contraction of the muscles with extension of the extremities and immediate loss of consciousness. Incontinence of bladder and bowel is common. Cyanosis may occur from contraction of airway and respiratory muscles. The tonic phase is followed by the clonic phase, which involves rhythmic bilateral contraction and relaxation of the extremities. At the end of the clonic phase, the person remains unconscious until the RAS begins to function again. This is called the *postictal phase*. The tonic-clonic phases last approximately 60 to 90 seconds.

Unclassified Seizures

Unclassified seizures are those that cannot be placed in one of the previous categories. These seizures are observed in the neonatal and infancy periods. Determination of whether the seizure is focal or generalized is not possible. Unclassified seizures are difficult to control with medication.

Diagnosis and Treatment

Diagnosis

The diagnosis of seizure disorders is based on a thorough history and neurologic examination, including a full description of the seizure.[9,61,65] The physical examination and laboratory studies help exclude any metabolic disorder (e.g., hyponatremia) that could precipitate seizures. MRI scans are used to identify structural defects such as temporal lobe sclerosis or underlying congenital malformations causing the seizure. One of the most useful diagnostic tests is the EEG, which is used to record changes in the brain's electrical activity. It is used to support the clinical diagnosis of epilepsy, to provide a guide for prognosis, and to assist in classifying the seizure disorder.

Pharmacologic Treatment

The management of seizure disorders focuses on treatment of the underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with antiepileptic medications or by surgery, and addressing psychological and social issues.[61] Treatment must be individualized for each patient based on the different types and causes of seizures as well as the efficacy and side effects of antiepileptic drugs. Persons with epilepsy should be advised to avoid situations that could be dangerous or life-threatening if seizures occur.

Antiepileptic drug therapy is the mainstay of treatment for most persons with epilepsy. Antiepileptic drugs act mainly by suppressing repetitive firing of isolated neurons that act as epileptogenic foci for seizure activity or by inhibiting the transmission of electrical impulses involved in seizure activity.[68] Because of their selective mechanisms of action, different drugs are used to treat the different types of seizures. For example, ethosuximide, which suppresses the brain wave activity associated with lapses of consciousness, is used in the treatment of absence seizures, but is not effective for tonic-clonic seizures that progress from partial seizures.

More than 20 drugs are available for the treatment of epilepsy. This group includes nine antiepileptic drugs that have been approved for use in the United States in the past several decades.[64] The goal of pharmacologic treatment is to bring the seizures under control with the least possible disruption in lifestyle and the minimum of side effects from medication.[64,65,69,70] Whenever possible, a single drug should be used. Monotherapy eliminates drug interactions and additive side effects. Determining the proper dose of the anticonvulsant drug is often a long and tedious process, which can be very frustrating for the person with epilepsy. Often blood tests are used to determine that the blood concentration is within the therapeutic range. Consistency in taking the medication is essential. Antiepileptic drug use never should be discontinued abruptly. Special consideration is needed when a person taking an antiepileptic medication becomes ill and must take additional medications. Some drugs act synergistically, and others interfere with the actions of other antiepileptic medications. This situation needs to be carefully monitored to avoid overmedication or interference with successful seizure control.

Women of child-bearing age require special consideration concerning fertility, contraception, and pregnancy. Many of the drugs interact with oral contraceptives; some affect hormone function or decrease fertility. All such women should be advised to take folic acid supplementation. For women with epilepsy who become pregnant, antiseizure drugs increase the risk for congenital abnormalities and other perinatal complications. Carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid can interfere with vitamin D metabolism and predispose to osteoporosis.

Surgical Therapy

Surgical treatment may be an option for persons with epilepsy that is refractory to drug treatment.[9,61] With the use of modern neuroimaging and surgical techniques, a single epileptogenic lesion can often be identified and removed without leaving a neurologic deficit. The most common surgery consists of removal of the amygdala and an anterior part of the hippocampus and entorhinal cortex, as well as a small part of the temporal pole, leaving the lateral temporal neocortex intact. Another surgical procedure involves partial removal of the corpus callosum to prevent spread of a unilateral seizure to a generalized seizure. Some refractory patients benefit from an implantable electrical stimulator of the vagus nerve.

Generalized Convulsive Status Epilepticus

Seizures that do not stop spontaneously or occur in succession without recovery are called *status epilepticus*. There

are as many types of status epilepticus as there are types of seizures. Tonic-clonic status epilepticus is a medical emergency and, if not promptly treated, may lead to respiratory failure and death. The disorder occurs most frequently in the young and old. Morbidity and mortality rates are highest in elderly persons and persons with acute symptomatic seizures, such as those related to anoxia or cerebral infarction.[61] If status epilepticus is caused by neurologic or systemic disease, the cause needs to be identified and treated immediately because the seizures probably will not respond until the underlying cause has been corrected.

Treatment consists of appropriate life support measures. Medications are given to control seizure activity. Intravenously administered diazepam or lorazepam is considered first-line therapy for the condition. The prognosis is related to the underlying cause as well as the duration of the seizures themselves.

In summary, seizures are caused by spontaneous transitory neuronal discharges from cortical centers in the brain. Seizures may occur as a reversible symptom of another disease condition or as a recurrent condition called *epilepsy.* Epileptic seizures are classified as partial or generalized seizures. Partial seizures have evidence of local onset, beginning in one hemisphere. They include simple partial seizures, in which consciousness is not lost, and complex partial seizures, which begin in one hemisphere but progress to involve both. Generalized seizures involve both hemispheres and include unconsciousness and rapidly occurring, widespread, bilateral symmetric motor responses. They include absence, atonic, myotonic, and tonic-clonic seizures. Control of seizures is the primary goal of treatment and is accomplished with anticonvulsant medications. Anticonvulsant medications can interact with each other and need to be monitored closely when more than one medication is used.

Disorders of Memory and Cognition

Memory is the process by which information is encoded, stored, and later retrieved, while cognition is the process by which information is reduced, elaborated, transformed, and used. Cognition involves the perception of sensory input and the ability to learn and manipulate new information, recognize familiar objects and recollect past experiences, solve problems, think abstractly, and make judgments. Cognition can be impaired as the result of a number of conditions, including global ischemia, traumatic brain injury, and stroke.

Dementia

Dementia or nonnormative cognitive decline can be caused by any disorder that permanently damages large association areas of the cerebral hemispheres or subcortical areas subserving memory and learning.[71,72] It is a common and disabling disorder in the elderly and is becoming a growing public heath problem, because of rapidly increasing numbers of elderly people.

Based on criteria in the fourth edition, text revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), the essential feature of dementia is impairment of short- and long-term memory, which is associated with deficits in abstract thinking, impaired judgment and other higher cortical functions, or personality change.[73] The disturbance should be sufficiently severe as to interfere significantly with work or social activities. Common causes of dementia are Alzheimer disease, vascular dementia, frontotemporal dementia, Wernicke-Korsakoff syndrome, and Huntington chorea.

The diagnosis of dementia is based on assessment of the presenting problem; history about the person that is provided by an informant (someone who has known the person, usually a family member); complete physical and neurologic examination; evaluation of cognitive, behavioral, and functional status; and laboratory and imaging studies. Depression is the most common treatable illness that may masquerade as dementia, and it must be excluded when a diagnosis of dementia is considered. This is important because cognitive functioning usually returns to baseline levels after depression is treated. Screening evaluations for subdural hematoma, cerebral infarcts, cerebral tumors, and normal-pressure hydrocephalus are also recommended. These and other reversible forms of dementia that should be ruled out can be remembered by the mnemonic DEMENTIA: *D*rugs (drugs with anticholinergic activity), *E*motional (depression), *M*etabolic (hypothyroidism), *E*yes and ears (declining vision and hearing), *N*ormal-pressure hydrocephalus, *T*umor or other space-occupying lesions, *I*nfection (human immunodeficiency virus infection or syphilis), *A*nemia (vitamin B_{12} or folate deficiency).[72]

Alzheimer Disease

Dementia of the Alzheimer type occurs in middle or late life and accounts for 60% to 80% of all cases of dementia. The disorder affects more than 4.5 million Americans and is the fourth leading cause of death in the United States.[72,74] The risk for development of Alzheimer disease increases with age, starting at a level of 1% for the 60- to 64-year-old population and increasing to 40% or more for the 85- to 89-year-old cohort.[1]

Alzheimer disease most often presents with a subtle onset of memory loss followed by slowly progressive dementia that has a course of several years. Pathologically, there is diffuse atrophy of the cerebral cortex with enlargement of the ventricles (Fig. 37-16). The major microscopic features of Alzheimer disease are the presence of neuritic (senile) plaques, neurofibrillary tangles, and amyloid angiopathy.[1,5] The *neuritic plaques* are patches or flat areas composed of clusters of degenerating nerve terminals arranged around a central amyloid core. The *neurofibrillary tangles,* found in the cytoplasm of abnormal neurons, consist of fibrous proteins that are

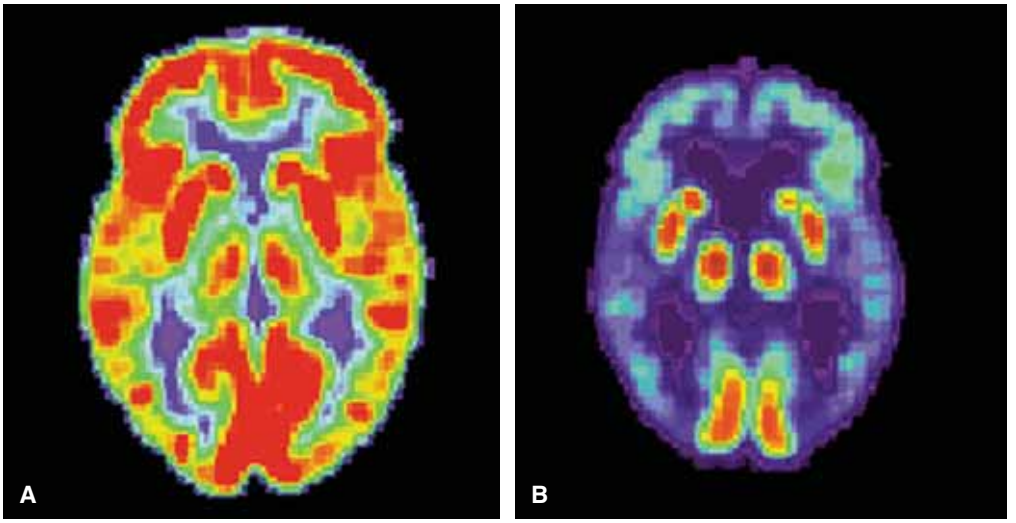


FIGURE 37-16. Functional imaging of the brain with positron emission tomography (PET). Perfusion and metabolism in a normal brain **(A)** and hypoperfusion and hypometabolism due to brain atrophy in a brain with Alzheimer disease **(B)** (From *Alzheimer's disease: Unraveling the mystery images.* National Institute of Health, National Institute of Aging.)

wound around each other in a helical fashion. These tangles are resistant to chemical or enzymatic breakdown, and they persist in brain tissue long after the neuron in which they arose has died and disappeared.

Evidence from familial forms of Alzheimer disease indicates that the accumulation of a peptide (amyloid beta or Aβ) in the brain initiates a chain of events that result in the morphologic changes of Alzheimer disease and dementia. This peptide is derived from a larger membrane-spanning protein known as *amyloid precursor protein* (APP), which can be processed in either of two ways. It can be cleaved by the enzymes, α-secretase and γ-secretase, in a proteolytic pathway that prevents the formation of Aβ, or it can be cleaved by β-secretase and γ-secretase in a pathway that generates Aβ.[1]

Some plaques and tangles can be found in the brains of older persons who do not show cognitive impairment. The number and distribution of the plaques and tangles appear to contribute to the intellectual deterioration that occurs with Alzheimer disease. In persons with the disease, the plaques and tangles are found throughout the neocortex and in the hippocampus and amygdala, with relative sparing of the primary sensory cortex.[1] Hippocampal function in particular may be compromised by the pathologic changes that occur in Alzheimer disease. The hippocampus is crucial to information processing, acquisition of new memories, and retrieval of old memories.

Neurochemically, Alzheimer disease has been associated with a decrease in the level of choline acetyltransferase activity in the cortex and hippocampus. This enzyme is required for the synthesis of acetylcholine, a neurotransmitter that is associated with memory. The reduction in choline acetyltransferase is quantitatively related to the numbers of neuritic plaques and severity of dementia.

It is likely that Alzheimer disease is caused by several factors that interact differently in different persons. Progress in the genetics of inherited early-onset Alzheimer disease shows that mutations in at least three genes—the *APP* gene on chromosome 21; presenilin-1 (*PS1*), a gene on chromosome 14; and presenilin-2 (*PS2*), a gene on chromosome 1—can cause Alzheimer disease in certain families.[1,5] The *APP* gene is associated with an autosomal dominant form of early-onset Alzheimer disease, and can be tested clinically. Virtually all persons with Down syndrome (trisomy 21) exhibit the pathologic features of Alzheimer disease as they age. PS1 and PS2, both intracellular proteins, are components of γ-secretase and possibly part of a multiprotein complex containing the proteolytic site for breakdown of Aβ. A fourth gene, an allele (ϵ4) of the apolipoprotein E (ApoE) gene found on chromosome 19, increases the risk of Alzheimer disease and lowers the age of onset of the disease.

Manifestations. Alzheimer-type dementia follows an insidious and progressive course.[74] The hallmark symptoms are loss of short-term memory and denial of such memory loss, with eventual disorientation, impaired abstract thinking, apraxias, and changes in personality and affect.[75] Various stages of the disease have been recognized, ranging from the initial to those represented by the advanced stages of the disease. All are characterized by progressive degenerative changes. The initial changes are often subtle, characterized by a short-term memory loss that often is difficult to differentiate from the normal memory loss that often occurs in the elderly, and usually is reported by caregivers and denied by the patient. Although most elderly persons have trouble retrieving from memory incidental information and proper names, persons with Alzheimer disease randomly forget important and unimportant details. They forget where things are placed, get

lost easily, and have trouble remembering appointments and performing novel tasks. Mild changes in personality, such as lack of spontaneity, social withdrawal, and loss of a previous sense of humor, occur during this stage.

As the disease progresses, the person with Alzheimer disease enters the moderate stage. This stage may last several years and is marked by a more global impairment of cognitive functioning. During this stage, there are changes in higher cortical functioning needed for language, spatial relationships, and problem solving. Depression may occur in persons who are aware of their deficits. There is extreme confusion, disorientation, lack of insight, and inability to carry out the activities of daily living. Personal hygiene is neglected, and language becomes impaired because of difficulty in remembering and retrieving words. Behavioral changes can include agitation, sleep problems, restlessness and wandering, aggression, and suspiciousness. Some persons may become hostile and abusive toward family members. Persons who enter this stage become unable to live alone and should be assisted in making decisions about supervised placement with family members or friends or in a community-based facility.

Severe Alzheimer disease is the last stage of the disease. It is characterized by a loss of ability to respond to the environment. Individuals in this stage require total care and spend most of their time bedridden. Death can occur as a result of complications related to chronic debilitation.

Diagnosis and Treatment. Alzheimer disease is essentially a diagnosis of exclusion. There are no peripheral biochemical markers or tests for the disease. The diagnosis can be confirmed only by microscopic examination of tissue obtained from a cerebral biopsy or at autopsy. The diagnosis is based on clinical findings.

The diagnostic procedures for Alzheimer disease involve numerous steps, and a Differential Diagnosis in Alzheimer Algorithm has been developed.[76] A diagnosis of Alzheimer disease requires the presence of dementia established by clinical examination and documented by results of a Mini-Mental State Examination, Blessed Dementia Test, or similar mental status test; no disturbance in consciousness; onset between 40 and 90 years of age, most often after 65 years of age; and absence of systemic or brain disorders that could account for the memory or cognitive deficits. Brain imaging, CT scan, or MRI is done to exclude other brain disease. Metabolic screening should be done for known reversible causes of dementia such as vitamin B_{12} deficiency, thyroid dysfunction, and electrolyte imbalance.

There is no curative treatment for Alzheimer dementia.[74] Drugs are used primarily to slow the progression and to control depression, agitation, or sleep disorders. Two major goals of care are maintaining the person's socialization and providing support for the family. Self-help groups that provide support for family and friends have become available, with support from the Alzheimer Disease and Related Disorders Association. Day care and respite centers are available in many areas to provide relief for caregivers and appropriate stimulation for the patient.

Although there is no current drug therapy that is curative for Alzheimer disease, some show promise in terms of slowing the progress of the disease. Cholinesterase inhibitors have been shown to be effective in slowing the progression of the disease by potentiating the action of available acetylcholine.[74,75] These drugs (e.g., donepezil, rivastigmine, and galantamine) inhibit acetylcholinesterase, preventing the metabolism of endogenous acetylcholine, and are used in the early stages of the disease for mild cognitive impairment. Thus far, such therapy has not halted disease progression, but it can slow the disease progression by approximately 6 to 12 months. The therapeutic effects cease when the medication is discontinued.

Memantine, an *N*-methyl-D-aspartate antagonist, was recently approved by the FDA for treatment of moderate to severe Alzheimer disease.[75] This medication may act by interfering with the glutamatergic excitotoxicity caused by the ischemia and amyloid deposits associated with the disease, or it may provide symptomatic improvement through effects on the function of hippocampal neurons. This medication, like the cholinesterase inhibitors, does not reverse the disease, but does provide a modest delay in functional loss.

Other treatments for Alzheimer disease include agents that are thought to have a neuroprotective effect.[75] Aβ seems to exert its neurotoxic effects through a variety of secondary mechanisms, including oxidative injury and lipid peroxidation of cell membranes, and inflammation. Several strategies have involved the use of anti-inflammatory agents and antioxidants (vitamins E and C and *Ginkgo biloba*).[71,75] Several, but not all, epidemiologic studies provide evidence supporting the concept that vitamin E and vitamin C have a role in delaying the onset of Alzheimer disease. In some, but not all, trials, *G. biloba* had small but statistically significant effects compared with placebo in persons with Alzheimer disease.

Psychotropic medications, such as antipsychotics and mood stabilizers, may be used to assist in the behavioral management of the disease. Interventions also include environmental adjustments, behavioral intervention, and education and support for caregivers. Supports for caregivers is essential because they are responsible for supervising persons who live in the community and continue to visit and provide support after the person has been institutionalized. They are also responsible for administering medications, implementing nonpharmacologic treatments, and promoting the person's general health and well-being.

Other Types of Dementia

Vascular Dementia. Vascular dementia is caused by brain injury resulting from ischemic or hemorrhagic damage. Approximately 20% to 25% of dementias are vascular in origin, making it the second most common cause of dementia. The incidence is closely associated with hypertension, but also with arrhythmias, myocardial infarction, peripheral vascular disease, lipid abnormalities, diabetes mellitus, autoimmune and infectious vasculitis, and smoking.[71,77] The usual onset is between

the ages of 55 and 70 years, and more men are affected than women.[71]

Vascular dementia differs from Alzheimer disease in its presentation and tissue abnormalities. Slowness in psychomotor functioning is a main clinical feature of this dementia, and symptoms of depression present in up to 60% of patients with this disease.[5] The onset may be gradual or abrupt, the course usually is a stepwise progression, and there are focal neurologic symptoms related to local areas of infarction.

Frontotemporal Dementia. Frontotemporal dementia (FTD) refers to a group of disorders associated with atrophy of the frontal and anterior temporal lobes of the brain.[74,78,79] Originally known as *Pick disease,* FTD now refers to a syndrome that includes primary progressive aphasia, corticobasal degeneration, progressive supranuclear palsy, and semantic dementias. The disease often begins between 50 and 70 years of age, with men and women being equally affected.[74]

There are two distinct clinical presentations that reflect the symptoms of FTD: behavior and language. The former is more common, with behavioral presentations of disinhibited and impulsive actions or apathy, with inappropriate social behavior. The behavioral abnormalities can be quite extreme, and can be misdiagnosed as schizophrenia or psychotic depression. The second type of FTD involves disturbances in understanding or expressing language.

Diagnosis is based on evidence of cognitive impairment and exclusion of other illnesses that cause cognitive and behavioral deficits. Neuroimaging can be helpful in distinguishing FTD from other types of cognitive disorders. Typically, structural imaging shows anterior temporal and frontal lobe atrophy. The course of the disease is relentless, with death ensuing within 2 to 10 years. The immediate cause of death usually is infection.

Creutzfeldt-Jakob Disease. Creutzfeldt-Jakob disease (CJD) is a rare, rapidly degenerative form of dementia thought to be caused by an infective protein agent called a *prion*[1,5,80] (see Chapter 14). Variants of the disease occur in animals, including scrapie in sheep and goats and bovine spongiform encephalopathy (BSE; mad cow disease) in cattle.

There are three categories of CJD: hereditary, sporadic, and iatrogenic.[80] Approximately 15% of cases of CJD are familial and associated with different mutations of various codons on chromosome 20. Iatrogenic CJD is rare, representing less than 1% of cases. It was first reported in 1974 in a patient who received a corneal transplant; in addition to corneal tissue, the disease can be spread through other cadaveric neural tissue and inadequately sterilized neurosurgical instruments.[80] Sporadic CJD, in which the disease occurs without known risk factors, is the most common form, accounting for up to 85% of the cases. In 1995, a new and distinct variant of human CJD emerged in the United Kingdom, known as variant CJD.[80] Several features contributed to its distinct clinical picture, including appearance in younger persons than in sporadic CJD and initial prominent psychiatric symptoms. The disease has been linked convincingly to BSE, although the exact mechanism of transmission remains unclear. The average age of onset for variant CJD is 29 years, compared to 65 years for sporadic forms of CJD.

CJD causes degeneration of the pyramidal and extrapyramidal systems and is distinguished most readily by its rapid course. Affected persons usually are demented within 6 months of onset. The disease is uniformly fatal, with death often occurring within months, although a few persons may survive for several years. The early symptoms consist of abnormalities in personality and visual-spatial coordination, and impaired memory and judgment. Extreme dementia, insomnia, and ataxia follow as the disease progresses. There is no medical treatment for the disease.

Wernicke-Korsakoff Syndrome. Wernicke-Korsakoff syndrome most commonly results from chronic alcoholism. Wernicke disease is characterized by acute weakness and paralysis of the extraocular muscles, nystagmus, ataxia, and confusion.[5] The affected person also may have signs of peripheral neuropathy. The person has an unsteady gait and complains of diplopia. There may be signs attributable to alcohol withdrawal such as delirium, confusion, and hallucinations. This disorder is caused by a deficiency of thiamine (vitamin B_{12}), which directly interferes with production of glucose, the brain's main nutrient. Many of the symptoms are reversed when nutrition is improved with supplemental thiamine.

The Korsakoff component of the syndrome involves the chronic phase with severe impairment of recent memory. There often is difficulty in dealing with abstractions, and the person's capacity to learn is defective. Confabulation (i.e., recitation of imaginary experiences to fill in gaps in memory) probably is the most distinctive feature of the disease. Polyneuritis also is common. Unlike Wernicke disease, Korsakoff psychosis does not improve significantly with treatment.

Huntington Disease. Huntington disease (HD) is a hereditary disorder characterized by chronic progressive chorea, psychological changes, and dementia.[1,81] Although the disease is inherited as an autosomal dominant disorder, the age of onset most commonly is in the fourth and fifth decades. By the time the disease has been diagnosed, the person often has passed the gene on to his or her children. Approximately 10% of HD cases involve juvenile onset.[82] Children with the disease rarely live to adulthood.

Huntington disease is caused by a polyglutamine trinucleotide repeat expansion in the HD gene. The HD gene, located on chromosome 4, encodes a protein known *huntingtin*.[1,81,83] Normal HD genes contain 6 to 35 copies of the trinucleotide repeat; an expansion of repeats beyond this level is associated with disease. There is an inverse relationship between repeat number and age of onset, such that longer repeats are associated with earlier onset. Repeat expansions occur during spermatogenesis, so that paternal transmission is associated with early onset in the next generation. Although the biologic function of normal huntingtin remains unknown, there is little evidence to suggest that the disease is caused by an

insufficiency related to the mutated gene. Rather, the expansion of the polyglutamine region of the HD gene seems to bestow a toxic gain of function on the protein.[1]

Huntington disease produces localized death of brain cells. The first and most severely affected neurons are neurons of the basal ganglia that modulate motor output. These neurons normally function to dampen motor activity; thus, their degeneration in HD results in increased motor output, often manifested as choreiform movements. Although chorea is the prototypical movement disorder, the full spectrum of motor impairment in HD includes eye movement disorders, myoclonus, ataxia, dysarthria and dysphagia, and spasticity. Depression and personality changes are the most common early psychological manifestations; memory loss often is accompanied by impulsive behavior, moodiness, antisocial behavior, and a tendency toward emotional outbursts.[71] An estimated 30% of persons with Huntington disease experience major depressive disorder or dysthymic disorder, with about 6% of deaths attributed to suicide.[71] Persons with HD universally go through cognitive decline, mental slowing, and impaired problem-solving abilities, and eventually become demented. Cognitive decline also heralds the juvenile onset of HD.

There is no cure for Huntington disease. The treatment is largely symptomatic. Drugs may be used to treat the dyskinesias and behavioral disturbances. Study of the genetics of Huntington disease led to the discovery that the gene for the disease is located on chromosome 4. The discovery of a marker probe for the gene locus has enabled testing that can predict whether a person will develop the disease.

In summary, cognition refers to all the processes by which sensory input is transformed, reduced, elaborated, stored, recovered, and used. It is important to differentiate what can be termed "normal cognitive aging" from disorders of memory and cognition. Memory problems that are associated with normal aging tend to reflect a generalized decrease in the efficiency with which information is processed and retrieved. Memory of a past event can be based on retrieval that is accompanied by recollection of specific details or on the feeling that the event is old or new based on its familiarity. There is evidence that recollection is more dependent on the hippocampus, whereas familiarity is more dependent on the entorhinal cortex, and that healthy aging has greater effects on recollection than familiarity.

Dementia represents a syndrome of deterioration in cognitive function severe enough to interfere with occupational or social performance. By far the most common cause of dementia (60% to 80%) is Alzheimer disease. It is characterized by cortical atrophy and loss of neurons and the presence of neuritic plaques, granulovacuolar degeneration, and cerebrovascular deposits of amyloid. The disease follows an insidious and progressive course that begins with memory impairment and terminates in an inability to recognize family or friends and the loss of control over bodily functions. Ischemic or hemorrhagic damage is associated with vascular dementia, and frontotemporal dementia with atrophy of the frontal and temporal lobes. Creutzfeldt-Jakob disease is a rare, rapidly progressive form of dementia. Wernicke-Korsakoff syndrome most often results from chronic alcoholism. Huntington disease is a hereditary disorder characterized by chronic and progressive chorea, psychological changes, and dementia.

REVIEW EXERCISES

1. A 20-year-old man who was an unbelted driver involved in a motor vehicle accident presents in coma.

- **A.** What are the clinical signs of coma?
- **B.** Where does the source of coma localize in the brain?
- **C.** Which complications of traumatic head injury might lead to coma?
- **D.** What are the key treatment options to manage elevated intracranial pressure?

2. A 65-year-old woman presents with a 1-hour history of right-sided weakness and aphasia. An immediate CT scan of the brain is negative.

- **A.** Where in the brain is the pathology?
- **B.** What are the indications to administer intravenous tissue plasminogen activator?
- **C.** What are the possible causes of this stroke, and what diagnostic tests would reveal the cause?

3. A child is taken to the emergency department with lethargy, fever, and a stiff neck on examination.

- **A.** What findings on initial lumbar puncture indicate bacterial versus viral meningitis?
- **B.** In the case of bacterial meningitis, what are the most likely organisms, and which antibiotics should be started?

4. A 60-year-old man develops involuntary shaking of his right arm that spreads to the face, after which he collapses with whole-body shaking and loss of consciousness. After 1 minute, the shaking stops and he is confused and disoriented.

- **A.** What type of seizure is suggested by the clinical manifestations?
- **B.** Assuming this is his first seizure, what diagnostic tests should be performed to identify a cause for the seizure?
- **C.** If he has a long history of similar recurrent seizures, what treatments should be instituted? What treatments should be considered if he has failed multiple adequate trials of anticonvulsant medications?

REFERENCES

1. Frosch M.P., Anthony D., DeGirofami U. (2010). The central nervous system. In Kumar V., Abbas A.K., Fausto N. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1279–1344). Philadelphia: Elsevier Saunders.
2. Meyer F.B. (1992). Brain metabolism, blood flow, and ischemic thresholds. In Awad I.A. (Ed.), *Neurosurgical topics: Cerebrovascular occlusive disease and brain ischemia* (pp. 1–24). Cleveland: American Association of Neurological Surgeons.
3. Harukuni I., Bhardwaj A. (2006). Mechanisms of brain injury after global cerebral ischemia. *Neurologic Clinics* 24, 1–21.
4. Neumar R.W., Nolan J.P., Adrie C., et al. (2008). Epidemiology, pathophysiology, treatment, and prognostication: A consensus statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council of Cardiovascular Surgery and Anesthesia; the Council of Cardiopulmonary, Perioperative, and Critical Care: the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 118, 2452–2483.
5. Trojanowsi J.Q., Kenyon L. (2008). The central nervous system. In Rubin R., Strayer D.E. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1171–1208). Philadelphia: Lippincott Williams & Wilkins.
6. Bernard S. (2009). Hypothermia after cardiac arrest: Expanding the therapeutic scope. *Critical Care Medicine* 37(Suppl), S227–S233.
7. Arundine M., Tymianski M. (2004). Molecular mechanisms of glutamate-dependent neurogeneration in ischemia and traumatic brain injury. *Cell and Molecular Life Science* 61, 657–668.
8. Kalia L.W., Kalia S.K., Salter M.W. (2008). NMDA receptors in clinical neurology: Excitatory times ahead. *Lancet Neurology* 7, 742–755.
9. Hickey J.V. (2008). *The clinical practice of neurological and neurosurgical nursing* (6th ed., pp. 270–307, 370–409, 496–520, 588–619, 646–664). Philadelphia: Lippincott-Raven.
10. Lang E.W., Chestnut R.M. (1995). Intracranial pressure and cerebral perfusion pressure in severe head injury. *New Horizons* 3, 400–409.
11. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 192, 761–767). Philadelphia: Elsevier Saunders.
12. Ropper A.H. (2006). Acute confusional states and coma. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 103–114). New York: McGraw-Hill.
13. Ghajar J. (2000). Traumatic brain injury. *Lancet* 356, 923–929.
14. Nolan S. (2005). Traumatic brain injury. *Critical Care Nursing Quarterly* 28(2), 188–194.
15. Ropper A.H. (2006). Concussion and other head injuries. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 225–232). New York: McGraw-Hill.
16. Chestnut R.M. (1995). Secondary brain insults after head injury: Clinical perspectives. *New Horizons* 3, 366–375.
17. Teasdale G.M. (1995). Head injury. *Journal of Neurology, Neurosurgery, and Psychiatry* 58, 526–539.
18. Ropper A.H., Gorson K.C. (2007). Concussion. *New England Journal of Medicine* 356, 166–172.
19. Plum F., Posner J.B. (1980). *The diagnosis of stupor and coma* (3rd ed.). Philadelphia: F.A. Davis.
20. Young G.B., Pigott S.E. (1999). Neurobiological basis of consciousness. *Archives of Neurology* 56, 153–157.
21. Stevens R.D., Bhardwaji A. (2006). Approach to the comatose patient. *Critical Care Medicine* 34, 31–41.
22. Ingersoll G.L., Leyden D.B. (1987). The Glasgow Coma Scale for patients with head injuries. *Critical Care Nursing* 7(5), 26–32.
23. Teasdale G.M. (2000). Revisiting the Glasgow Coma Scale and Coma Score. *Intensive Care Medicine* 26, 153–154.
24. Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (3rd ed., pp. 927–933). Philadelphia: Lippincott Williams & Wilkins.
25. Smith W.S., Johnston S.C., Easton J.D. (2006). Cerebrovascular disease. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 233–271). New York: McGraw-Hill.
26. American Stroke Association. (2009). *Heart disease and stroke statistics—2009 update*. Dallas: American Stroke Association.
27. Grysiewicz R.A., Thomas K., Pandey D.K. (2008). Epidemiology of ischemic and hemorrhagic stroke: Incidence, prevalence, mortality, and risk factors. *Neurologic Clinics* 26, 871–895.
28. Goldstein L.B., Chair. (2006). Primary prevention of stroke: A guideline from the American Heart Association/American Stroke Council; cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Therapy, and Metabolism Council; the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Stroke* 37, 1583–1633.
29. Blank-Reid C. (1996). How to have a stroke at an early age: The effects of crack, cocaine, and other illicit drugs. *Journal of Neuroscience Nursing* 28(1), 19–27.
30. Paciaroni M., Caso V., Agnelli G. (2009). The concept of ischemic penumbra in acute stroke and therapeutic opportunities. *European Neurology* 61, 321–330.
31. Easton J.D., Chair. (2009). Definition and evaluation of transient ischemic attack: A scientific statement from the American Heart Association/American Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke* 40, 2276–2293.
32. Johnston S.C. (2002). Transient ischemic attack. *New England Journal of Medicine* 347, 1687–1692.
33. Fewel M.E., Thompson M.G., Hoff J.T. (2003). Spontaneous intracerebral hemorrhage: A review. *Neurosurgical Focus* 15, 1–17.
34. Broderick J., Chair. (2007). Guidelines for management of spontaneous intracerebral hemorrhage in adults: A guideline from the American Heart Association/American Stroke Association, High Blood Pressure Research Council, and Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 38, 2001–2023.
35. Adams H.P. Jr., del Zorro G., Alberts M.J., et al. (2007). Guidelines for early management of adults with ischemic stroke. *Stroke* 38, 1655–1711.
36. Caulfield A.F., Wijman C.A.C. (2008). Management of acute ischemic stroke. *Neurologic Clinics* 26, 345–371.
37. van der Worp H.B., van Gijn J. (2007). Acute ischemic stroke. *New England Journal of Medicine* 357(6), 572–579.
38. Alberts M.J., Hademenos G., Latchaw R.E., et al. (2000). Recommendations for the establishment of primary stroke centers. *Journal of the American Medical Association* 283, 3102–3109.
39. Gorelick A.R., Gorelick P., Sloan E.P. (2008). Emergency department evaluation and management of stroke: Acute assessment, stroke teams and care pathways. *Neurologic Clinics* 26, 923–942.
40. Alberts W.A., Chair. (1998). Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 114, 683S–698S.
41. del Zoppo G.J., Saver J.L., Jauch E.C., et al. (2009). Expansion of the time window for acute ischemic stroke: A science advisory from the American Heart Association/American Stroke Association. *Stroke* 40, 2945–2948.
42. Duncan P.W., Zorowitz R., Bates B., et al. (2005). Management of adult stroke rehabilitation care: A clinical practice guideline. *Stroke* 36, e100–e143.

43. Suarez J.I., Tarr R.W., Selman W.R. (2006). Aneurysmal subarachnoid hemorrhage. *New England Journal of Medicine* 354, 387–396.
44. Bederson J.B., Chair. (2009). Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 40, 994–1025.
45. Fleetwood I.G., Steinberg G.K. (2002). Arteriovenous malformations. *Lancet* 359, 893.
46. Friedlander R.M. (2007). Arteriovenous malformations of the brain. *New England Journal of Medicine* 356, 2704–2712.
47. Ogilvy C.S., Chair, Special Writing Group of the Stroke Council, American Heart Association. (2001). Recommendations for management of intracranial arteriovenous malformations. *Stroke* 32, 1458–1471.
48. Roos K.L., Tyler K.L. (2006). Meningitis, encephalitis, brain abscesses, and empyema. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 423–455). New York: McGraw-Hill.
49. van de Beek D., de Gans J., Tunkel A.R., et al. (2006). Community-acquired bacterial meningitis in adults. *New England Journal of Medicine* 354, 44–53.
50. Tunkel A.R., Hartman B.J., Kaplan B.A., et al. (2004). Practice guidelines for management of bacterial meningitis. *Clinical Infectious Diseases* 39, 1267–1284.
51. Rosenstein N.E., Perkins B.A., Stephens D.S., et al. (2001). Meningococcal disease. *New England Journal of Medicine* 344(18), 1378–1388.
52. Centers for Disease Control and Prevention. (2007). Revised recommendations of the Advisory Committee on Immunization Practices to vaccinate all persons aged 11–18 years with meningococcal conjugate vaccine. *MMWR Morbidity and Mortality Weekly Report* 56(31), 794–795.
53. Chandana S.R., Movva S., Arora M., et al. (2008). Primary brain tumors in adults. *American Family Physician* 77(10), 423–1430.
54. DeAngelis L.M. (2001). Brain tumors. *New England Journal of Medicine* 344, 114–123.
55. Kuttesch J.F. Jr., Ater J.L. (2006). Brain tumors in childhood. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2128–2140). Philadelphia: Saunders Elsevier.
56. Sagar S.M., Isrel M.A. (2006). Primary and metastatic tumors of the nervous system. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 365–380). New York: McGraw-Hill.
57. Behin A., Hoang-Xuan K., Carpenter A.F., et al. (2003). Primary brain tumors in adults. *Lancet* 361, 323–331.
58. Wen P.Y., Kesari S. (2008). Malignant gliomas in adults. *New England Journal of Medicine* 359(5), 492–507.
59. Packer R.J., MacDonald T. (2008). Central nervous system tumors. *Pediatric Clinics of North America* 55, 121–145.
60. Nguyen T.D., DeAngelis L.M. (2007). Brain metastases. *Neurology Clinics* 25, 1173–1192.
61. Lowenstein D.H. (2006). Seizures and epilepsy. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 187–212). New York: McGraw-Hill.
62. Johnston M.V. (2006). Seizures in childhood. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2457–2470). Philadelphia: Saunders Elsevier.
63. Chang B.S., Lowenstein D.H. (2003). Mechanisms of disease: Epilepsy. *New England Journal of Medicine* 349, 1257–1266.
64. French J.A., Pedley T.A. (2008). Initial management of epilepsy. *New England Journal of Medicine* 359(2), 166–176.
65. Schachter S.C. (2009). Seizure disorders. *Medical Clinics of North America* 93, 343–351.
66. Commission on Classification and Terminology of the International League Against Epilepsy. (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 22, 489–501.
67. Commission on Classification and Terminology of the International League Against Epilepsy. (1989). Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 30, 389–399.
68. Porter R.J., Meldrum M.B. (2007). Antiseizure drugs. In Katzung B.G. (Ed.), *Basic and clinical pharmacology* (10th ed., pp. 375–394). New York: McGraw-Hill Medical.
69. Nguyen D.K., Spencer S.S. (2003). Recent advances in the treatment of epilepsy. *Archives of Neurology* 60, 929–935.
70. Nardkarini S., LaJoie J., Devinsky O. (2005). Current treatments in epilepsy. *Neurology* 64(Suppl 3), S2–S11.
71. Millsap P. (2007). Neurologic system. In Linton A.D., Lach H.W. (Ed.), *Matteson & McConnel's gerontological nursing: Concepts and practice* (3rd ed., pp. 406–441). St. Louis: Elsevier Saunders.
72. Josshi S., Morley J.E. (2006). Cognitive impairment. *Medical Clinics of North America* 90, 769–787.
73. American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.
74. Bird T.D., Miller B.L. (2006). Alzheimer's disease and other dementias. In Hauser S.L. (Ed.), *Harrison's neurology in clinical practice* (pp. 273–293). New York: McGraw-Hill.
75. Cummings J.L. (2004). Alzheimer disease. *New England Journal of Medicine* 351, 56–67.
76. Alzheimer's Association. (2009). *Diagnostic overview.* [Online] Available: http://www.alz.org/professionals_and_researchers_diagnostic_overview.asp. Accessed November 28, 2009.
77. Román G. (2002). Vascular dementia revisited: Diagnosis, pathogenesis, treatment, and prevention. *Medical Clinics of North America* 86, 477–499.
78. Kertez A., Munoz D.G. (2002). Frontotemporal dementia. *Medical Clinics of North America* 86, 501–518.
79. Josephs K.A. (2007). Frontotemporal lobar degeneration. *Neurologic Clinics* 25, 683–696.
80. Eggenberger E. (2007). Prion disease. *Neurologic Clinics* 25, 833–842.
81. Greenamyre J.T. (2007). Huntington's disease—Making connections. *New England Journal of Medicine* 365(5), 518–520.
82. Huntington's Disease Society of America. (2007). *A juvenile HD handbook*. [Online] Available: http://www.hdsa.org/images/content/1/1/11702.pdf. Accessed December 8, 2009.
83. Cardosa F. (2009). Huntington disease and other choreas. *Neurologic Clinics* 27, 719–736.

The Eye and Disorders of Vision
The Conjunctiva
Conjunctivitis
The Cornea
Corneal Trauma
Keratitis
The Lens
Disorders of Refraction
Disorders of Accommodation
Cataracts
The Retina
Retinal Blood Supply
Retinopathies
Retinal Detachment
Macular Degeneration
Intraocular Pressure and Glaucoma
Open-Angle Glaucoma
Angle-Closure Glaucoma
Congenital and Infantile Glaucoma
Neural Pathways and Cortical Centers
Disorders of the Optic Pathways
Visual Field Defects
The Extraocular Eye Muscles and Disorders of Eye Movement
Strabismus
Amblyopia
The Ear and Disorders of Auditory Function
The External Ear
Disorders of the External Ear
The Middle Ear and Eustachian Tube
Disorders of the Eustachian Tube
Otitis Media
Otosclerosis
The Inner Ear and Central Auditory Pathways
Tinnitus
Disorders of the Central Auditory Pathways
Hearing Loss
Conductive Hearing Loss
Sensorineural Hearing Loss
Diagnosis and Treatment of Hearing Loss
Hearing Loss in Infants and Children
Hearing Loss in the Elderly
The Vestibular System and Disorders of Equilibrium
The Vestibular System
Nystagmus
Vertigo
Disorders of Peripheral Vestibular Function
Benign Paroxysmal Positional Vertigo
Acute Vestibular Neuronitis
Ménière Disease
Disorders of Central Vestibular Function
Diagnosis and Treatment
Tests of Vestibular Function
Treatment of Vestibular Disorders

Chapter 38

Disorders of Special Sensory Function: Vision, Hearing, and Vestibular Function

The special senses allow us to view and hear what is going on around us, to maintain our balance, and to communicate effectively with others. This chapter focuses on the eye and disorders of vision; the ear and disorders of hearing; and the vestibular system and disorders of equilibrium and balance.

The Eye and Disorders of Vision

There are 161 million people worldwide who are visually impaired—37 million are blind and 124 million have partial vision loss that cannot be corrected.[1] Among the people who are blind worldwide, 4% are under 14 years of age and 58% are 60 years of age or older. Disorders of vision can result from a number of conditions including those that affect the conjunctiva (conjunctivitis), lens (cataract), vitreous humor and retina (retinopathy and macular degeneration), intraocular pressure (glaucoma), optic pathways and visual cortex, and extraocular muscles and eye movement (Fig. 38-1).

The optic globe, commonly called the *eyeball,* is a remarkably mobile, nearly spherical structure contained in a pyramid-shaped cavity of the skull called the *orbit*. Only the anterior one fifth of the orbit is occupied by the eyeball; the remainder is filled with muscles, nerves, the lacrimal gland, and adipose tissue that support the normal position of the optic globe (Fig. 38-2). The eyeball is composed of three layers: an outer layer, which includes the white, opaque sclera and the transparent cornea; a middle vascular layer called the *uvea*, which includes the choroid and the stroma of the ciliary body and iris; and an inner neural layer, which includes an outer pigment epithelium and inner neural retina.[2] Exposed surfaces of the eyes are protected by the

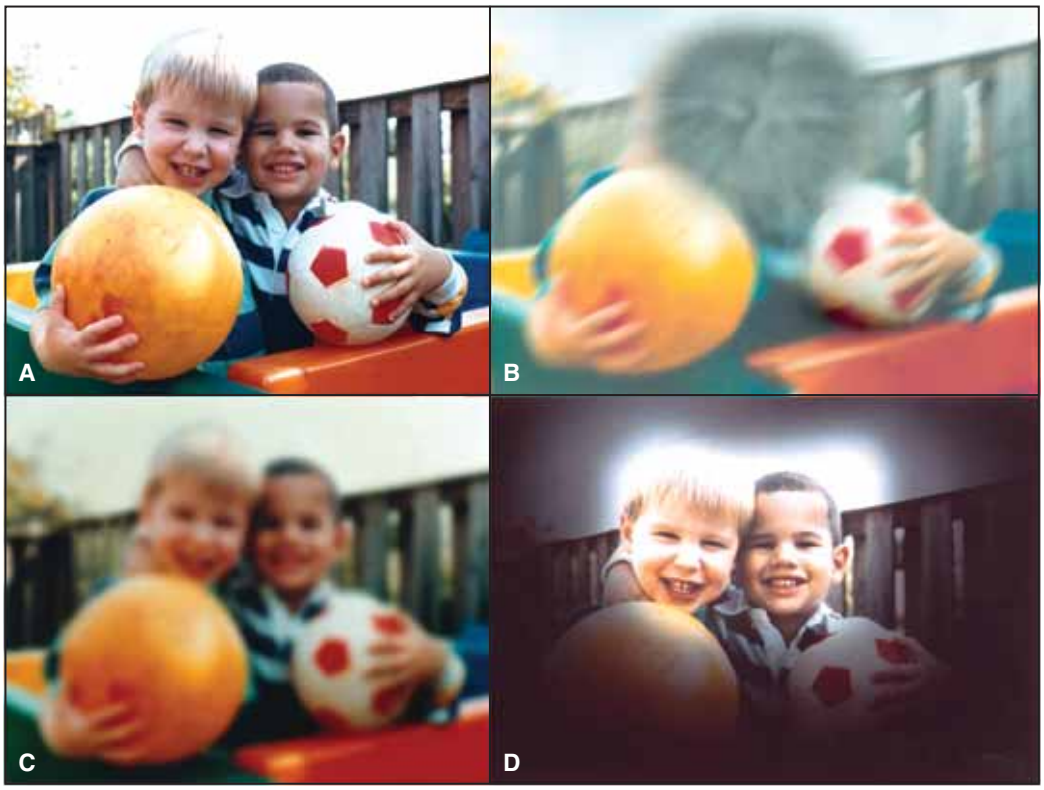


FIGURE 38-1. A scene as it might be viewed by a person with **(A)** normal vision, **(B)** age-related macular degeneration, **(C)** cataract, and **(D)** glaucoma. (From National Eye Institute, National Institutes of Health.)

eyelids, which are mucous membrane–lined skin flaps that provide a means for shutting out most light. Tears bathe the anterior surface of the eye; they prevent friction between it and the lid, maintain hydration of the cornea, and protect the eye from infection and irritation by foreign objects.

The Conjunctiva

The conjunctiva is a thin layer of mucous membrane that lines the anterior surface of both eyelids as the *palpebral conjunctiva* and folds back over the anterior surface of the optic globe as the *ocular* or *bulbar conjunctiva* (see

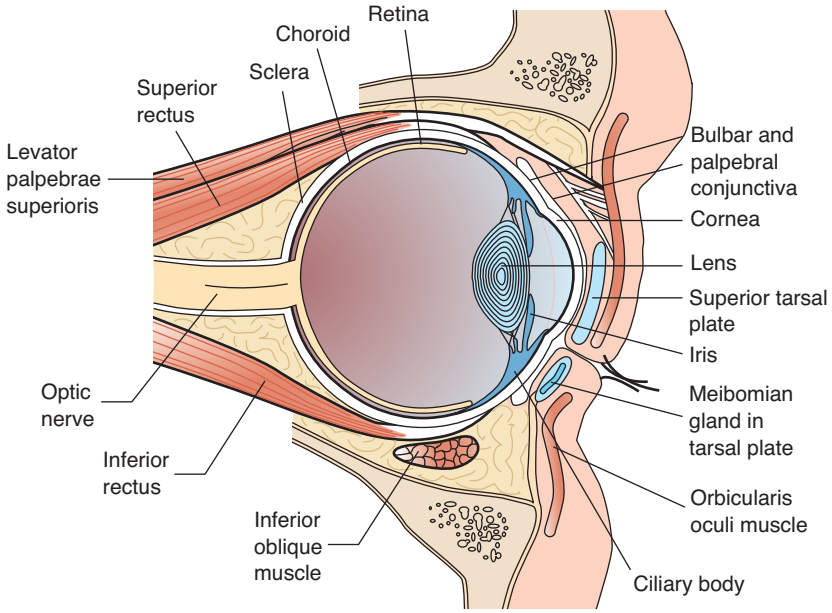


FIGURE 38-2. The eye and its appendages: lateral view.

Fig. 38-2). The ocular conjunctiva covers only the sclera or white portion of the optic globe, not the cornea. When both eyes are closed, the conjunctiva lines the closed conjunctival sac. Although the conjunctiva protects the eye by preventing foreign objects from entering beyond the conjunctival sac, its main function is the production of a lubricating mucus that bathes the eye and keeps it moist.

Conjunctivitis

Conjunctivitis, or inflammation of the conjunctiva (i.e., red or pink eye), is one of the most common forms of eye disease.[3–5] It may result from bacterial or viral infection, allergens, chemical agents, physical irritants, or radiant energy.

Depending on the cause, conjunctivitis can vary in severity from a mild hyperemia (redness) with tearing to severe conjunctivitis with purulent drainage. The conjunctiva is extremely sensitive to irritation and inflammation. Symptoms of conjunctivitis are a foreign body sensation, a scratching or burning sensation, itching, and photophobia. Severe pain suggests corneal rather than conjunctival disease. A discharge, or exudate, may be present. It is usually watery when the conjunctivitis is caused by allergy, a foreign body, or viral infection, and mucopurulent in the presence of bacterial or fungal infection. Infectious forms of conjunctivitis are usually bilateral and may involve other family members and associates. Unilateral disease suggests sources of irritation such as foreign bodies or chemical irritation.

The diagnosis of conjunctivitis is based on history, physical examination, and microscopic and culture studies to identify the cause. Because a red eye may be the sign of several eye conditions, it is important to differentiate between redness caused by conjunctivitis and that caused by more serious eye disorders, such as corneal lesions and acute glaucoma. In contrast to corneal lesions and acute glaucoma, conjunctivitis produces injection (i.e., enlargement and redness) of the peripheral conjunctival blood vessels rather than those radiating around the corneal limbus (Fig. 38-3). Conjunctivitis also produces only mild discomfort compared with the moderate to severe discomfort associated with corneal lesions or the severe and deep pain associated with acute glaucoma.

FIGURE 38-3. Gonococcal conjunctivitis of right eye. Note injection of the peripheral conjunctival blood vessels. (From Centers for Disease Control and Prevention, Public Health Images Library.)

Bacterial Conjunctivitis. Bacterial conjunctivitis may present as an acute, a hyperacute, or a chronic infection. Common agents of *acute bacterial conjunctivitis* are *Streptococcus pneumoniae, Staphylococcus aureus,* and *Haemophilus influenzae*. The infection usually is characterized by large amounts of yellow-green drainage. The eyelids are sticky, and there may be excoriation of the lid margins. Treatment may include local application of antimicrobial agents. The disorder usually is self-limited, lasting approximately 10 to 14 days if untreated and 1 to 3 days if properly treated.[3]

Hyperacute conjunctivitis is a severe, sight-threatening ocular infection. The most common causes of hyperacute purulent conjunctivitis are *Neisseria gonorrhoeae* and *Neisseria meningitidis,* with *N. gonorrhoeae* being the most common.[3–5] The symptoms, which typically are progressive, include conjunctival redness and chemosis (edema); lid swelling and tenderness; and swollen preauricular lymph nodes. Treatment includes systemic antimicrobial drugs supplemented with ocular antimicrobials. Because of the increasing prevalence of penicillin-resistant *N. gonorrhoeae,* the choice of an antimicrobial agent should be determined by current information regarding antimicrobial sensitivity. Gonococcal ocular infections that are left untreated may cause corneal ulceration with ultimate perforation, and sometimes permanent loss of vision.

Chronic bacterial conjunctivitis most commonly occurs in people with obstruction of the nasolacrimal duct or chronic infection of the lacrimal sac (dacryocystitis) and is usually unilateral.[3] The symptoms of chronic bacterial conjunctivitis vary and can include itching, burning, foreign body sensation, and morning eyelash crusting. There may be flaky debris and erythema along the lid margins, as well as eyelash loss and eye redness. Treatment includes good eyelid hygiene and application of topical antimicrobial drugs.

Chlamydial Conjunctivitis. Chlamydial conjunctivitis is usually a benign suppurative conjunctivitis transmitted by the type of *Chlamydia trachomatis* (serotypes D through K) that causes venereal infections[3–6] (see Chapter 41). It is commonly spread by contact with genital secretions and occurs in newborns of mothers with *C. trachomatis* infections of the birth canal. It also can be contracted through swimming in unchlorinated pools. The incubation period varies from 5 to 12 days, and the disease may last for several months if untreated. The infection is usually treated with appropriate oral antimicrobial agents.

A more serious form of infection is caused by a different strain of *C. trachomatis* (serotypes A, B, and C).[6] This form of chlamydial infection affects the conjunctiva and causes ulceration and scarring of the cornea. It is the leading cause of preventable blindness in the world. Although the agent is widespread, it is seen mostly in developing countries, particularly those of Africa, Asia, and the Middle East.[6] It is transmitted by direct human contact, contaminated objects (fomites), and flies.

Viral Conjunctivitis. One of the most common causes of viral conjunctivitis is adenoviruses types 3 and 7 and other serotypes.[3] The infection, which causes generalized conjunctival hyperemia, copious tearing, and minimal exudate, is usually accompanied by pharyngitis, fever, and malaise. Children are affected more often than adults. Swimming pools contaminated because of inadequate chlorination are common sources of infection.

Viral epidemic keratoconjunctivitis is caused by adenoviruses types 8 and 19.[3] It presents with marked discomfort and is highly contagious, with rapid spread from person to person. The disease usually lasts for at least 2 weeks and may be complicated by visual symptoms due to epithelial and subepithelial corneal involvement. There is no specific treatment for this type of viral conjunctivitis. Preventive measures include hygienic measures and avoiding shared use of eyedroppers, eye makeup, goggles, and towels. Persons who use contact lenses should avoid them and wear their prescription glasses until the infection clears.

Allergic Conjunctivitis. Allergic conjunctivitis encompasses a spectrum of conjunctival conditions usually characterized by itching. The most common of these is seasonal allergic rhinoconjunctivitis, or hay fever. Seasonal allergic conjunctivitis is an immunoglobulin E (IgE)-mediated hypersensitivity reaction precipitated by small air-borne allergens such as pollens.[7] It typically causes bilateral tearing, itching, and redness of the eyes.

The treatment of seasonal allergic rhinoconjunctivitis includes allergen avoidance and the use of cold compresses and eye washes with tear substitute. Allergic conjunctivitis also has been successfully treated with topical mast cell stabilizers, histamine type 1 (H_1) receptor antagonists, and topical nonsteroidal anti-inflammatory drugs.[7] Systemic antihistamines may be useful in prolonged allergic conjunctivitis. In severe cases, a short course of topical corticosteroids may be required to afford symptomatic relief.

The Cornea

The cornea functions as a protective membrane and transparent window through which light passes as it moves toward the retina (Fig. 38-4). The cornea also contributes to the refraction (i.e., bending) of light rays and focusing of vision. Three layers of tissue form the cornea: an extremely thin outer epithelial layer, which is continuous with the bulbar conjunctiva; a middle layer called the *substantia propria* or *stroma;* and an inner endothelial layer, which lies next to the aqueous humor of the anterior chamber.[2,8] The substantia propria is composed of regularly arranged collagen bundles embedded in a mucopolysaccharide matrix. This organization of the collagen fibers, which makes the substantia propria transparent, is necessary for light transmission. Hydration within a limited range is necessary to maintain the spacing of the collagen fibers and transparency. The three layers of the cornea are separated by two important basement membranes: Bowman and Descemet membranes. *Bowman membrane,* which lies between the corneal epithelium and the underlying corneal stroma, acts as a barrier to infection. It does not regenerate; if damaged, an opaque scar forms that can impair vision. *Descemet membrane,* which lies between the corneal endothelium and stroma, has a feltlike appearance and consists of interwoven fibers and pores. Unlike Bowman membrane, it regenerates readily after injury.

The cornea is avascular and obtains its nutrient and oxygen supply by diffusion from the blood vessels of the adjacent sclera, the aqueous humor at its deep surface, and tears that bathe its surface. The corneal epithelium is heavily innervated by sensory neurons. Epithelial damage causes discomfort that ranges from a foreign body sensation and burning of the eyes to severe, incapacitating pain. Reflex lacrimation is common.

Corneal Trauma

The integrity of the epithelium and the endothelium is necessary to maintain hydration of the cornea within a limited range.[8] The integrity of the endothelium is more important than the epithelium, and damage to the endothelium is far more serious than damage to the epithelium. Destruction of endothelial cells causes edema of the cornea and loss of transparency. With corneal edema, the cornea appears dull, uneven, and hazy; visual acuity decreases, and iridescent vision (i.e., rainbows around lights) occurs.

Trauma that causes abrasions of the cornea can be extremely painful, but if minor, the abrasions usually heal in a few days. The epithelial layer can regenerate, and small defects heal without scarring. If the stroma is damaged, healing occurs more slowly, and the danger of infection is increased. Injuries to the Bowman membrane and the stromal layer heal with scar formation that impairs the transmission of light.

Keratitis

Keratitis refers to inflammation of the cornea. It can be caused by infections, misuse of contact lenses, hypersensitivity reactions, ischemia, trauma, defects in tearing, and interruption in sensory innervation, as occurs with local anesthesia. Scar tissue formation due to keratitis is the leading cause of blindness and impaired vision throughout the world. Most of this vision loss is preventable if the condition is diagnosed early and appropriate treatment is begun.

Keratitis can be divided into two types: nonulcerative and ulcerative.[8] In *nonulcerative* keratitis, all the layers of the epithelium may be affected, but the epithelium remains intact. There are a number of causes of epithelial keratitis, including epidemic keratoconjunctivitis caused by adenoviruses 8 and 19. *Ulcerative keratitis* is an inflammatory process in which parts of the epithelium, stroma, or both are destroyed. Causes of ulcerative keratitis include infectious agents such as those causing conjunctivitis (e.g., *S. aureus, S. pneumoniae, C. trachomatis*), exposure trauma, and use of extended-wear contact lenses (i.e., *Pseudomonas* and *Acanthamoeba* keratitis). Bacterial keratitis is aggressive and demands immediate care. Mooren ulcer is a chronic,

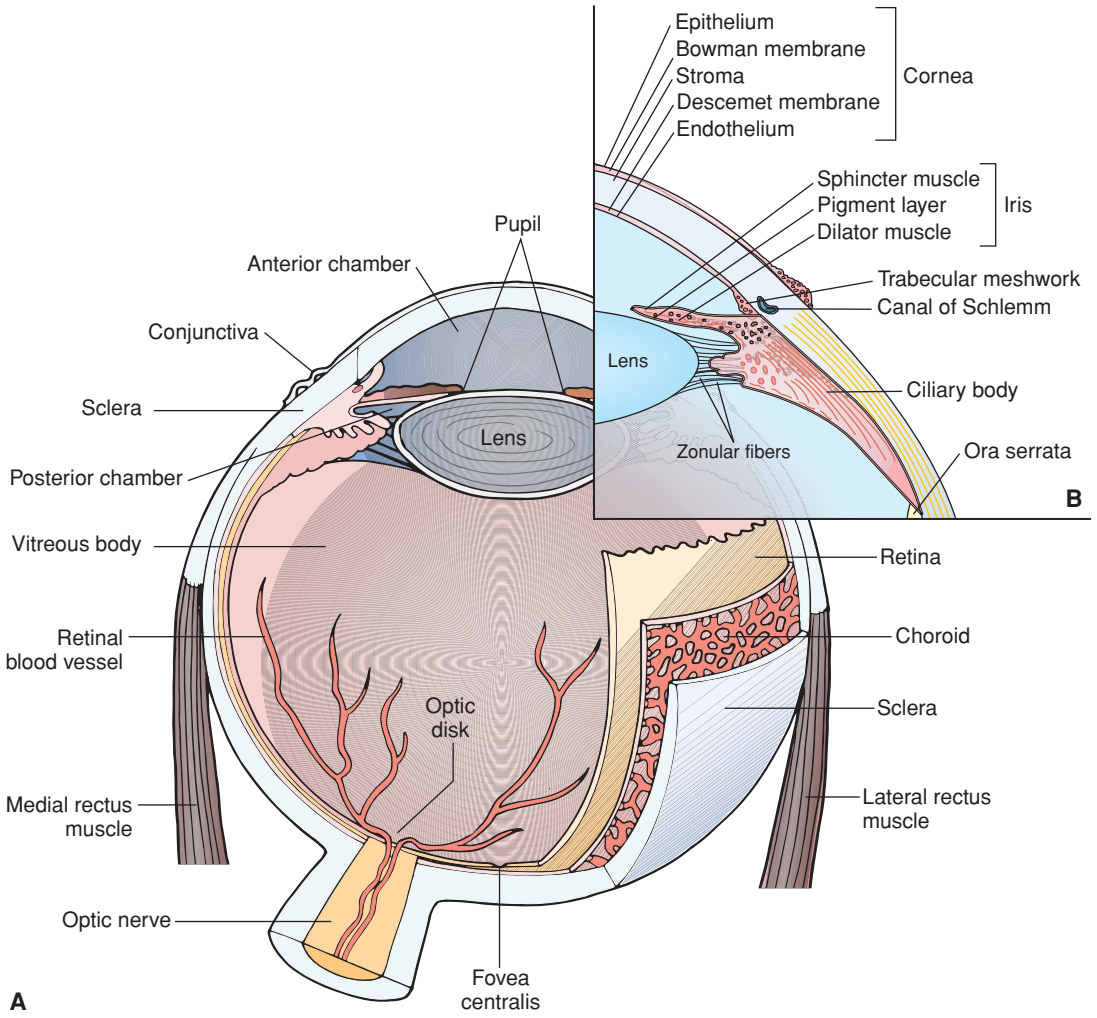


FIGURE 38-4. **(A)** Transverse section of the eyeball. **(B)** Enlargement of the anterior and posterior chambers of the eye, showing the layers of the cornea, the structures of the iris, the aqueous drainage system (trabecular meshwork, canal of Schlemm), and the ciliary process and ciliary muscle.

painful, indolent ulcer that occurs in the absence of infection. It is usually seen in older persons and may affect both eyes. Although the cause is unknown, an autoimmune origin is suspected.

Herpes Simplex Keratitis. Herpes simplex virus (HSV) keratitis is an important cause of ocular morbidity.[8–10] With the exception of neonatal infections, which are usually due to HSV type 2 (genital herpes) acquired during the birth process, most cases of herpes keratitis are caused by HSV type 1 (labial [lip] herpes). The disease can occur as either a primary or recurrent infection. Primary epithelial infections are the optical counterpart of labial herpes with similar immunologic and pathologic features as well as a similar time course (see Chapter 46). During childhood, mild primary HSV infection may go unnoticed. The ability of the virus to colonize the trigeminal ganglion can lead to recurrence precipitated by immunodeficiency or stress-related factors that reactivate the virus. Involvement is usually unilateral.

The first manifestations of recurrent herpes keratitis are irritation, photophobia, and tearing. Some reduction in vision may occur when the lesion affects the central part of the cornea. Because corneal anesthesia occurs early in the disease, the symptoms may be minimal, and the person may delay seeking medical care. A history of fever blisters or other herpetic infection is often noted, but corneal lesions may be the only sign of recurrent herpes infection. Typically, the corneal lesion involves the epithelium and has a typical dendritic (branching) pattern. These epithelial lesions heal without scarring. Herpetic lesions that involve the stromal layer of the cornea produce increasingly severe corneal opacities.

The treatment of HSV keratitis includes the use of topical antiviral agents to promote healing.[8] Oral antiviral agents (e.g., acyclovir) may be helpful for treatment of severe keratitis and as prophylaxis against recurrence, particularly in persons with compromised immune function. Although corticosteroids may control the damaging inflammatory responses, they do so at the expense of

facilitating viral replication. With a few exceptions, their use is contraindicated.[10]

Varicella Zoster Ophthalmicus. Herpes zoster or *shingles* is a relatively common infection due to the herpesvirus that causes varicella (chickenpox).[8,11] Herpes ophthalmicus, which represents 10% to 25% of all cases of herpes zoster, occurs when reactivation of the latent virus occurs in the ganglia of the ophthalmic division of the trigeminal nerve.[11] Immunocompromised persons, particularly those with human immunodeficiency virus (HIV) infection, are at higher risk for developing herpes zoster ophthalmicus than those with a normally functioning immune system.

Herpes zoster ophthalmicus usually presents with malaise, fever, headache, and burning and itching of the periorbital area. These symptoms commonly precede the ocular eruption by a day or two. The rash, which is initially vesicular, becomes pustular and then crusting (see Chapter 46). Involvement of the tip of the nose and lid margins indicates a high likelihood of ocular involvement. Ocular signs include conjunctivitis, keratitis, and anterior uveitis, often with elevated intraocular pressure. Persons with corneal disease present with varying degrees of decreased vision, pain, and sensitivity to light.

Treatment includes the use of oral and intravenous antiviral drugs. Initiation of treatment within the first 72 hours after the appearance of the rash reduces the incidence of ocular complications but not the postherpetic neuralgia[8] (see Chapter 35). Many cases of herpes zoster and herpes zoster ophthalmicus can now be prevented with the herpes zoster vaccine.

Acanthamoeba Keratitis. *Acanthamoeba* is a free-living cyst-forming protozoan that thrives in polluted water containing bacteria and organic material.[8,10,12] *Acanthamoeba* keratitis is a rare but serious and sight-threatening complication associated with wearing of soft contact lens, particularly if they are worn overnight or beyond doctor-recommended periods or when poor disinfection techniques are used. It also may occur in non–contact lens wearers after exposure to contaminated water or soil. *Acanthamoeba* keratitis is characterized by pain that is disproportionate to the clinical manifestations, redness of the eye, and photophobia. The disorder may be misdiagnosed as herpes keratitis. Diagnosis is confirmed by scrapings and culture with specially prepared medium. In the early stages of infection, epithelial débridement may be beneficial. Treatment includes intensive use of topical antimicrobials. However, the organism may encyst within the corneal stroma, making treatment more difficult. Keratoplasty may be necessary in advanced disease to arrest the progression of the infection.

The Lens

The lens is a remarkable structure that functions to bring images into focus on the retina. The lens is an avascular, transparent, biconvex body, the posterior side of which is more convex than the anterior side.[2,13] It is positioned just posterior to the iris and is held in place by suspensory ligaments known as the *zonules*, which are composed of numerous fibrils that arise from the ciliary body (see Fig. 38-4). The pull of the zonular fibers and lens capsule is normally under tension, causing the lens to have a flattened shape for distant vision. Relaxation of the fibers allows the lens to relax to a more spherical shape for near vision.

The lens has three principal components: the lens capsule, a subcapsular epithelium, and lens fibers. The lens capsule is a transparent elastic structure that envelops the entire lens. The subcapsular epithelium is a cuboidal layer of cells that is present on the anterior surface of the lens. The lens fibers, which constitute the bulk of the lens, are derived from the subcapsular epithelium. The subcapsular epithelium continues to produce new lens fibers throughout life, with the older fibers being compressed into the central nucleus of the lens. This causes the lens to gradually become larger and less elastic with age. There are no pain fibers, blood vessels, or nerves in the lens.

Refraction refers to deflection or bending of light as it passes from one transparent medium to another of different density. When parallel light rays pass through the center of a lens, their direction is not changed; however, the divergent rays passing peripherally through a lens are bent (Fig. 38-5). The refractive power of a lens is usually described as the distance (in meters) from its surface to the point at which the rays come into focus on the retina (i.e., focal length). Usually, this is reported as the reciprocal of this distance (i.e., diopters).[14] For example, a lens that brings an object into focus at 0.5 m has a refractive power of 2 diopters (1.0/0.5 = 2.0). The closer the object, the more divergent the peripheral rays, and the stronger and more precise the focusing system must be.

In the eye, the major refraction of light begins at the convex corneal surface. Further refraction occurs as light moves from the posterior corneal surface to the aqueous humor, from the aqueous humor to the anterior lens surface, from the anterior lens surface to the posterior lens surface, and from the posterior lens surface to the vitreous humor.

Disorders of Refraction

A perfectly shaped optic globe and cornea result in optimal visual acuity, producing a sharp image in focus at all points on the retinal surface in the posterior part, or fundus, of the eye. Unfortunately, individual differences in formation and growth of the eyeball and cornea frequently result in inappropriate focal image formation. If the anterior-posterior dimension of the eyeball is too short, the image is theoretically focused posterior to (behind) the retina. This is called *hyperopia,* or *farsightedness* (see Fig. 38-5B). In such cases, the accommodative changes of the lens can bring distant images into focus, but near images become blurred. Hyperopia is corrected by appropriate convex-surface lenses. If the anterior-posterior dimension of the eyeball is too long, the focus point for an infinitely distant target is anterior to the

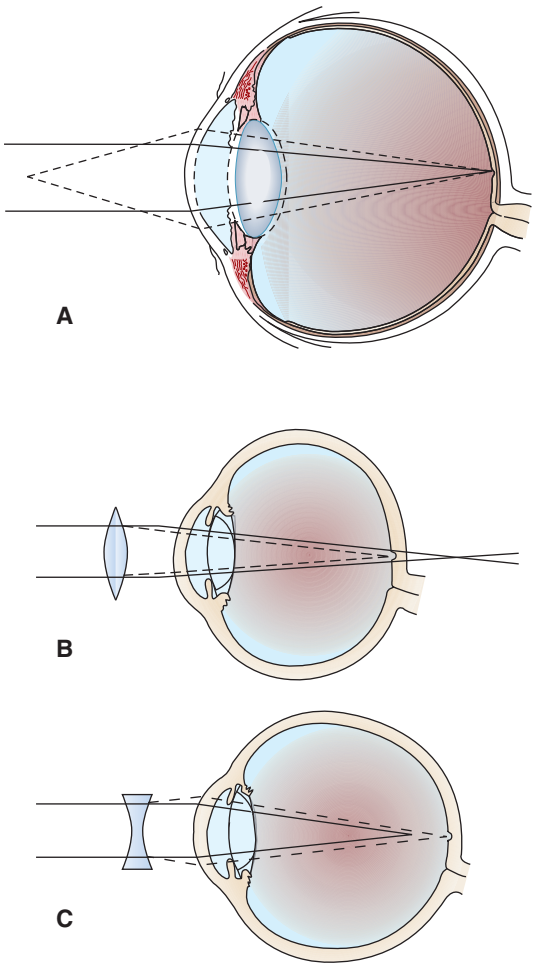


FIGURE 38-5. **(A)** Accommodation. The *solid lines* represent rays of light from a distant object, and the *dotted lines* represent rays from a near object. The lens is flatter for the former and more convex for the latter. In each case, the rays of light are brought to a focus on the retina. **(B)** Hyperopia corrected by a biconvex lens, shown by the *dotted lines.* **(C)** Myopia corrected by a biconcave lens, shown by the *dotted lines.*

retina. This condition is called *myopia*, or *nearsightedness* (see Fig. 38-5C). Persons with myopia can see close objects without problems because accommodative changes in their lens bring near objects into focus, but distant objects are blurred. Myopia can be corrected with an appropriate concave-surface lens. Refractive corneal surgeries such as laser in situ keratomileusis (LASIK), photorefractive keratectomy, and radial keratotomy can be performed to correct the corneal curvature to create accurate optical focus.[15]

Refractive defects of the corneal surface do not permit the formation of a sharp image. Nonuniform curvature of the refractive medium with regard to the horizontal and vertical planes is called *astigmatism*. Astigmatism is usually the result of an asymmetric bowing of the cornea, but it can result from defects in the cornea, lens, or retina. Lens correction is available to sharpen focus in case of such refractive error.

Disorders of Accommodation

Because the retina is at a fixed distance from the lens, adjustability in the refractive power of the lens is needed so that a clear image is maintained as gaze is shifted from a far to a near object. The process by which the refractive power of the lens is increased and the diverging light rays are bent more sharply is called *accommodation*. Accommodation is neurologically associated with convergence of the eyes and pupillary constriction, and results from thickening of the lens through contraction of the ciliary muscle. Contraction of muscle fibers in the ciliary body is controlled mainly by the parasympathetic fibers of the oculomotor cranial nerve (CN III). Paralysis of the ciliary muscle, with loss of accommodation, is called *cycloplegia*. Pharmacologic cycloplegia, using a topical anticholinergic agent, is sometimes necessary to aid refractive examination of the eye, especially in small children who are unable to hold a steady degree of accommodation during the examination.

The term *presbyopia* refers to a decrease in accommodation that occurs because of aging. The normal proliferative process in the lens nucleus that occurs throughout life causes the lens to thicken and its capsule to become less elastic with aging, so that the range of focus or accommodation is diminished. The person with emmetropic eyes (no refractive error) will begin to notice inability to read small print or discriminate close objects. This is usually worse in dim light and usually worse on arising in the morning or when the person is fatigued.

Cataracts

A cataract is a lens opacity that interferes with the transmission of light to the retina. Cataracts are the most common cause of blindness in the world, accounting for nearly 48% of all blindness.[16] Aging is the most common cause of cataracts, with an estimated prevalence of 50% in persons between the ages of 65 and 74 years, and increasing to 75% in those over 75 years of age.[1]

As the lens ages, new layers of fibers are added and the lens nucleus is compressed and becomes harder (nuclear sclerosis cataract), with associated yellowing of the lens. Nuclear sclerosis progresses slowly, over years. The earliest symptom may be improved near vision without glasses. This occurs from an increase in the focus power of the leans, creating a myopic shift in vision.[13,17] With further progression there can be loss of color discrimination and also loss of vision, typically greater for distance than for near vision.

Although aging is the most important cause of cataracts, other factors such as heredity, environmental and metabolic influences, drugs, and trauma may be involved.[13,16] Long-term exposure to sunlight (ultraviolet radiation) and heavy smoking have been associated with increased risk of cataract formation. Metabolically induced cataracts are caused by disorders of carbohydrate metabolism (diabetes) or inborn errors of metabolism. Occasionally, cataracts occur as a developmental defect (i.e., congenital cataracts) or secondary to trauma. Corticosteroids drugs have been implicated as causative agents in cataract formation. Both systemic and inhaled

corticosteroids have been cited as risk factors.[18] Traumatic cataracts are usually caused by foreign body injury to the lens or blunt trauma to the eye. Foreign body injury that interrupts the lens capsule allows aqueous and vitreous humor to enter the lens and initiate cataract formation. Other causes of traumatic cataract are overexposure to heat (e.g., glassblower cataract) or to ionizing radiation. The radiation dose necessary to cause a cataract varies with the amount and type of energy; younger lenses are most vulnerable.

Clinical Manifestations. The manifestations of cataract depend on the extent of opacity and whether the defect is bilateral or unilateral. With the exception of traumatic or congenital cataract, most cataracts are bilateral. Age-related cataracts, which are the most common type, are characterized by increasingly blurred vision and visual distortion[13,17] (see Fig. 38-1C). Dilation of the pupil in dim light improves vision. With nuclear cataracts (those involving the lens nucleus), the refractive power of the anterior segment often increases to produce an acquired myopia, the so-called second sight. Central lens opacities may divide the visual axis and cause an optical defect in which two or more blurred images are seen. Posterior subcapsular cataracts are located in the posterior cortical layer and usually involve the central visual axis. In addition to decreased visual acuity, cataracts tend to cause light entering the eye to be scattered, thereby producing glare or the abnormal presence of light in the visual field.

Diagnosis and Treatment. Diagnosis of cataract is based on ophthalmoscopic examination and the degree of visual impairment on the Snellen vision test. On ophthalmoscopic examination, cataracts may appear as a gross opacity filling the pupillary aperture or as an opacity silhouetted against the red background of the fundus. Other tests that determine the potential ability to see well after surgery, such as electrophysiologic testing in which the response to visual stimuli is measured electronically, may be done.

There is no effective medical treatment for cataract. Strong bifocal lenses, magnification, appropriate lighting, and visual aids may be used as the cataract progresses. Surgery is the only treatment for correcting cataract-related vision loss.[13,17] Surgery usually involves lens extraction and intraocular lens implantation. It is commonly performed on an outpatient basis with the use of local anesthesia. The use of extracapsular surgery, which leaves the posterior capsule of the lens intact, has significantly improved the outcomes of cataract surgery. The cataract lens is usually removed using phacoemulsification techniques. Phacoemulsification involves ultrasonic fragmentation of the lens into fine pieces, which then are aspirated from the eye.

One of the greatest advances in cataract surgery has been the development of reliable intraocular implants. Monofocal intraocular lenses that correct for distance vision are available, and eyeglasses may be needed for near vision, although this has been addressed by the recent introduction of multifocal intraocular lenses.

Congenital Cataract. A congenital cataract is one that is present at birth.[13] About 30% of congenital cataracts are hereditary; another 30% are secondary to metabolic or infectious diseases or associated with a variety of syndromes; and the remaining 30% are due to undetermined causes. Cataracts and other developmental defects of the ocular apparatus depend on the total dose of the agent and the embryonic stage at the time of exposure. During the last trimester of fetal life, genetically or environmentally influenced malformation of the superficial lens fibers can occur. Congenital lens opacities may occur in children of diabetic mothers. Most congenital cataracts are not progressive and are not dense enough to cause significant visual impairment. However, cataracts that are dense, central, and larger than 2 mm in diameter require surgical management on an urgent basis. If not treated within the first 2 months of life, deprivation amblyopia will result (to be discussed).[13]

The Retina

The function of the retina is to receive visual images, partially analyze them, and transmit this modified information to the brain.[14] Disorders of the retina and its function include disorders of the retinal vessels such as retinopathies that cause hemorrhage and the development of opacities; separation of the pigment and sensory layers of the retina (i.e., retinal detachment); and macular degeneration. Because the retina has no pain fibers, most diseases of the retina are painless and do not cause redness of the eye.

The retina is composed of two layers: an outer pigment (melanin-containing) epithelium and an inner neural layer[19] (Fig. 38-6A). The outer surface of the pigmented layer, a single-cell–thick lining called the *Bruch membrane,* abuts the choroid and extends anteriorly to cover the ciliary body and the posterior side of the iris. Its pigmented epithelial cells, like those of the choroid, absorb light and prevent it from scattering. The pigment layer stores large quantities of vitamin A, which is an important precursor of the photosensitive visual pigments.

The inner light-sensitive neural retina covers the inner aspect of the eyeball.[14,19] The neural retina is composed of three layers of neurons: a posterior layer of photoreceptors (rods and cones), a middle layer of bipolar cells, and an inner layer of ganglion cells that communicate with the photoreceptors (see Fig. 38-6B). Light must pass through the transparent inner layers of the sensory retina before it reaches the photoreceptors. Impulses produced in response to light spread from the photoreceptors to the bipolar neurons and other interneurons and then to the ganglionic cells, where action potentials are generated. The interneurons, which have cell bodies in the bipolar layer, play an important role in modulating retinal function. The optic disk, where the optic nerve exits the eye, is the weak part of the eye because it is not reinforced by the sclera. It also forms the blind spot because it is not backed by photoreceptors, and light focused on it cannot be seen. People do not notice the blind spot because of a sophisticated visual

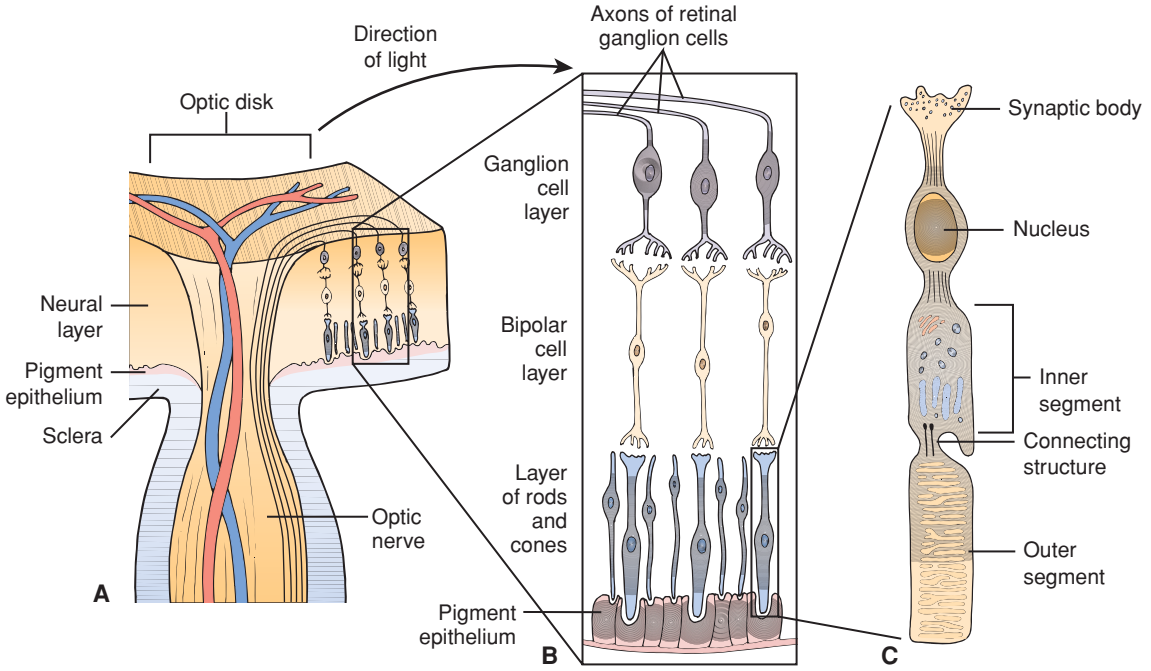


FIGURE 38-6. Organization of the retina. **(A)** Organization of the retina showing the inner neural layer and the outer pigment epithelium. **(B)** The three layers of the neural retina: a posterior layer of photoreceptors (rods and cones), a middle layer of bipolar cells, and an inner layer of ganglionic cells. **(C)** Photoreceptor structure: a retinal rod, showing its component parts and distribution of organelles.

function called "filling in," which the brain uses to deal with missing visual input.

Two types of photoreceptors are present in the retina: rods capable of black–white discrimination and cones capable of color discrimination.[14,19,20] Rod-based vision is particularly sensitive to detecting light, especially moving light stimuli, at the expense of clear pattern discrimination. Rod vision is particularly adapted for night and low-level illumination. Dark adaptation is the process by which rod sensitivity increases to the optimum level. This requires approximately 4 hours in total or near-total darkness and is referred to as *scotopic vision* (night vision). Cone receptors, which are selectively sensitive to different wavelengths of light, provide the basis for color vision. Three types of cones, or cone-color systems, respond to the blue, green, and red portions of the visible electromagnetic spectrum. Cones do not have the dark adaptation capability of rods. Consequently, the dark-adapted eye is a rod receptor eye with only black–gray–white experience (scotopic or night vision). The light-adapted eye (*photopic vision*) adds the capacity for color discrimination.

Both rods and cones contain chemicals that change configuration on exposure to light and, in the process, generate currents that lead to the action potentials generated by the ganglionic cells. The light-sensitive chemical in rods is called *rhodopsin*, and the light-sensitive chemicals in cones are called *cone* or *color pigments*. Both types of photoreceptors are thin, elongated, mitochondria-filled cells with a single, highly modified cilium (Fig. 38-6C). The cilium has a short base, or inner segment, and a highly modified outer segment. The plasma membrane of the outer segment is tightly folded to form membranous disks (rods) or conical shapes (cones) containing visual pigment. These disks are continuously synthesized at the base of the outer segment and shed at the distal end. Discarded membranes are phagocytized by the retinal pigment cells. If this phagocytosis is disrupted, as in a condition called *retinitis pigmentosa*, the sensory retina degenerates.

An area approximately 1.5 mm in diameter near the center of the retina, called the *macula lutea* (i.e., "yellow spot"), is especially adapted for acute and detailed vision.[16,19] This area is composed entirely of cones. In the central portion of the macula, the *fovea centralis* (foveola), the blood vessels and innermost layers are displaced to one side instead of resting on top of the cones. This allows light to pass unimpeded to the cones without passing through several layers of the retina. Many of these cones are connected one to one with ganglionic cells, an arrangement that favors high acuity.

Retinal Blood Supply

The blood supply for the retina is derived from two sources: the choriocapillaris (i.e., the capillary layer of the choroid) and branches of the central retinal artery (Fig. 38-7A). Oxygen and other nutritional substances

needed by the retina and its component parts (pigment cells, rods, and cones) are supplied by diffusion from blood vessels in the choroid. Because the choriocapillaris provides the only blood supply for the fovea centralis, detachment of this part of the sensory retina from the pigment epithelium causes irreparable visual loss. The central artery, which is a branch of the ophthalmic artery, supplies the rest of the retina. Retinal veins follow a distribution parallel to the arterial branches and carry venous blood to the central vein of the retina, which exits the back of the eye through the optic disk.

Funduscopic examination of the eye with an ophthalmoscope provides the means for examining the retinal blood vessels and other aspects of the retina (Fig. 38-7B). Because the retina is an embryonic outgrowth of the brain and the blood vessels are to a considerable extent representative of brain blood vessels, the ophthalmoscopic

Disorders of the Retinal Blood Supply

- The blood supply for the retina is derived from the central retinal artery, which supplies blood flow for the entire inside of the retina, and from vessels in the choroid, which supply the rods and cones.
- The retinopathies, which are disorders of the retinal vessels, interrupt blood flow to the visual receptors, leading to visual impairment.
- Retinal detachment separates the visual receptors from the choroid, which provides their major blood supply.

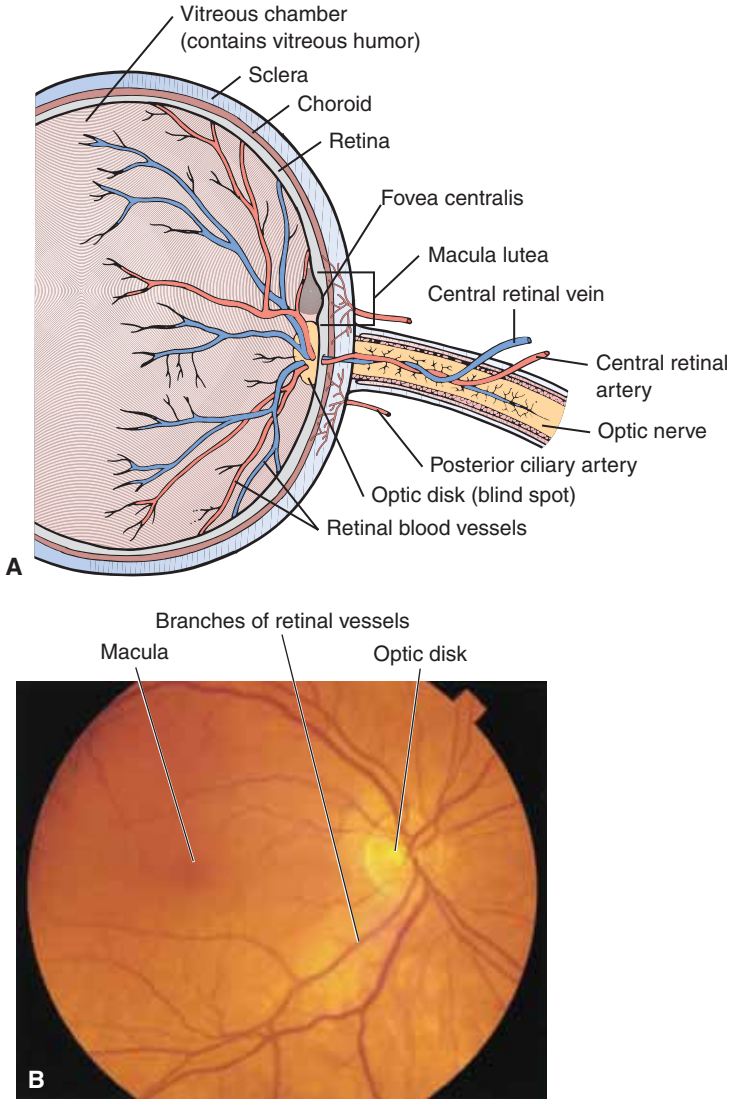


FIGURE 38-7. **(A)** Retinal circulation showing the distribution of the central retinal and posterior ciliary arteries and the central retinal vein. **(B)** Funduscopic image of the normal retina (From Moore K.L., Daley A.F. [2006]. Clinically oriented anatomy [5th ed., p. 967]. Philadelphia: Lippincott Williams & Wilkins.)

examination of the fundus of the eye permits the study and diagnosis of metabolic and vascular diseases of the brain as well as pathologic processes that are specific to the retina.

Papilledema. The central retinal artery enters the eye through the optic papilla in the center of the optic nerve. An accompanying vein exits the eye along the same path. The entrance and exit of the central retinal artery and vein through the tough scleral tissue at the optic papilla can be compromised by any condition causing persistent increased intracranial pressure. The most common of these conditions are cerebral tumors, subdural hematomas, hydrocephalus, and malignant hypertension.

Usually, the thin-walled, low-pressure veins are the first to collapse, with the consequent backup and slowing of arterial blood flow. Under these conditions, capillary permeability increases and leakage of fluid results in edema of the optic papilla, called *papilledema*.[6,21] The interior surface of the papilla is normally cup shaped and can be evaluated for cupping with an ophthalmoscope. With papilledema, sometimes called *choked disk*, the optic cup is distorted by protrusion into the interior of the eye (Fig. 38-8). Because this sign does not occur until the intracranial pressure is significantly elevated, compression damage to fibers of the optic nerve may have begun. As a warning sign, papilledema occurs quite late. Unresolved papilledema results in the destruction of the optic nerve axons and blindness.

Retinopathies

Retinopathies, which involve the small blood vessels of the retina, are characterized by changes in vessel structure and the development of microaneurysms, neovascularization, hemorrhage, and retinal opacities.[22] *Microaneurysms* are outpouchings of the retinal vasculature. On ophthalmoscopic examination, they appear as minute, unchanging red dots associated with blood vessels. Microaneurysms tend to leak plasma, resulting in localized edema that gives the retina a hazy appearance. They may also bleed, but areas of hemorrhage and edema tend to clear spontaneously. However, they reduce visual acuity if they encroach on the macula and cause degeneration before they are absorbed. *Neovascularization* involves the formation of new blood vessels. They can develop from the choriocapillaris, extending between the pigment layer and the sensory layer, or from the retinal veins, extending between the sensory retina and the vitreous cavity and sometimes into the vitreous. These new blood vessels are fragile, leak protein, and are likely to bleed. Although the cause of neovascularization is uncertain, research links the process with a vascular endothelial growth factor (VEGF) produced by the lining of blood vessels.[23,24] Hypoxia is a key regulator of VEGF-induced retinal neovascularization. It is likely that other growth factors and signaling systems are also involved.

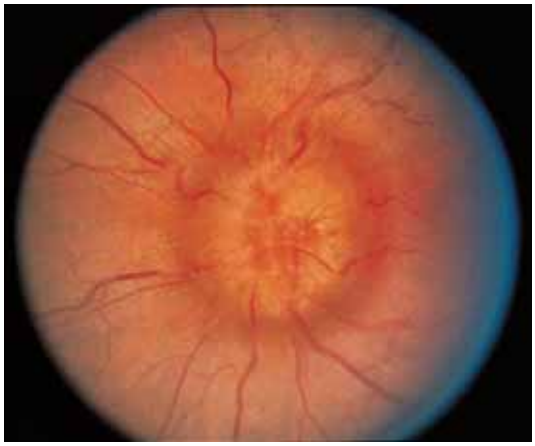


FIGURE 38-8. Chronic papilledema. The optic nerve head is congested and protrudes anteriorly toward the interior of the eye. It has blurred margins, and vessels within it are poorly seen. (From Klintworth G.K. [2008]. The eye. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1262]. Philadelphia: Lippincott Williams & Wilkins.)

Opacities represent loss of retinal transparency due to hemorrhages, exudates, cotton-wool spots, edema, and tissue proliferation. *Exudates* are opacities resulting from inflammatory processes. The development of exudates often results in the destruction of the underlying retinal pigment and choroid layer. *Cotton-wool patches* are retinal opacities with hazy, irregular outlines. They occur in the nerve fiber layer and contain cell organelles. Cotton-wool patches are associated with retinal trauma, severe anemia, papilledema, and diabetic retinopathy.

Diabetic Retinopathy. Diabetic retinopathy is one of the leading causes of blindness in the Western world, particularly among individuals of working age.[6,20,22] Chronic hyperglycemia, hypertension, hypercholesteremia, and smoking are all risk factors for the development and progression of the disorder. People with type 1 (insulin-dependent) diabetes do not develop retinopathy for at least 3 to 5 years after the onset of the disease, whereas those with type 2 diabetes may have retinopathy at the time of diagnosis and it may be a presenting symptom.[20]

Diabetic retinopathy can be divided into two types: nonproliferative (i.e., background) and proliferative retinopathy.[6,20,22,25] *Background* or *nonproliferative* retinopathy is confined to the retina. It involves engorgement of the retinal veins, thickening of the capillary endothelial basement membrane, and development of capillary microaneurysms (Fig. 38-9A, B). Small intraretinal hemorrhages may develop and microinfarcts may cause cotton-wool spots and leakage of exudates. A sensation of glare (because of the scattering of light) is a common complaint. The most common cause of decreased vision in persons with background retinopathy is macular edema. The edema is caused primarily by the breakdown of the blood-retina barrier at the level of the capillary endothelium, allowing leakage of fluid and plasma constituents into the surrounding retina. Diabetic macular edema is more common in persons with type 2 diabetes and requires treatment once it becomes clinically significant.

Proliferative diabetic retinopathy represents a more severe retinal change than background retinopathy

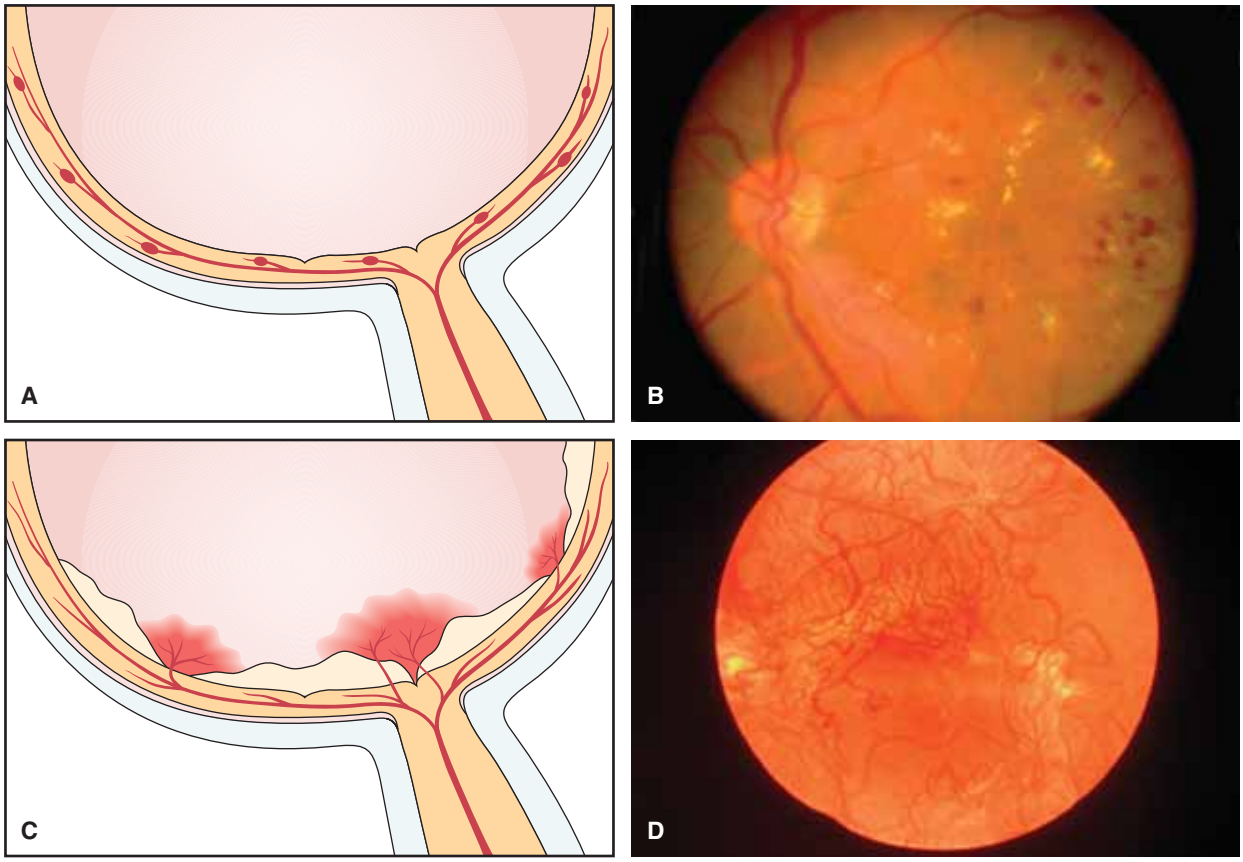


FIGURE 38-9. **(A)** Nonproliferative (background) retinopathy showing microaneurysms. **(B)** Ocular fundus of a patient with background diabetic retinopathy. Several yellowish "hard" exudates (which are rich in lipids) and several relatively small retinal hemorrhages are present. **(C)** Proliferative retinopathy. **(D)** Ocular fundus in a patient with proliferative retinopathy. A vascular frond (branching pattern of preretinal neovascularization) has extended anterior to the retina. (B and D from Klintworth G.K. [2008]. The eye. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1257]. Philadelphia: Lippincott Williams & Wilkins.)

(Fig. 38-9C, D). It is characterized by formation of new, fragile blood vessels (i.e., neovascularization) at the optic disk and elsewhere in the retina. These vessels grow in front of the retina along the posterior surface of the vitreous or into the vitreous. They threaten vision in two ways. First, because they are abnormal, they often bleed easily, leaking blood into the vitreous cavity and decreasing visual acuity. Second, the blood vessels attach firmly to the retinal surface and posterior surface of the vitreous, such that normal movement of the vitreous may exert a pull on the retina, causing retinal detachment and progressive blindness. While diabetic macular edema is more prevalent in type 2 diabetes, proliferative diabetic retinopathy is the most common sight-threatening lesion in type 1 diabetes.

Because early proliferative diabetic retinopathy is likely to be asymptomatic, it must be identified early, before bleeding occurs and obscures the view of the fundus or leads to fibrosis and retinal detachment. Current guidelines recommend that persons with diabetes have yearly eye examinations, although deviations from this guideline are appropriate in certain low-risk groups.[24] For persons with moderate to severe nonproliferative retinopathy, more frequent examinations are often necessary to determine when to initiate treatment. Persons with any levels of macular edema, severe nonproliferative diabetic retinopathy, or any proliferative retinopathy require the prompt care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. Women with preexisting diabetes who plan to become pregnant or become pregnant should have a comprehensive eye examination and be counseled about the risk for initiation or progression of diabetic retinopathy.

Preventing diabetic retinopathy from developing or progressing is considered the best approach to preserving vision. Growing evidence suggests that careful control of blood glucose levels in persons with diabetes mellitus may retard the onset and progression of retinopathy. There also is a need for intensive management of hypertension and hyperlipidemia, both of which have been shown to increase the risk of diabetic retinopathy in persons with diabetes.[24]

Photocoagulation using an argon laser provides the major direct treatment modality for diabetic retinopathy.[20] Treatment strategies include laser photocoagulation

applied directly to leaking microaneurysms and grid photocoagulation with a checkerboard pattern of laser burns applied to diffuse areas of leakage and thickening. Because laser photocoagulation destroys the proliferating vessels and the ischemic retina, it reduces the stimulus for further neovascularization. Intravitreal injections of anti-VEGF agents are also being used to reduce active neovascularization and vitreous hemorrhage.[20] Vitrectomy may be used for removing vitreous hemorrhage and severing vitreoretinal membranes that develop.

Hypertensive Retinopathy. As with other blood vessels in the body, the retinal vessels undergo changes in response to chronically elevated blood pressure. In the initial, vasoconstrictor stage, there is vasospasm and an increase in retinal arterial tone because of local autoregulatory mechanisms. On ophthalmoscopy, this stage is represented by a general narrowing of the retinal arterioles. Persistently elevated blood pressure results in the compensatory thickening of arteriolar walls, which effectively reduces capillary perfusion pressure.[26] With severe uncontrolled hypertension, there is disruption of the blood-retina barrier, necrosis of smooth muscle and endothelial cells, exudation of blood and lipids, and retinal ischemia. These changes are manifested in the retina by microaneurysms, intraretinal hemorrhages, hard exudates, and cotton-wool patches. Swelling of the optic disk may occur at this stage and usually indicates severely elevated blood pressure (malignant hypertension). Elderly persons often have more rigid vessels that are unable to respond to the same degree as those in younger individuals.

Retinal Detachment

Retinal detachment involves the separation of the neurosensory retina from the pigment epithelium (Fig. 38-10). It occurs when traction on the inner sensory layer or a tear in this layer allows fluid, usually vitreous, to accumulate between the two layers.[6,20,27] There are three types of retinal detachments: exudative, traction, and rhegmatogenous.

Exudative (or serous) *retinal detachment* results from the accumulation of serous or hemorrhagic fluid in the subretinal space due to severe hypertension, inflammation, or neoplastic effusions. It usually resolves with successful treatment of the underlying disease and without visual impairment. *Traction retinal deattachment* occurs with mechanical forces on the retina, usually mediated by fibrotic tissue, resulting from previous hemorrhage (e.g., from diabetic retinopathy), injury, infection, or inflammation. Intraocular surgery such as cataract extraction may produce traction on the peripheral retina that causes eventual detachment months or even years after surgery. Correction of traction retinal detachment requires disengaging scar tissue from the retinal surface, and vision outcomes are often poor.

Rhegmatogenous detachment (*rhegma* is the Greek word for "rent" or "hole") is the most common type of retinal detachment. The vitreous is a hydrated gel whose

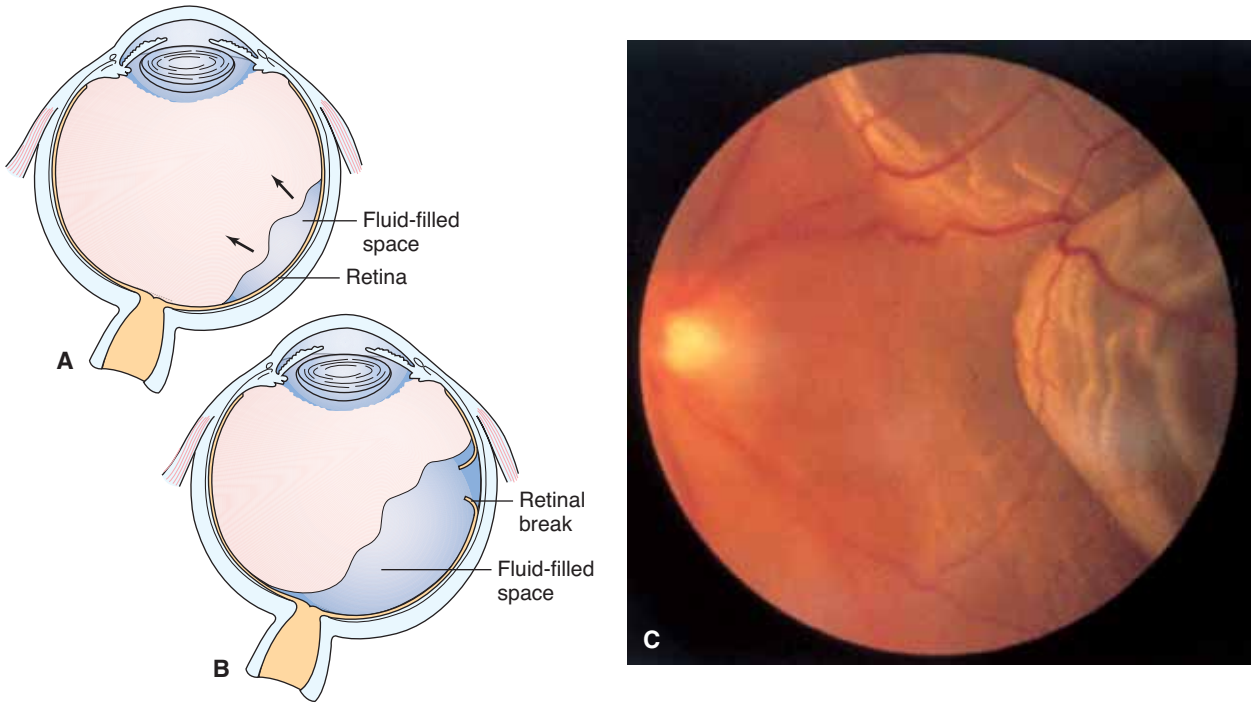


FIGURE 38-10. Pathogenesis of rhegmatogenous retinal detachment. **(A)** Changes in the vitreous structure cause it to shrink and separate from the retina, causing posterior vitreous detachment. **(B)** Sustained fluid collection and tractional forces cause the retina to tear (rhegmatogenous retinal detachment). **(C)** Ophthalmoscopic photograph of retinal detachment. (From Moore K.L., Dalley A.F. [2006]. *Clinically oriented anatomy* [5th ed., p. 967]. Philadelphia: Lippincott Williams & Wilkins.)

structure is maintained by a collagenous and mucopolysaccharide matrix. As persons age, this macromolecular network begins to liquefy and collapse. As this occurs, the vitreous shrinks and partly separates from the retinal surface, a condition known as *posterior vitreous detachment* (see Fig. 38-10A). Rhegmatogenous detachment occurs when the liquid vitreous enters the subretinal space through the retinal tear (see Fig. 38-10B). Detachment of the neural retina from the retinal pigment layer separates the receptors from their major blood supply, the choroid. If retinal detachment continues for some time, permanent destruction and blindness of that part of the retina occur. Risk factors that predispose to retinal detachment include advancing age and myopia. Approximately one in four persons between the ages of 61 and 70 years develops a posterior vitreous detachment. In about 10% to 15% of these persons, a retinal tear or hole forms as the vitreous pulls away from the retina, especially in the periphery where the retina is thinner.[27] Persons with high grades of myopia may have abnormalities in the peripheral retina that predispose to sudden detachment. In moderate to severe myopia or nearsightedness, the axial (anteroposterior) length of the eye is increased, and the retina tends to be thinner and more prone to formation of a hole or tear.[27] As a result, there is greater vitreoretinal traction, and posterior vitreous detachment may occur at a younger age than in persons without myopia. Other, less common risk factors include a family history of retinal detachment, a history of congenital eye disease (glaucoma, cataracts), and hereditary vitreopathies with abnormal vitreous gel.

The primary symptom of retinal detachment consists of painless changes in vision. Commonly, flashing lights or sparks, followed by small floaters or spots in the field of vision, occur as the vitreous pulls away from the posterior pole of the eye. As detachment progresses, the person perceives a shadow or dark curtain progressing across the visual field. Because the process begins in the periphery and spreads circumferentially and posteriorly, initial visual disturbances may involve only one quadrant of the visual field. Large peripheral detachments may occur without involvement of the macula, so that visual acuity remains unaffected.

Diagnosis is based on a history of visual disturbances (e.g., presence of floaters, luminous rays, or light flashes) and the ophthalmoscopic appearance of the retina. The direct (hand-held) ophthalmoscope is useful in detecting an altered red reflex sometimes associated with retinal detachment. However, because the view is narrow, a negative examination with direct ophthalmoscopy cannot exclude the diagnosis of retinal detachment. Ophthalmologists and optometrists use indirect examination techniques that greatly enhance visualization of the peripheral retina (Fig. 38-10C).[27]

Because there is a variable interval between a retinal break and retinal detachment, treatment methods focus on early detection and prevention of further vitreous detachment and retinal tear formation. Symptomatic retinal breaks are usually treated with laser or cryotherapy to seal the retinal tears so that the vitreous can no longer leak into the subretinal space. The treatment is more than 95% effective in preventing progression of a retinal tear and preventing retinal detachment.[27] The primary treatment of traction retinal detachment is vitreoretinal surgery and may involve vitrectomy, membrane removal, scleral buckling, or pneumatic retinopexy. Scleral buckling is the primary surgical procedure performed to reattach the retina.[20,27] With scleral buckling, a piece of silicone (i.e., the buckle) is sutured and infolded into the sclera, physically indenting the sclera so it contacts the separated pigment and retinal layers. A less invasive procedure, pneumatic retinopexy, involves the intraocular injection of an expandable gas instead of a piece of silicone to form the indentation.

Macular Degeneration

Macular degeneration is characterized by degenerative changes in the central portion of the retina (the macula) that result primarily in loss of central vision (see Fig. 38-1B). Age-related macular degeneration is the most common cause of reduced vision in the elderly population.[20,22,28–30] The causes of age-related macular degeneration are poorly understood. In addition to older age, identifiable risk factors include female sex, white race, and cigarette smoking. Increasing evidence suggests that genetic factors may play a role.

Age-related macular degeneration is commonly described as *nonneovascular* (nonexudative or "dry") or neovascular (exudative or "wet"). The nonneovascular form of age-related macular degeneration is characterized by various degrees of atrophy and degeneration of the outer retina, Bruch membrane, and choriocapillaris. It does not involve leakage of blood or serum; hence, it is called *dry age-related macular degeneration.* On ophthalmoscopic examination, there are visible changes in the retinal pigmentary epithelium and pale yellow spots, called *drusen,* that may occur individually or in groups throughout the macula (Fig. 38-11A). With time, the drusen enlarge, coalesce, and increase in number. The level of associated visual impairment is variable and may be minimal. Most people with macular drusen do not experience significant loss of central vision, and the atrophic changes may stabilize or progress slowly. However, people with the nonneovascular form of age-related macular degeneration need to be followed closely because the exudative stage may develop suddenly, at any time. Careful monitoring for *metamorphopsia*, or distorted vision of straight lines, can aid in the early detection of retinal damage.

The *neovascular* form of age-related macular degeneration is characterized by the formation of a choroidal neovascular membrane that separates the pigmented epithelium from the neuroretina. These new blood vessels have weaker walls than normal and are prone to leakage. The leakage of serous or hemorrhagic fluid into the subretinal space causes separation of the pigmented epithelium from the neurosensory retina. Over time, the subretinal hemorrhages organize to form scar tissue, causing death of the underlying retinal tissue and loss of all visual function in the corresponding macular area (see Fig. 38-11B). The early stages of subretinal neovascularization

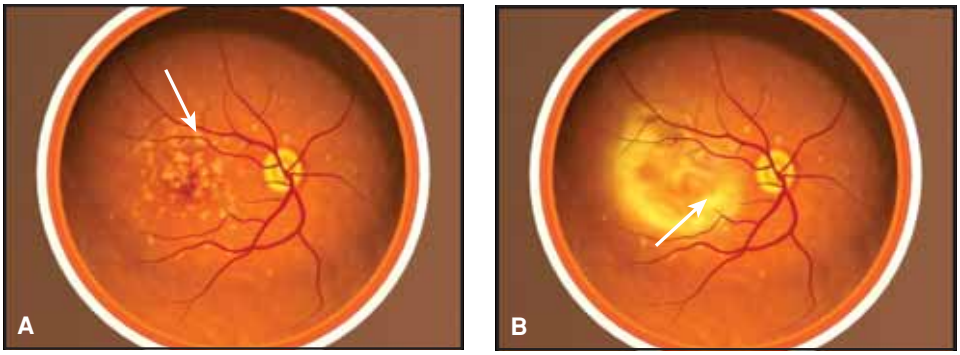


FIGURE 38-11. Funduscopic view of age-related macular degeneration (AMD). **(A)** Intermediate AMD with pale yellow spots or drusen scattered throughout the retina. **(B)** Advanced AMD with formation of scar tissue representing loss of death of the underlying retinal tissue and loss of all visual function in the corresponding macular area. (From the National Eye Institute, National Institutes of Health.)

may be difficult to detect with an ophthalmoscope. Therefore, there is a need to be alert for recent or sudden changes in central vision, blurred vision, or scotomata (visual field areas in which vision is depressed or absent) in persons with evidence of age-related macular degeneration. Although some subretinal neovascular membranes may regress spontaneously, the natural course of exudative macular degeneration is toward irreversible loss of central vision. Persons with late-stage disease often find it difficult to see at long distances (e.g., in driving), do close work (e.g., reading), see faces clearly, or distinguish colors. However, they may not be severely incapacitated because the peripheral retinal function usually remains intact. With the use of low-vision aids, many of them are able to continue many of their normal activities.

Effective therapies for the proliferative or exudative type macular degeneration include thermal laser photocoagulation, photodynamic therapy, intravitreal and periocular corticosteroid injections, and intravitreal injections of VEGF inhibitors.[20,28–30] The decision about specific therapies must take into account the likelihood of visual recovery, which is greater with smaller, more recent lesions, as well as the risks of the various therapies. Conventional retinal laser photocoagulation can achieve direct destruction of a choroidal neovascular membrane. Photodynamic laser therapy involves the intravenous injection of a dye that is subsequently activated by retinal laser irradiation to produce selective vascular damage. The corticosteroids have an angiostatic activity that appears to be independent of their hormone activity. The intravitreal injection of these agents bypasses the blood-ocular barrier, achieving therapeutic levels in the eye while avoiding systemic side effects.[20,29] Vascular endothelial growth factor plays a crucial role in the expansion of choroidal neovascular membranes. It induces both angiogenesis and increased permeability. The intravitreal injection of VEGF inhibitors has been shown to be beneficial for treating choroidal neovascularization.[20,29]

In addition to currently used and forthcoming treatments, there is interest in the so-called preventative category of treatments. Tobacco smoking is consistently identified as a preventable age-related macular degeneration risk; thus, its elimination should be one the first therapeutic recommendations. Preventative recommendations also include dietary supplementation with antioxidants and minerals such as vitamin E (α-tocopherol), vitamin C (ascorbic acid), zinc, and β-carotene for persons at risk for developing macular degeneration and for slowing the progression of age-related macular degeneration in persons with the disease.[30] However, more experimental data and randomized clinical trials are needed to support their therapeutic value, the most effective composition in terms of single- or multiple-supplement combinations, and dosing of the particular supplements.

Intraocular Pressure and Glaucoma

Glaucoma is a chronic, degenerative optic neuropathy characterized by optic disk cupping and visual field loss. It usually is associated with an elevation in intraocular pressure. Glaucoma is the second leading cause of blindness in the world.[1] About 100,000 Americans are blind from glaucoma, making it the leading cause of preventable blindness in the United States.[31] The condition often is asymptomatic, and a significant loss of peripheral vision may occur before medical attention is sought (see Fig. 38-1D).

The intraocular pressure largely reflects that of the aqueous humor that fills the anterior and posterior chambers of the eye. The aqueous humor is produced by the ciliary body and passes from the posterior chamber through the pupil into the anterior chamber[6,22,31] (Fig. 38-12A). Aqueous humor leaves through the iridocorneal angle between the anterior surface of the iris and the sclera. Here it filters through the trabecular meshwork and enters the canal of Schlemm, a thin-walled vein that extends circumferentially around the iris of the eye, for return to the venous circulation. Intraocular pressure results from a balance of several factors, including the rate of aqueous humor production by the ciliary body, the resistance to flow between the iris and ciliary body, and its rate of removal by the drainage system (trabecular meshwork and canal of Schlemm). Normally, the rate of aqueous humor secretion is equal to

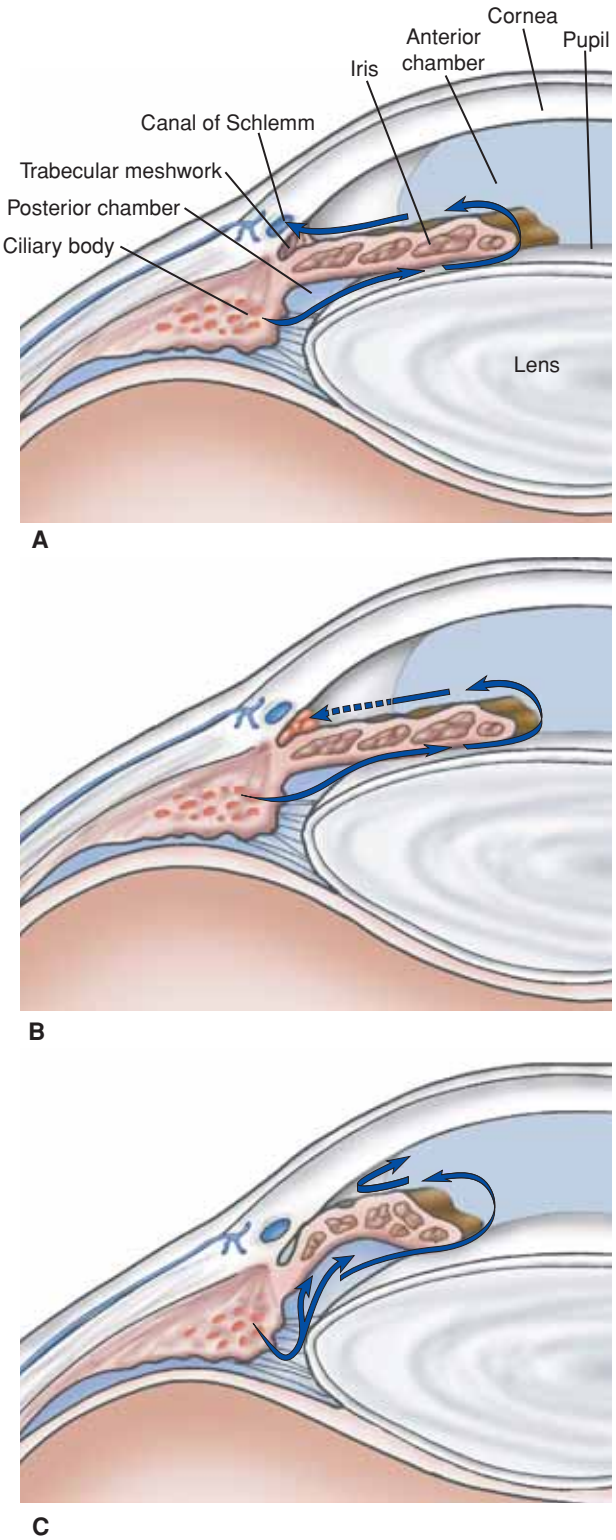


FIGURE 38-12. **(A)** Normally, aqueous humor, which is secreted in the posterior chamber, gains access to the anterior chamber by flowing through the pupil. In the angle of the anterior chamber, it passes through the canal of Schlemm into the venous system. **(B)** In open-angle glaucoma, the outflow of aqueous humor is obstructed at the trabecular meshwork. **(C)** In angle-closure glaucoma, the aqueous humor encounters resistance to flow through the pupil. Increased pressure in the posterior chamber produces a forward bowing of the peripheral iris, so that the iris blocks the trabecular meshwork.

the rate of outflow, and the intraocular pressure is maintained within a normal range of 10 to 21 mm Hg.[31]

Glaucoma usually results from congenital or acquired lesions of the anterior segment of the eye that mechanically obstruct aqueous outflow. Glaucoma is commonly classified as open-angle or angle-closure glaucoma depending on the appearance of the iridocorneal angle, and according to whether it is a primary or secondary disorder.[6,22,31] In *open-angle glaucoma*, impaired outflow results from dysfunction of the drainage system, and in *angle-closure glaucoma*, impaired outflow results from occlusion of the iridocorneal angle itself, impairing access to the drainage system.

In persons with glaucoma, permanent impairment of vision results from degenerative changes in the optic nerve. Damage to optic nerve axons can be recognized on ophthalmoscopic examination. The normal optic disk has a central depression called the *optic nerve cup*. In glaucoma, the neuroretinal rim of the optic nerve becomes progressively thinner, thereby enlarging the optic nerve cup, a phenomenon referred to as *optic nerve cupping*. Its cause is loss of retinal ganglionic cell axons, along with supporting glia and vasculature (see Fig. 38-7). The loss of nerve fibers causes a permanently decreased visual field. Because changes in the optic cup precede visual field loss, regular ophthalmoscopic examinations are important for detecting eye changes that occur with increased intraocular pressure. Advances in computer technology allow detection and quantification of visual changes due to glaucoma. These tests include white-on-white and blue-on-yellow visual field testing, testing of contrast sensitivity, and dark adaptation. Scanning laser technology and optical coherence tomography tests can often detect damage to retinal ganglion axons before visual field loss occurs.

Open-Angle Glaucoma

Open-angle glaucoma is the most common form of glaucoma.[32,33] The chief pathologic feature in primary open-angle glaucoma is an abnormality of the trabecular meshwork that controls the flow of aqueous humor into the canal of Schlemm (see Fig. 38-12B). It occurs without obstruction at the iridocorneal angle, hence the name *open-angle glaucoma*. Open-angle glaucoma is usually asymptomatic and chronic, causing progressive damage to the optic nerve and visual field loss unless it is appropriately treated. Elevated intraocular pressure is a primary factor in open-angle glaucoma, but it is not the only diagnostic factor. Some eyes tolerate elevated intraocular pressure without developing disk or visual field changes; others develop glaucomatous changes with consistently normal intraocular pressures (normal-tension glaucoma).

Open-angle glaucoma can develop as a primary or secondary condition. Primary glaucoma occurs in anatomically predisposed eyes without other pathology. Major risk factors include an age of 40 years and older, black race, a family history of glaucoma, and severe myopia.[32,33] Primary open-angle glaucoma includes both adult-onset disease (occurring after 40 years of age) and juvenile-onset disease (occurring before 40 years of age). Approximately 4% of persons with adult-onset and more than 10% of those with juvenile-onset primary-angle glaucoma have

mutations that have been mapped to a glaucoma-related gene on chromosome 1.[32] Secondary open-angle glaucoma occurs as a result of conditions such as inflammatory processes that affect the eye, formation of red cell fragments after trauma, lens changes, and intraocular tumors. Other risk factors include hypertension, type 2 diabetes, hyperthyroidism, and migraine headaches. In some persons, the use of moderate amounts of topical or inhaled corticosteroid medications can cause an increase in intraocular pressure. Sensitive persons also may sustain an increase in intraocular pressure with the use of systemic corticosteroid drugs.

Diagnostic methods include applanation tonometry (measurement of intraocular pressure), ophthalmoscopic visualization of the optic nerve, and central visual field testing. Measurement of intraocular pressures provides a means of assessing glaucoma risk. Because the condition is usually asymptomatic, persons at risk for open-angle glaucoma should have regular direct ophthalmoscopic examinations, on both eyes, concentrating on the optic disk. Optic disk changes frequently are noted before visual field defects become apparent.

The elevation in intraocular pressure in persons with open-angle glaucoma is usually treated pharmacologically or, in cases where pharmacologic treatment fails, by increasing aqueous outflow through a surgically created pathway. Drugs used in the long-term management of glaucoma fall into five classes: β-adrenergic antagonists, prostaglandin analogs, adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agonists.[31,34] Most glaucoma drugs are applied topically. However, systemic side effects may occur.

Topical β-adrenergic antagonists are usually the drugs of first choice for lowering intraocular pressure. The β-adrenergic antagonists are thought to lower intraocular pressure by decreasing aqueous humor production in the ciliary body. Prostaglandin analogs increase the outflow of aqueous humor through the iris root and ciliary body, either by decreasing the extracellular matrix or by relaxing the ciliary musculature. They are highly effective first-line or adjuvant agents.[31] Adrenergic agonists cause an early decrease in production of aqueous humor by constricting the vessels supplying the ciliary body. Carbonic anhydrase inhibitors reduce the secretion of aqueous humor by the ciliary epithelium. Until recently, these drugs had to be taken orally, and systemic side effects were common. A topical carbonic anhydrase inhibitor, which acts locally, is now available. Cholinergic drugs exert their effects by increasing the effects of acetylcholine. Acetylcholine is the postganglionic neurotransmitter for the parasympathetic nervous system; it increases aqueous outflow through contraction of the ciliary muscle and pupillary constriction (miosis). Pilocarpine, a parasympathomimetic miotic and once the mainstay of treatment, has largely been replaced by newer and more effective drugs.

When a reduction in intraocular pressure cannot be maintained through pharmacologic methods, laser or surgical trabeculoplasty may become necessary.[31] With laser trabeculoplasty, the microburns created by the laser treatment scar rather than penetrate the trabecular meshwork, a process thought to enlarge the outflow channels by increasing the tension exerted on the trabecular meshwork. Cryotherapy, diathermy, and high-frequency ultrasound may be used in some cases to destroy the ciliary epithelium and reduce aqueous humor production.

Angle-Closure Glaucoma

Angle-closure glaucoma results from occlusion of the anterior chamber angle by the iris (see Fig. 38-12C). It is most likely to develop in eyes with preexisting shallow anterior chambers. An acute attack is often precipitated by pupillary dilation, which causes the iris to thicken, thus blocking the circulation between the posterior and anterior chambers.[6,22,31] Angle-closure glaucoma usually occurs as the result of an inherited anatomic defect that causes a shallow anterior chamber. It is seen more commonly in people of Asian or Inuit (Eskimo) descent and in people with hypermetropic eyes. This defect is exaggerated by the anterior displacement of the peripheral iris that occurs in older persons because of the increase in lens thickness that occurs with aging.

Manifestations of acute angle-closure glaucoma are related to sudden, intermittent increases in intraocular pressure. These occur after prolonged periods in the dark, emotional upset, and other conditions that cause extensive and prolonged dilation of the pupil. Administration of pharmacologic agents such as atropine that cause pupillary dilation (mydriasis) also can precipitate an acute episode of increased intraocular pressure in persons with the potential for angle-closure glaucoma. Attacks of increased intraocular pressure are manifested by ocular pain and blurred or iridescent vision caused by corneal edema. The pupil may be enlarged and fixed. Symptoms are often spontaneously relieved by sleep and conditions that promote pupillary constriction. With repeated or prolonged attacks, the eye becomes reddened, and edema of the cornea may develop, giving the cornea a hazy appearance. A unilateral, often excruciating, headache is common. Nausea and vomiting may occur, causing the headache to be confused with migraine.

Acute angle-closure glaucoma is an ophthalmic emergency. Treatment is initially directed at reducing the intraocular pressure, usually with pharmacologic agents. Once the intraocular pressure is under control, a laser peripheral iridotomy may be performed to create a permanent opening between the anterior and posterior chambers, allowing the aqueous humor to bypass the pupillary block. The anatomic abnormalities responsible for angle-closure glaucoma are usually bilateral, and prophylactic surgery is often performed on the other eye.

Subacute angle-closure glaucoma is characterized by episodes of elevated intraocular pressure that are of short duration and subside spontaneously. There are recurrent short episodes of unilateral pain, conjunctival redness, and blurring of vision associated with halos around lights. Attacks often occur in the evenings and resolve overnight.[31] Examination between attacks may show only a narrow anterior chamber angle. Although the episodes of angle closure resolve spontaneously, there is accumulated damage to the anterior chamber angle. Subacute angle closure may also progress to acute angle closure.

Congenital and Infantile Glaucoma

Infantile (congenital) glaucoma is defined as glaucoma that begins within the first 3 years of life.[31,35,36] It can occur as a primary or secondary condition. Primary infantile glaucoma is caused by an isolated anomaly in development of the anterior chamber. In secondary glaucoma, other ocular defects or systemic disorders are present.

The clinical manifestations of infantile glaucoma include excessive lacrimation (tearing), conjunctival injection (redness of the eye), photophobia (sensitivity to light), and blepharospasm (eyelid squeezing). Affected infants tend to be fussy, have poor eating habits, and rub their eyes frequently. Because the sclera and cornea are more elastic in early childhood than later in life, chronic elevation of the intraocular pressure causes enlargement of the entire optic globe, including the cornea, and development of what is termed *buphthalmos* ("ox eye"). Diffuse edema of the cornea usually occurs, giving the eye a grayish-white appearance. Children with unilateral glaucoma generally present earlier because differences in the corneal size between the two eyes can be noticed. When both eyes are affected, the parents may not recognize the increased corneal size. Early surgical treatment is necessary to prevent blindness. Many children require several surgeries, as well as long-term medical therapy to maintain a lowering of their intraocular pressure.

Neural Pathways and Cortical Centers

Full visual function requires the normally developed brain-related functions of photoreception and the pupillary reflex. These functions depend on the integrity of all visual pathways, including retinal circuitry and the pathway from the optic nerve to the visual cortex and other visual regions of the brain and brain stem.[14,19,21]

Visual information is carried to the brain by axons of the retinal ganglion cells, which form the optic nerve. The two optic nerves meet and fuse in the optic chiasm, beyond which they are continued as the optic tracts (Fig. 38-13). In the optic chiasm, axons from the nasal retina of each eye cross to the opposite side and join with the axons of the temporal retina of the contralateral eye to form the optic tracts. One optic tract contains fibers from both eyes that transmit information from the same visual field.

Fibers of the optic tracts synapse in the lateral geniculate nucleus (LGN) of the thalamus. Axons from these neurons in the LGN form the optic radiations to the primary visual cortex in the occipital lobe. The pattern of information transmission established in the optic tract is retained in the optic radiations. For example, the axons from the right visual field, represented by the nasal retina of the right eye and the temporal retina of the left eye, are united at the chiasm. They continue through the left optic tract and left optic radiation to the left visual cortex, where visual experience is first perceived. The left primary visual cortex receives two representations of the right visual field. Physical separation of information from the left and right visual fields is maintained in the visual cortex. Interaction between these disparate representations occurs and provides the basis for the sensation of depth in the near visual field.

The primary visual cortex (area 17) surrounds the calcarine fissure, which lies in the occipital lobe. It is at this level that visual sensation is first experienced (Fig. 38-14). Immediately surrounding area 17 are the visual association cortices (areas 18 and 19) and several other association cortices. These association cortices, with their thalamic nuclei, must be functional for added meaningfulness of

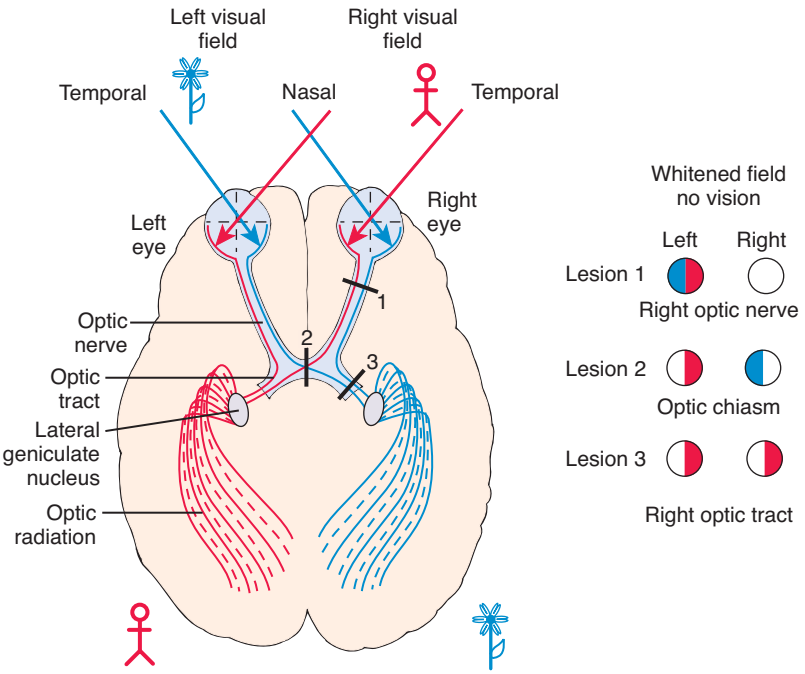


FIGURE 38-13. Diagram of optic pathways. The *red lines* indicate the right visual field and the *blue lines* the left visual field. Note the crossing of fibers from the medial half of each retina at the optic chiasm. Lesion 1 (right optic nerve) produces unilateral blindness. Lesion 2 (optic chiasm) may involve only those fibers that originate in the nasal half of each retina and cross to the opposite side in the optic chiasm; visual loss involves the temporal half of each field (bitemporal hemianopia). Lesion 3 (right optic tract) interrupts fibers (and vision) originating on the same side of both eyes (homonymous), with loss of vision from half of each field (hemianopia).

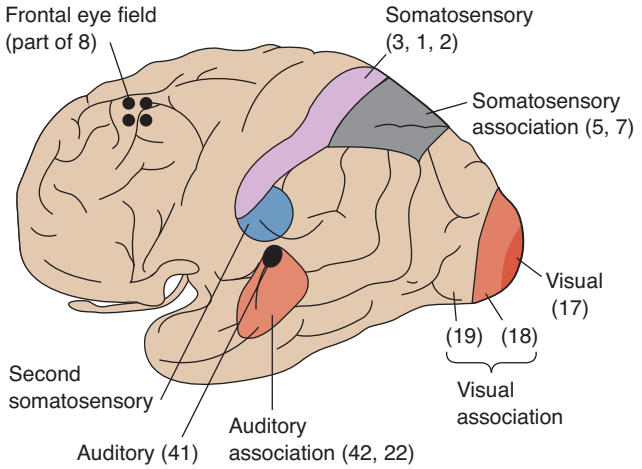


FIGURE 38-14. Lateral view of the cortex illustrating the location of the visual, visual association, auditory, and auditory association areas.

visual perception. This higher-order aspect of the visual experience depends on previous learning.

Disorders of the Optic Pathways

Among the disorders that can interrupt the visual pathway are trauma, tumors, and vascular lesions. Trauma and tumors can produce direct injury or impinge on the optic pathways. Vascular insufficiency in any one of the arterial systems of the retina or visual pathways can seriously affect vision. For example, normal visual function depends on the adequacy of blood flow in the ophthalmic artery and its branches—the central retinal artery; the anterior and middle cerebral arteries, which supply the intracranial optic nerve, chiasm, and optic tracts; and the posterior cerebral artery, which supplies the LGN, optic radiation, and visual cortex. The adequacy of posterior cerebral artery function depends on that of the vertebral and basilar arteries that supply the brain stem.

Visual Field Defects

The *visual field* refers to the area that is visible during fixation of vision in one direction[14,19,21] (see Fig. 38-13). As with a camera, the simple lens system of the eye inverts the image of the external world on each retina. In addition, the right and left sides of the visual field also are reversed. The right binocular visual field (the nasal half of the right eye and the temporal half of the left eye) is seen by the left retinal halves of each eye. Likewise, the left binocular field is seen by the right retinal halves of each eye.

Most of the visual field is *binocular,* or seen by both eyes. This binocular field is subdivided into *central* and *peripheral* portions. Central portions of the retina provide high visual acuity and correspond to the field focused on the central fovea. The peripheral and surrounding portion provides the capacity to detect objects, particularly moving objects. Beyond the visual field shared by both eyes, the left lateral periphery of the visual field is seen exclusively by the left nasal retina, and the right peripheral field by the right nasal retina.

Visual field defects result from damage to the visual pathways or the visual cortex (see Fig. 38-13). The testing of visual fields of each eye and of the two eyes together is useful in localizing lesions affecting the system. Perimetry or visual field testing, in which the visual field of each eye is measured and plotted in an arc, is used to identify defects and determine the location of lesions.

Blindness in one eye is called *anopia*. If half of the visual field for one eye is lost, the defect is called *hemianopia*; if a quarter of the field is lost, it is called *quadrantanopia*. Loss of the temporal or peripheral visual fields on both sides results in a narrow binocular field, commonly called *tunnel vision*. The loss of different half-fields in the two eyes is called a *heteronymous loss,* and the abnormality is called *heteronymous hemianopia*. Destruction of one or both lateral halves of the chiasm is common with multiple aneurysms of the circle of Willis (see Chapter 37). In this condition, the function of one or both temporal retinas is lost, and the nasal fields of one or both eyes are lost. The loss of the temporal fields (nasal retina) of both eyes is called *bitemporal heteronymous anopia*. With both eyes open, the person with bilateral defects still has the full binocular visual field.

Loss of the optic tract, LGN, full optic radiation, or complete visual cortex on one side results in loss of the corresponding visual half-fields in each eye. *Homonymous* means "the same" for both eyes. In left-side lesions, the right visual field is lost for each eye and is called *complete right homonymous hemianopia*. Partial injury to the left optic tract, LGN, or optic radiation can result in the loss of a quarter of the visual field in both eyes. This is called *homonymous quadrantanopia,* and depending on the lesion, it can involve the upper (superior) or lower (inferior) fields. The LGN, optic radiation, and visual cortex all receive their major blood supply from the posterior cerebral artery; unilateral occlusion of this artery results in complete loss of the opposite field (i.e., homonymous hemianopia). Bilateral occlusion of these arteries results in total cortical blindness.

The Extraocular Eye Muscles and Disorders of Eye Movement

For complete function of the eyes, it is necessary that the two eyes point toward the same fixation point and that the retinal and central nervous system (CNS) visual acuity mechanisms function. Despite slight variations in the view of the external world for each eye, it is important that these two images become fused, which is a forebrain function. Binocular fusion is controlled by ocular reflex mechanisms that adjust the orientation of each eye to produce a single image. If these reflexes fail, diplopia or double vision occurs.

Binocular vision depends on three pairs of extraocular muscles—the medial and lateral recti, the superior and inferior recti, and the superior and inferior obliques[14] (Fig. 38-15). Each of the three sets of muscles in each eye is reciprocally innervated so that one muscle relaxes

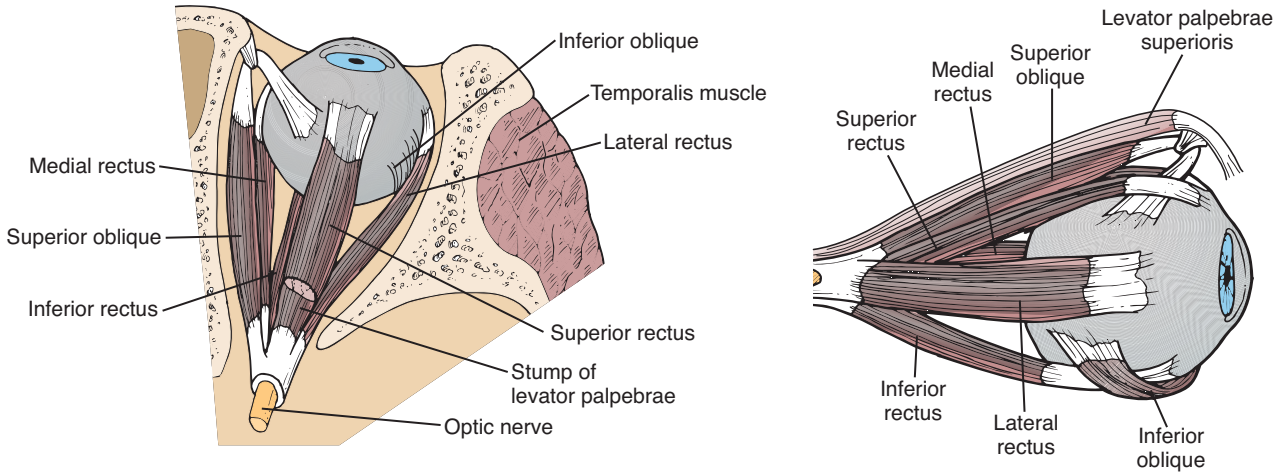


FIGURE 38-15. Extraocular muscles of the right eye.

when the other contracts. Reciprocal contraction of the medial and lateral recti moves the eye from side to side (adduction and abduction); the superior and inferior recti move the eye up and down (elevation and depression). The oblique muscles rotate (intorsion and extorsion) the eye around its optic axis. A seventh muscle, the levator palpebrae superioris, elevates the upper lid.

The extraocular muscles are innervated by three cranial nerves. The trochlear nerve (CN IV) innervates the superior oblique, the abducens nerve (CN VI) innervates the lateral rectus, and the oculomotor nerve (CN III) innervates the remaining four muscles. Table 38-1 describes the function and innervation of the extraocular muscles.

Normal vision depends on the coordinated action of the entire visual system and a number of central control systems. It is through these mechanisms that an object is simultaneously imaged on the fovea of both eyes and perceived as a single image. Strabismus and amblyopia are two disorders that affect this highly integrated system. Although strabismus may develop in later life, it is seen most commonly in children.

Strabismus

Strabismus, or squint, refers to any abnormality of eye coordination or alignment that results in loss of binocular vision. Strabismus affects approximately 4% of children younger than 6 years of age.[36–38] Because 30% to 50% of these children sustain permanent secondary loss

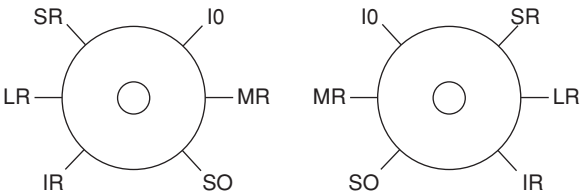


TABLE 38-1 Innervation and Function of the Ocular Muscles

Muscle*	CN Innervation	Primary	Secondary	Tertiary
Medial rectus (MR)	III	Adduction		
Lateral rectus (LR)	VI	Abduction		
Superior rectus (SR)	III	Elevation	Intorsion	Adduction
Inferior rectus (IR)	III	Depression	Extorsion	Adduction
Superior oblique (SO)	IV	Intorsion	Depression	Abduction
Inferior oblique (IO)	III	Extorsion	Elevation	Abduction

*In the schema of the functional roles of the six extraocular muscles, the major directional force applied by each muscle is indicated on the top. These muscles are arranged in functionally opposing pairs per eye and in parallel opposing pairs for conjugate movements of the two eyes. CN, cranial nerve.

of vision, or amblyopia, if the condition is left untreated, early diagnosis and treatment are essential.

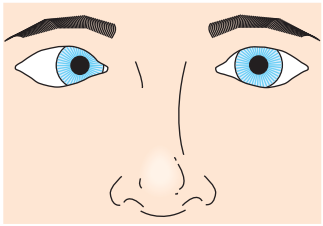
In standard terminology, the disorders of eye movement are described according to the direction of movement. *Esotropia* refers to medial deviation, *exotropia* to lateral deviation, *hypertropia* to upward deviation, *hypotropia* to downward deviation, and *cyclotropia* to torsional deviation. A *concomitant strabismus* refers to strabismus with equal deviation in all directions of gaze, and a *nonconcomitant strabismus* to one that varies with the direction of gaze. Strabismus may be divided into paralytic (nonconcomitant) forms, in which there is weakness or paralysis of one or more of the extraocular muscles, and nonparalytic (concomitant) forms, in which there is no primary muscle impairment. Strabismus is called *intermittent,* or *periodic,* when there are periods in which the eyes are parallel. It is monocular when the same eye always deviates and the fellow eye fixates. Figure 38-16 illustrates abnormalities in eye movement associated with esotropia, hypertropia, and exotropia.

Nonparalytic Strabismus. Nonparalytic esotropia is the most common type of strabismus. The individual ocular muscles have no obvious defect and the amount of deviation is constant or relatively constant in the various directions of gaze. With persistent deviation, secondary abnormalities may develop because of overactivity or underactivity of the extraocular muscles in some fields of gaze.

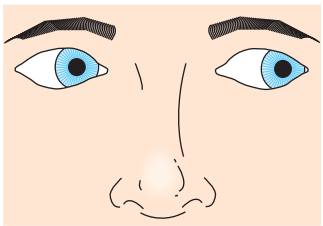
The disorder may be nonaccommodative, accommodative, or a combination of the two. Infantile esotropia is the most common cause of nonaccommodative strabismus. It occurs in the first 6 months of life, with large-angle deviations, in an otherwise developmentally and neurologically normal infant. Eye movements are full, and the child often uses each eye independently to alter fixation (cross-fixation). The cause of the disorder is unclear. Research suggests that idiopathic strabismus may have a genetic basis; siblings often present with similar disorders. Accommodative strabismus is caused by disorders such as uncorrected hyperopia of a significant degree, in which the esotropia occurs with accommodation that is undertaken to focus clearly. Onset of this type of esotropia characteristically occurs between 18 months and 4 years of age because accommodation is not well developed until that time. The disorder most often is monocular but may be alternating.

Paralytic Strabismus. Paralytic strabismus results from paresis (i.e., weakness) or plegia (i.e., paralysis) of one or more of the extraocular muscles. When the normal eye fixates, the affected eye is in the position of primary deviation. In the case of esotropia, there is weakness of one of the lateral rectus muscles. When the affected eye fixates, the unaffected eye is in a position of secondary deviation.[36]

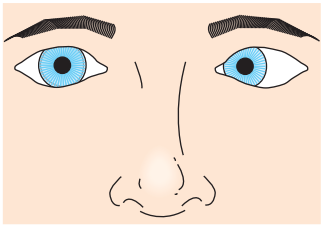
Paralytic strabismus is uncommon in children but accounts for nearly all cases of adult strabismus; it can



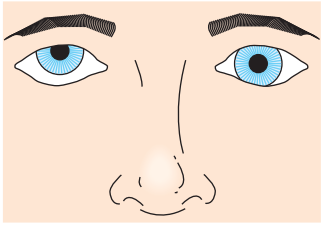
A Primary position: right esotropia



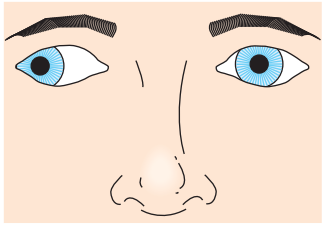
B Left gaze: no deviation



C Right gaze: left esotropia



D Right hypertropia



E Right exotropia

FIGURE 38-16. **(A–C)** Paralytic strabismus associated with paralysis of the right lateral rectus muscle: **(A)** primary position of the eyes (looking straight ahead); **(B)** left gaze with no deviation; **(C)** right gaze with left esotropia. **(D)** Primary position of the eyes with weakness of the right inferior rectus and right hypertropia. **(E)** Primary position of the eyes with weakness of the right medial rectus and right exotropia.

be caused by infiltrative processes (e.g., Graves disease; see Chapter 32), myasthenia gravis, stroke, and direct optical trauma.[38] In infants, paralytic strabismus can be caused by birth injuries affecting the extraocular muscles or the cranial nerves supplying these muscles. In general, paralytic strabismus in an older child or adult does not produce amblyopia, and binocular vision can be maintained when the strabismus is corrected. Most adult strabismus represents deterioration of childhood strabismus, which can occur even decades after good ocular alignment.

Treatment of strabismus is directed toward the development of normal visual acuity, correction of the deviation, and superimposition of the retinal images to provide binocular vision. Early and adequate treatment is crucial because a delay in or lack of treatment can lead to amblyopia and permanent loss of vision.

Treatment includes both surgical and nonsurgical methods. Infantile esotropia is usually treated surgically by weakening the medial rectus muscle on each eye while the infant is under general anesthesia. Surgery in children with esotropia should be done as early as possible to preserve stereoptic acuity. Early surgical treatment also appears to result in better outcomes than later intervention. Recurrent strabismus is common with infantile esotropia, and multiple surgeries are often required.

Nonsurgical treatment includes glasses, occlusive patching, and eye exercises (i.e., pleoptics). Glasses are often used in the treatment of accommodative esotropia that occurs with hypermetropia (farsightedness). Because accommodation is linked with convergence, focusing drives the eyes inward, producing esotropia. Intermittent exotropia is commonly treated with patching, use of over-minus glasses, and eye exercises. Although no appreciable deviation is present when the child with intermittent strabismus sees near objects, the deviation becomes obvious when the child views distant objects or is fatigued. Patching for 1 to 2 hours daily for several months exerts its effects by preventing, rather than treating, suppression of an eye. Patching is most effective in infants, and the efficacy is limited in children older than 3 years of age. The use of over-minus glasses stimulates accommodative convergences, which contracts the exotropic drift. Vision therapy involves exercises to stimulate convergence (e.g., focusing on reading-distance targets up to 30 minutes several times a day) and techniques to train the visual system to recognize the suppressed images. Surgical treatment of intermittent exotropia is indicted when conservative methods fail to correct the deviation. Early treatment of children with intermittent exotropia is not as crucial as it is for those with constant deviations because stereopsis can still develop.

A relatively new form of treatment involves the injection of botulinum toxin type A (Botox) into the extraocular muscle to produce a dose-dependent paralysis of that extraocular muscle.[36] Paralysis of the muscle shifts the eye into the field of action of the antagonist muscle. During the time the eye is deviated, the paralyzed muscle is stretched, whereas the antagonistic muscle is contracted. Usually two or more injections of the drug are necessary to obtain a lasting effect.

Amblyopia

Amblyopia, sometimes called *lazy eye,* describes a decrease in visual acuity resulting from abnormal visual development in infancy or early childhood.[39–41] The vision loss ranges from mild (worse than 20/25) to severe (legal blindness, 20/200 or worse). It is the leading cause of visual impairment, affecting 1% to 4% of the population. With early detection and treatment, most cases of amblyopia are reversible and the most severe forms of the condition can be prevented.

Normal development of the thalamic and cortical circuitry necessary for binocular visual perception requires simultaneous binocular use of each fovea during a critical period early in life (0 to 5 years). Amblyopia can result from visual deprivation (e.g., cataracts, ptosis) or abnormal binocular interactions (e.g., strabismus, anisometropia) during visual immaturity. In infants with unilateral cataracts that are dense, central, and larger than 2 mm in diameter, this period is before 2 months of age.[39] In conditions causing abnormal binocular interactions, one image is suppressed to provide clearer vision. In esotropia, vision of the deviated eye is suppressed to prevent diplopia. A similar situation exists in anisometropia, in which the refractive indexes of the two eyes are different. Although the eyes are correctly aligned, they are unable to focus together, and the image of one eye is suppressed.

The reversibility of amblyopia depends on the maturity of the visual system at the time of onset and the duration of the abnormal experience. Occasionally in strabismus, some persons alternate eye fixation and do not experience deep amblyopia or diplopia. With late adolescent or adult onset, this habit pattern must be unlearned after correction. Amblyopia is remarkably responsive to treatment if the treatment is initiated early in life; thus, all infants and young children should be evaluated for visual conditions that could lead to amblyopia.

The American Academy of Pediatrics in association with the American Association of Certified Orthoptists, American Association of Pediatric Ophthalmology and Strabismus, and American Academy of Ophthalmology recommends that all newborn infants be examined in the nursery for structural abnormalities and have a red reflex test performed to check for abnormalities in the back of the eye (posterior segment) and opacities in the visual axis, such as cataracts or corneal opacity.[42] Visual examinations should then be performed on all well-child visits. These should include age-appropriate evaluation of visual acuity, ocular alignment, and ocular media clarity (cataracts, tumors). Every effort should be made to ensure that eye examinations are performed by properly prepared examiners, using appropriate testing conditions, instruments, and techniques.[42,43]

The treatment of children with the potential for development of amblyopia must be instituted well before the age of 6 years to avoid the suppression phenomenon. Surgery for congenital cataracts and ptosis should be done early. Severe refractive errors should be corrected. In children with strabismus, the alternate blocking of the

vision in one eye and then the other forces the child to use both eyes for form discrimination. The duration of occlusion of vision in the good eye must be short (several hours per day) and closely monitored, or deprivation amblyopia can develop in the good eye as well. Although amblyopia is not likely to occur after 8 or 9 years of age, some plasticity in central circuitry is evident even in adulthood. For example, after refractive correction for long-standing astigmatism in adults, visual acuity improves slowly, requiring several months to reach normal levels.

In summary, the optic globe, or eyeball, is a nearly spherical structure protected posteriorly by the bony structures of the orbit and anteriorly by the eyelids. A conjunctiva lines the inner surface of the eyelids and covers the optic globe to the junction of the cornea and sclera. Conjunctivitis, also called *red eye* or *pink eye,* may result from bacterial or viral infection, allergic reactions, or the injurious effects of chemical agents, physical agents, or radiant energy. Keratitis, or inflammation of the cornea, can be caused by infections, hypersensitivity reactions, ischemia, defects in tearing, or trauma. Trauma or disease that involves the stromal layer of the cornea heals with scar formation and permanent opacification. These opacities interfere with the transmission of light and may impair vision.

The lens is a biconvex, transparent, flexible structure that can change shape to allow precise focusing of light on the retina. Refraction refers to the ability of the lens to bend light rays in order to focus an object on the retina. In hyperopia, or farsightedness, the image falls behind the retina. In myopia, or nearsightedness, the image falls in front of the retina. Accommodation is the process by which a clear image is maintained as the gaze is shifted from a far object to a near object. Presbyopia is a change in the lens that occurs because of aging such that the lens becomes thicker and less able to change shape and accommodate for near vision. A cataract is characterized by increased lens opacity. It can occur as the result of congenital influences, metabolic disturbances, infection, injury, and aging.

The retina covers the inner aspect of the posterior two thirds of the eyeball and is continuous with the optic nerve. It contains the photoreceptors for vision: the rods, for black and white discrimination, and the cones, for color vision. Disorders of retinal vessels can result from a number of local and systemic disorders, including diabetes mellitus and hypertension. The retinopathies involve the small blood vessels of the retina, with changes in blood vessel structure and the development of microaneurysms, neovascularization, hemorrhage, and retinal opacities. Retinal detachment involves separation of the sensory receptors from their blood supply; it causes blindness unless reattachment is accomplished promptly. Macular degeneration, which is a leading cause of blindness in the elderly, is characterized by loss of central vision resulting from destructive changes in the central fovea.

Glaucoma is a chronic, degenerative optic neuropathy characterized by optic disk cupping and visual field loss. It is usually associated with an increase in intraocular pressure that occurs because of impaired outflow of aqueous humor from the anterior chamber of the eye. Glaucoma is commonly classified as open-angle glaucoma, in which impaired outflow of aqueous humor is due to dysfunction of the drainage system, and angle-closure glaucoma, in which impaired outflow results from occlusion of the anterior chamber angle itself, impairing access to the drainage system.

Visual information is carried to the brain by axons of the retinal ganglion cells that form the optic nerve. The two optic nerves meet and cross at the optic chiasm, with the axons from each nasal retina joining the uncrossed fibers of the temporal retina of the opposite eye in the optic tract. The fibers in the optic tract pass to the LGN in the thalamus and then to the primary visual cortex, which is located in the occipital lobe. Damage to the visual pathways causes visual field defects that can be identified through visual field testing or perimetry.

Eye movement, which is controlled by the extraocular muscles, provides for alignment of the eyes and binocular vision. Strabismus refers to abnormalities in the coordination of eye movements with loss of binocular eye alignment. This inability to focus a visual image on corresponding parts of the two retinas results in diplopia. Paralytic strabismus is caused by weakness or paralysis of the extraocular muscles. Nonparalytic strabismus results from the inappropriate length or insertion of the extraocular muscles or from accommodation disorders. The neural pathways for vision develop during infancy. Amblyopia (i.e., lazy eye) is a condition of diminished vision that cannot be corrected by lenses and in which no detectable organic lesion in the eye can be observed. It results from inadequately developed CNS circuitry because of visual deprivation (e.g., cataracts) or abnormal binocular interactions (e.g., strabismus) during the period of visual immaturity.

The Ear and Disorders of Auditory Function

The ears are paired organs consisting of an external and middle ear, which function in capturing, transmitting, and amplifying sound, and an inner ear, which contains the receptive organs that are stimulated by sound waves (i.e., hearing) or head position and movement (i.e., vestibular function).

The External Ear

The external ear is a funnel-shaped structure that conducts sound waves to the tympanic membrane. It consists of the auricle, the external acoustic meatus, and the lateral surface of the tympanic membrane[2,44] (Fig. 38-17). A thin layer of skin containing fine hairs, sebaceous

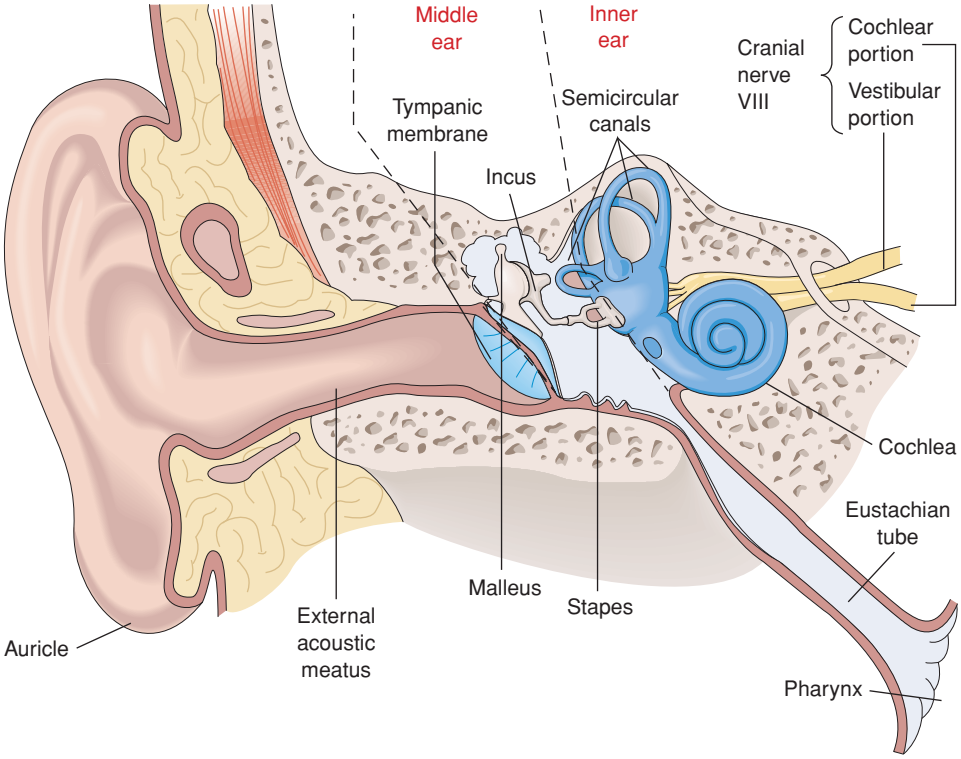


FIGURE 38-17. External, middle, and internal subdivisions of the ear.

glands, and ceruminous glands lines the ear canal. Ceruminous glands secrete cerumen, or earwax, which has certain antimicrobial properties and is thought to serve a protective function.

The tympanic membrane, approximately 1 cm in diameter, is a thin, transparent membrane that separates the external ear from the middle ear. The tympanic membrane is covered with thin skin externally and the mucous membrane of the middle ear internally. The tympanic membrane is attached in a manner that allows it to vibrate freely when audible sound waves enter the external auditory canal. Movements of the membrane are transmitted through the middle ear to the inner ear.

Disorders of the External Ear

The function of the external ear is disturbed when sound transmission is obstructed by impacted cerumen, inflammation (otitis externa), or drainage (otorrhea).

Impacted Cerumen. Cerumen, or earwax, is a protective secretion produced by the sebaceous and ceruminous glands of the skin that lines the ear canal. Although the ear normally is self-cleaning, the cerumen can accumulate and narrow the canal, causing reversible hearing loss.[45,46] Impacted cerumen usually produces no symptoms unless it hardens and touches the tympanic membrane, or the canal becomes irritated by a buildup of hardened cerumen. Clinical symptoms may include pain, itching, and a sensation of fullness. As the canal becomes completely occluded, a person may experience a feeling of fullness, a conductive hearing loss, and tinnitus (i.e., ringing in the ears).

In most cases, cerumen can be removed by gentle irrigation using a bulb syringe and warm tap water. Alternatively, health care professionals may remove cerumen using an otoscope and a wire loop or blunt cerumen curette.

Otitis Externa. Otitis externa is an inflammation of the external ear that can vary in severity from mild allergic dermatitis to severe cellulitis.[46] It can be caused by infectious agents, irritation (e.g., wearing hearing aids or earphones), or allergic reactions. Predisposing factors include frequent exposure to moisture in the ear canal (i.e., swimmer's ear), trauma to the canal caused by cleaning or scratching, and allergies or skin conditions such as psoriasis. The most common bacterial pathogens are gram-negative rods (*Pseudomonas aeruginosa, Proteus* species) and fungi (*Aspergillus*) that grow in the presence of excess moisture.[5] Otitis externa commonly occurs in the summer and is manifested by itching, redness, tenderness, and narrowing of the ear canal because of swelling. Inflammation of the pinna or canal makes movement of the ear painful. There may be watery or purulent drainage and intermittent hearing loss. Treatment usually includes the use of ear drops containing an appropriate antimicrobial or antifungal agent in combination with a corticosteroid to reduce inflammation.

Acute cellulitis of the auricle and external auditory canal is usually caused by *S. aureus*. The skin is red, hot, and firm with a sharply defined border. Fever may be present with little or no exudate in the ear. Treatment usually involves the parenteral administration of an appropriate antimicrobial agent.

The Middle Ear and Eustachian Tube

The middle ear, or tympanic cavity, is a small, mucosa-lined cavity in the petrous portion of the temporal bone[2,44] (see Fig. 38-17). It is spanned by three small bones, the auditory ossicles, which are connected by two synovial joints and are covered with the epithelial lining of the cavity. The middle ear also contains the eustachian (auditory) tube as well as the muscles that attach to the ossicles. The middle ear is bounded anteriorly by the tympanic membrane and posteriorly it is connected with small air pockets in the temporal bone called *mastoid air spaces* or *cells*.

The primary function of the middle ear is to convert sound waves arriving from the external ear into mechanical vibrations that are transmitted to the inner ear. Two openings in the medial wall of the middle ear, the oval (vestibular) window and the round (cochlear) window, are essential components of this conversion process.[2]

Three tiny bones, the auditory ossicles, connect the tympanic membrane with the oval window: the malleus, the incus, and the stapes.[2,44] The *malleus* ("hammer") has its handle firmly fixed to the upper portion of the tympanic membrane. The head of the malleus articulates with the *incus* ("anvil"), which links the malleus to the *stapes* ("stirrup"), whose footplate fits into the oval window. Arrangement of the ear ossicles is such that their lever movements transmit vibrations from the tympanic membrane to the oval window and from there to the fluid in the inner ear.

The middle ear is connected to the nasopharynx by the eustachian or auditory tube, which is located in a gap in the bone between the anterior and medial walls of the middle ear (see Fig. 38-17). The eustachian tube serves three basic functions: (1) ventilation of the middle ear, along with equalization of middle ear and ambient pressures; (2) protection of the middle ear from unwanted nasopharyngeal sound waves and secretions; and (3) drainage of middle ear secretions into the nasopharynx.[47] The nasopharyngeal entrance to the eustachian tube, which usually is closed, is opened by the action of the *tensor veli palatini muscle*, which is innervated by the trigeminal cranial nerve (CN V). Opening of the eustachian tube, which normally occurs with swallowing and yawning reflexes, provides the mechanism for equalizing the pressure of the middle ear with that of the atmosphere. This equalization ensures that the pressures on both sides of the tympanic membrane are the same, so that sound transmission is not reduced and rupture does not result from sudden changes in atmospheric pressure, as occurs during airplane travel. The eustachian tube is lined with a mucous membrane that is continuous with the pharynx and the mastoid air cells. Infections from the nasopharynx can travel from the nasopharynx along the mucous membrane of the eustachian tube to the middle ear, causing acute otitis media. Toward the nasopharynx, the eustachian tube becomes lined by columnar epithelium with mucus-secreting cells. Hypertrophy of the mucus-secreting cells is thought to contribute to the mucoid secretions that develop during certain types of otitis media.

Disorders of the Eustachian Tube

Abnormalities in eustachian tube function are important factors in the pathogenesis of middle ear infections.

Disorders of the Middle Ear

- The middle ear is a small, air-filled compartment in the temporal bone. It is separated from the outer ear by the tympanic membrane; communication between the nasopharynx and the middle ear occurs through the eustachian tube; and tiny bony ossicles that span the middle ear transmit sound to the sensory receptors in the inner ear.
- Otitis media (OM) refers to inflammation of the middle ear. It can represent an acute otitis media (AOM) that has an abrupt onset and is usually related to bacterial infection, or otitis media with effusion (OME) that is associated with fluid in the middle ear without the manifestations of infection and which does not usually require treatment with antimicrobial agents.
- The function of the middle ear is to conduct sound waves from the external to the inner ear. Impaired conduction of sound waves and hearing loss occur when the tympanic membrane has been perforated; air in the middle ear has been replaced with fluid (OME); or the function of the bony ossicles has been impaired (otosclerosis).

There are two important types of eustachian tube dysfunction: abnormal patency and obstruction (Fig. 38-18). The *abnormally patent tube* either does not close or does not close completely. In infants and children with an abnormally patent tube, air and secretions often are pumped into the eustachian tube during crying and nose blowing.

Obstruction can be functional or mechanical. *Functional obstruction* results from the persistent collapse of the eustachian tube due to a lack of tubal stiffness or poor function of the tensor veli palatini muscle that controls the opening of the eustachian tube. It is common in infants and young children because the amount and stiffness of the cartilage supporting the eustachian tube are less than in older children and adults. Changes in the craniofacial base also render the tensor muscle less efficient for opening the eustachian tube in this age group. In addition, craniofacial disorders, such as a cleft palate, alter the attachment of the tensor muscle, producing functional obstruction of the eustachian tube.

Mechanical obstruction results from internal obstruction or external compression of the eustachian tube. Ethnic differences in the structure of the palate may increase the likelihood of obstruction. The most common internal obstruction is caused by swelling and secretions resulting from allergy and viral respiratory infections. With obstruction, air in the middle ear is absorbed, causing a negative pressure and the transudation of serous capillary fluid into the middle ear.

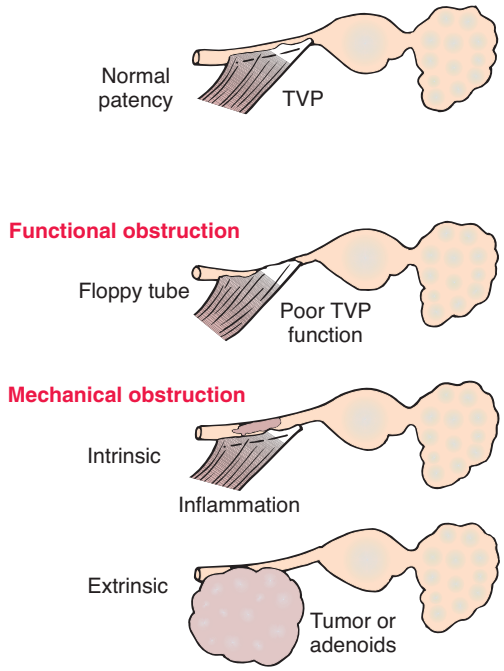


FIGURE 38-18. Pathophysiology of the eustachian tube. TVP, tensor veli palatini. (Developed from Bluestone C.D. [1981]. Recent advances in the pathogenesis, diagnosis, and management of otitis media. *Pediatric Clinics of North America* 28, 737. With permission from Elsevier Science.)

Otitis Media

Otitis media (OM) refers to inflammation of the middle ear without reference to etiology or pathogenesis (Fig. 38-19A). Inflammation of the middle ear may present as acute otitis media or otitis media with effusion.[48–50] *Acute otitis media* (AOM) refers to an acute middle ear infection.[51] It usually has an abrupt onset of signs and symptoms related to middle ear inflammation and effusion. *Otitis media with effusion* (OME) refers to the presence of fluid in the middle ear without signs and symptoms of acute ear infection.[52] OME may occur spontaneously because of poor eustachian tube function or as an inflammatory response following AOM. Because OME does not usually require treatment with antimicrobial agents, it is important to differentiate OME from AOM to avoid unnecessary use of antimicrobial agents.

Risk Factors. Otitis media may occur in any age group, but is seen most frequently in preschool-age children. Infants and young children between the ages of 3 months and 3 years are at highest risk for OM, with the peak incidence between 6 and 11 months.[50] There is a second peak incidence at about 5 years of age that is believed to be associated with entrance into school.[50] Risk factors include premature birth, male gender, ethnicity (Native American, Inuit), family history of recurrent otitis media, presence of siblings in the household, genetic syndromes, and low socioeconomic status.[50,51] Otitis media is more frequent in children with orofacial abnormalities such as cleft lip and palate.

The most important factor that contributes to OM is believed to be a dysfunction of the eustachian tube that allows reflux of fluid and bacteria into the middle ear space from the nasopharynx. There are two reasons for the increased risk of OM in infants and young children: the eustachian tube is shorter, more horizontal, and wider in this age group than in older children and adults; and infection can spread more easily through the eustachian canal

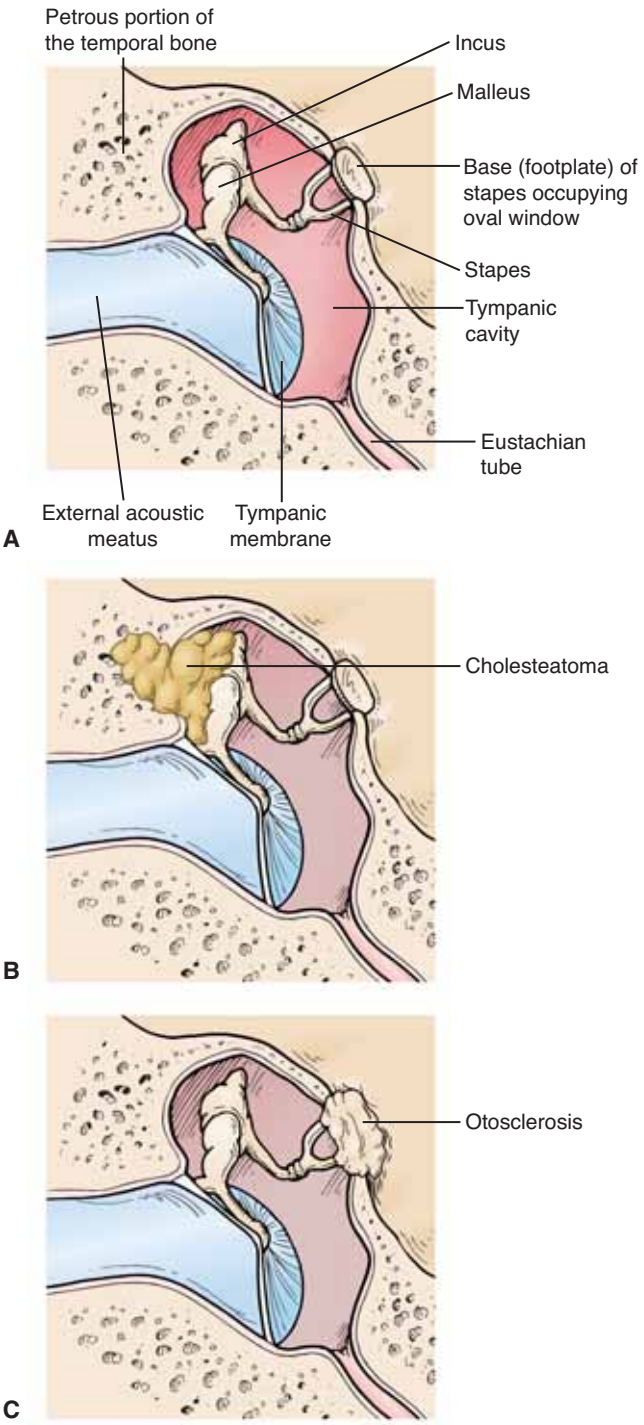


FIGURE 38-19. Disorders of the middle ear. **(A)** Otitis media. Otitis involves inflammation of the tympanic cavity. Infection often enters through the eustachian tube. **(B)** Cholesteatoma, a cystlike mass of the middle ear that often extends to involve the temporal bone. **(C)** Otosclerosis involving formation of new, spongy bone around the stapes and oval window.

of infants who spend most of their day in the supine position.[51] Bottle-fed infants have a higher incidence of OM than breast-fed infants, probably because they are held in a more horizontal position during feeding, and swallowing while in the horizontal position facilitates the reflux of milk into the middle ear. Breast-feeding also provides for the transfer of protective maternal antibodies to the infant.

Measures to reduce the risk for development of OM during the first 6 months of life include breast-feeding and reduction or elimination of pacifier use.[51] Other ways to reduce the risk of developing OM include minimal exposure to group settings and the avoidance or elimination of bottle propping as well as exposure to passive tobacco smoke. Efficacy in prevention of OM during the respiratory illness season has been demonstrated by immunoprophylaxis with influenza vaccines. Immunization with pneumococcal vaccine has also been reported to reduce the incidence of OM caused by vaccine-serotype *Pneumococcus,* but the overall effect has been small.[51]

Etiology. Most cases of AOM follow an uncomplicated upper respiratory tract infection that has been present for several days. The most common bacteria in AOM are *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.*[48–51] Penicillin-resistant *S. pneumoniae* is the most common cause of recurrent and persistent AOM. Evidence of respiratory viruses is also found in the middle ear exudates in children with AOM, either alone or, more commonly, in association with pathogenic bacteria. Of these viruses, rhinovirus and respiratory syncytial virus (RSV) are found most often.[49] It remains unclear whether viruses alone can cause AOM or whether their role is limited to setting the stage for bacterial invasion and, perhaps, amplifying the inflammatory response.[49]

The etiology of AOM and OME are interrelated. Acute infection is usually followed by residual inflammation and effusion that, in turn, predisposes to recurrent infection. Middle ear effusion, which is a component of both AOM and OME, is an expression of underlying mucosal inflammation. Persistent middle ear effusion results in decreased motility of the tympanic membrane and serves as a barrier to sound conduction.

Clinical Manifestations. Acute otitis media is characterized by acute onset of otalgia (or pulling of the ears in an infant), fever, and hearing loss. Children older than 3 years of age may have rhinorrhea or running nose, vomiting, and diarrhea. In contrast, younger children often have nonspecific signs and symptoms that manifest as ear tugging, irritability, nighttime awakening, and poor feeding. Key diagnostic criteria include distinct otalgia (earache that interferes with activity or sleep) or tympanic membrane erythema, and middle ear effusion.[51] Ear pain usually increases as the effusion accumulates behind the tympanic membrane. Perforation of the tympanic membrane may occur acutely, allowing purulent material from the middle ear to drain into the external auditory canal. This may prevent spread of the infection into the temporal bone or intracranial cavity. Healing of the tympanic membrane usually follows resolution of the middle ear infection.

Otitis media with effusion is often an asymptomatic condition.[52] There may be mild intermittent ear pain, complaints of ear fullness, and "popping." Secondary manifestations in infants may include ear rubbing, excessive irritability, and sleep disturbances. Hearing loss, even when not suggested by the child, is evidenced by a seeming lack of attentiveness, behavioral changes, and failure to respond to conversation-level speech. There may be problems related to school performance, balance problems and unexplained clumsiness, or delayed speech and language development.[52] The duration of the effusion may range from less than 3 weeks to more than 3 months. Many cases of OME resolve spontaneously, but 30% to 40% of children have recurrent OME, and 5% to 10% of episodes last 1 year or longer.[52]

Diagnosis. Distinguishing between AOM and OME on clinical grounds is often straightforward, but because each condition may evolve into the other without any clearly differentiating physical findings, any system for distinguishing between them is somewhat arbitrary.

Both AOM without otorrhea (drainage from the ear) and OME are accompanied by otoscopic signs of middle ear effusion, namely, the presence of at least two of three tympanic membrane abnormalities: white, yellow, amber, or occasionally blue discoloration; opacification other than scarring; and decreased or absent motility. With OME the tympanic membrane is often cloudy with distinct impairment of mobility, and an air–fluid level or bubble may be visible in the middle ear.

A definitive diagnosis of AOM requires the following: history of acute onset of signs and symptoms, the presence of middle ear effusion, and signs and symptoms of middle ear inflammation.[51] Signs of middle ear inflammation include fullness or bulging of the tympanic membrane with or without erythema, limited or absent mobility of the tympanic membrane, a purulent (pus-containing) effusion, and ear pain that interferes with normal activity.

Although the diagnosis of AOM often can be made by otoscopic examination alone, pneumatic otoscopy usually is performed to document middle ear effusion and immobility of the tympanic membrane. The use of the pneumatic otoscope permits the introduction of air into the ear canal for the purpose of determining tympanic membrane flexibility. The movement of the tympanic membrane is decreased in some cases of AOM and absent in chronic middle ear infection. The diagnosis of AOM can also be confirmed using tympanometry or acoustic reflectometry. A *tympanogram* is obtained by using a small probe that is placed snugly into the external ear canal. A sound stimulus generator then transmits acoustic energy into the canal, while a vacuum pump introduces positive and negative pressures into the ear canal. A microphone in the instrument detects returning sound energy. The tympanogram provides a determination of the degree of negative pressure present in the middle ear. It detects disease when present but is less reliable when disease is absent. *Acoustic reflectometry* detects reflected sound waves from the middle ear and provides information on whether an effusion is absent or present.

Increased reflected sound correlates with an increased likelihood of effusion. This technique is most useful in children older than 3 months, and its success depends on user technique.

Tympanocentesis (puncture of the tympanic membrane with a needle) may be done to relieve pain from an effusion or to obtain a specimen of middle ear fluid for culture and sensitivity testing. In instances where the tympanic membrane has perforated with resultant drainage into the external ear, a specimen can be obtained and microbiologic studies can be done to identify the organism.

Treatment. The treatment of AOM focuses on symptom control and management of the underlying pathologic process. A number of options for pain management are available, including the local application of heat and use of analgesic drugs such as acetaminophen and ibuprofen.[51] Myringotomy (incision in the tympanic membrane) can be used for relief of pressure in the child with severe pain, providing almost immediate relief.

The extensive use of antimicrobial agents contributes to the development of bacterial resistance, and evidence exists for the efficacy and safety of two alternative approaches to routine antimicrobial prescription: delayed prescription and watchful waiting.[51] Observation without antimicrobial agents is an option in a child with uncomplicated AOM. These approaches involve waiting for 72 hours to see if symptoms improve before institution of antimicrobial therapy. Factors to consider when deciding whether to defer treatment include the child's age, severity of illness, and certainty of the diagnosis. Antimicrobial drugs are recommended for children younger than 6 months, for those 6 months to 2 years of age when the diagnosis is certain, and for all children older than 2 years of age with severe infection.[49,51] If observation is recommended, it is essential that the parent or caregiver have ready access to communication, follow-up, and a mechanism for obtaining medication if needed.

Most cases of OME resolve spontaneously within a 3-week to 3-month period. The management options for this duration include observation only, antimicrobial therapy, or combination antimicrobial and corticosteroid therapy. Topical and systemic decongestants usually are of little value in clearing middle ear effusion.[52] Because there is concern over hearing loss and its effect on learning and speech, a hearing evaluation is recommended when OME persists for 3 months or longer or at any time that language delay, learning problems, or a significant hearing loss is suspected.[52] Children with recurrent OM should be evaluated to rule out any anatomic variations (e.g., enlarged adenoids), allergies, and immunologic abnormalities. Referral to an otolaryngologist is indicated if the effusion persists for 4 months or longer.

Surgical treatment (e.g., tympanostomy tubes, adenoidectomy) for OME may be indicated if the effusion has persisted for 4 months or longer and is accompanied by persistent hearing loss and other manifestations; if recurrent or persistent effusion occurs in children at risk regardless of hearing status; or if there is structural damage to the tympanic membrane or middle ear.[52] Tympanostomy tube insertion is the preferred initial procedure and does not typically include the removal of adenoids unless the child has additional indications, such as postnasal obstruction from enlarged adenoids. The tubes usually are inserted under general anesthesia. The ears of children with tubes must be kept out of water. The adverse effects of tube placement include recurrent otorrhea; persistent perforation, scarring, and atrophy of the tympanic membrane; and cholesteatoma. Adenoidectomy plus myringotomy (without tube insertion) has been shown to have comparable efficacy in children 4 years of age or older, but is more invasive, with additional surgical and anesthetic risks.[52]

Complications of Otitis Media. The complications of OM include hearing loss and extratemporal complications, including those affecting the middle ear, mastoid, adjacent structures of the temporal bone, and intracranial structures.

Hearing loss, which is a common complication of OM, usually is conductive and temporary based on the duration of the effusion. Hearing loss that is associated with fluid collection usually resolves when the effusion clears. Permanent hearing loss may occur as the result of damage to the tympanic membrane or other middle ear structures. Cases of sensorineural hearing loss are rare.

The mastoid antrum and air cells constitute a portion of the temporal bone and may become inflamed as an extension of acute or chronic OM.[48] The disorder causes necrosis of the mastoid process and destruction of the bony intercellular matrix, which are visible by radiologic examination. Mastoid tenderness and drainage of exudate through a perforated tympanic membrane can occur. Chronic mastoiditis can develop as the result of chronic middle ear infection. The usefulness of antimicrobial agents for this condition is limited. Mastoid or middle ear surgery, along with other medical treatment, may be indicated.

Cholesteatomas are cystlike lesions of the middle ear, usually associated with chronic otitis media (see Fig. 38-19B). Measuring 1 to 4 cm in diameter, they are lined with keratinizing squamous epithelium or mucus-secreting epithelium and filled with amorphous debris (derived largely from desquamated epithelium).[48,53,54] Although precise mechanisms involved in their development are unclear, it is proposed that chronic inflammation and perforation of the ear drum with ingrowth of squamous epithelium or metaplasia of the secretory epithelium of the middle ear are contributing factors. These lesions can erode the ossicles, the labyrinth, the adjacent mastoid bone, and the surrounding soft tissues. Although often thought of as a complication of otitis media, a cholesteatoma may also occur as a congenital condition. Symptoms commonly include painless drainage from the ear and hearing loss. Treatment involves microsurgical techniques to remove the cholesteatomatous material.

Intracranial complications are uncommon since the advent of antimicrobial therapy. Although rare, these complications can develop when the infection spreads through vascular channels, by direct extension, or through preformed pathways such as the round window.[48] These complications are seen more often with chronic suppurative

OM and mastoiditis. They include otogenic meningitis, brain abscess, lateral sinus thrombophlebitis or thrombosis, labyrinthitis, and facial nerve paralysis. Any child who develops persistent headache, tinnitus, stiff neck, or visual or other neurologic symptoms should be investigated for possible intracranial complications.

Otosclerosis

Otosclerosis refers to the formation of new spongy bone around the stapes and oval window, which results in progressive deafness[54,55] (see Fig. 38-19C). In most cases, the condition is familial and follows an autosomal dominant pattern with variable penetrance. Otosclerosis may begin at any time in life but usually does not appear until after puberty, most frequently between the ages of 20 and 30 years. The disease process accelerates during pregnancy.

Otosclerosis begins with resorption of bone in one or more foci. During active bone resorption, the bone structure appears spongy and softer than normal (i.e., otospongiosis). The resorbed bone is replaced by an overgrowth of new, hard, sclerotic bone. The process is slowly progressive, involving more areas of the temporal bone, especially in front of and posterior to the stapes footplate. As it invades the footplate, the pathologic bone increasingly immobilizes the stapes, reducing the transmission of sound. Pressure of otosclerotic bone on middle ear structures or the vestibulocochlear nerve (CN VIII) may contribute to the development of tinnitus, sensorineural hearing loss, and vertigo.

The symptoms of otosclerosis involve an insidious conductive hearing loss. Initially, the affected person is unable to hear a whisper or someone speaking at a distance. In the earliest stages, the bone conduction by which the person's own voice is heard remains relatively unaffected. At this point, the person's own voice sounds unusually loud, and the sound of chewing becomes intensified. Because of bone conduction, most of these persons can hear fairly well on the telephone, which provides an amplified signal.

The treatment of otosclerosis can be medical or surgical. A carefully selected, well-fitting hearing aid may allow a person with conductive deafness to lead a normal life. Sodium fluoride has been used with some success in the medical treatment of otospongiosis.[55] Because much of the conductive hearing loss associated with otosclerosis is caused by stapedial fixation, surgical treatment involves stapedectomy with stapedial reconstruction using the patient's own stapes or a stapedial prosthesis. The argon laser may be used in the surgical procedure.

The Inner Ear and Central Auditory Pathways

The inner ear contains a labyrinth, or system of intercommunicating channels, and the receptors for hearing and position sense.[14,19] An outer bony wall, or bony labyrinth, encloses a thin-walled, membranous labyrinth, which floats in the bony labyrinth (Fig. 38-20). Two separate fluids are found in the inner ear: the *perilymph* or *periotic fluid*, which separates the bony labyrinth from the membranous labyrinth, and the *endolymph* or *otic fluid*, which fills the membranous labyrinth. Localized dilatations of the membranous labyrinth develop into three specialized sensory regions: the ampulla of each semicircular canal, the maculae of the utricle and sacculus, and the cochlea. The receptors in the cochlea are sensitive to sound, and those in semicircular canals and maculae are sensitive to changes in head position and maintenance of balance.

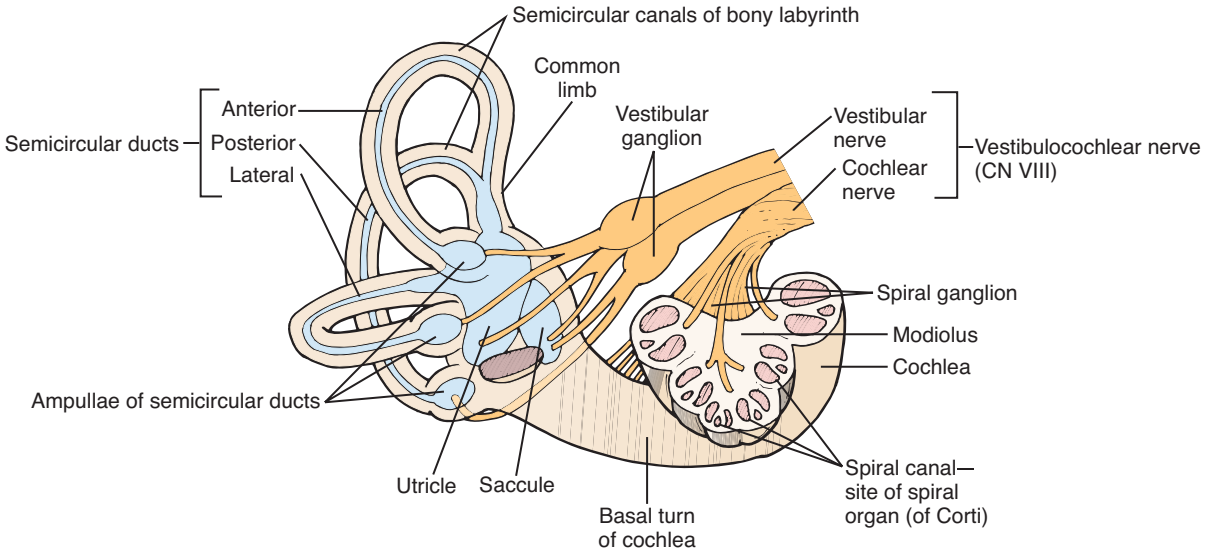


FIGURE 38-20. Schematic lateral view of the bony canals of the vestibular system showing the membranous labyrinth in a closed system of ducts and chambers filled with endolymph and bathed in perilymph with the bony labyrinth. Observe the parts of the membranous labyrinth: the semicircular ducts and the saccule and utricle within the vestibule. (Adapted from Moore K.L., Dalley A.F. [1999]. *Clinically oriented anatomy* [4th ed., p. 1102]. Philadelphia: Lippincott Williams & Wilkins.)

The cochlea is a shell-shaped part of the bony labyrinth that consists of three parallel compartments: the scala media or middle compartment of the cochlear canal, the scala vestibuli, and the scala tympani (Fig. 38-21A). The scala media is an endolymph-containing space that is continuous with the lumen of the saccule and contains the spiral organ of Corti, the receptor organs for hearing. The scala vestibuli and scala tympani are perilymph spaces that communicate with each other at the apex of the cochlea through a small channel called the *helicotrema*. The scala vestibuli begins at the oval window, and the scala tympani ends at the round window.

The organ of Corti, which rests atop the basilar membrane in the scala media, is composed of supporting cells and several long rows of cochlear hair cells: one row of inner hair cells and three rows of outer hair cells (see Fig. 38-21B). Afferent fibers from the cochlear nerve are coiled around the bases of the hair cells. Sound waves, delivered to the oval window by the stapes footplate, are transmitted to the perilymph in the scala vestibuli and scala tympani. Transduction of sound stimuli occurs when the trapped cilia of the hair cells in the organ of Corti are bent by the sound-induced movement of the basilar membrane.

Afferent fibers from the organ of Corti have their cell bodies in the spiral ganglion in the central portion of the cochlea. Nerve fibers from the spiral ganglion (i.e., vestibulocochlear or auditory nerve [CN VIII]) travel to the cochlear nuclei in the caudal pons. Many secondary nerve fibers from the cochlear nuclei pass to the nuclei on the opposite side of the pons or rostrally toward the inferior colliculus of the midbrain. From the inferior colliculus, the auditory pathway passes to the primary auditory cortex (area 41) in the temporal lobe through relays in the medial geniculate nucleus of the thalamus (see Fig. 38-14). The auditory association cortex (areas 42 and 22), which is necessary for the meaningfulness of sound, borders the primary cortex. Because some of the fibers from each ear cross, each auditory cortex receives impulses from both ears.

Tinnitus

Tinnitus is the perception of abnormal ear or head noises not produced by an external stimulus.[56–58] Although it often is described as "ringing of the ears," it may also assume a hissing, roaring, buzzing, or humming sound. Tinnitus may be constant, intermittent, and unilateral or bilateral. The condition affects both sexes equally, is most prevalent between 40 and 70 years of age, and occasionally affects children.

Although tinnitus is a subjective experience, for clinical purposes it is subdivided into objective and subjective tinnitus. *Objective tinnitus* refers to those rare cases in which the sound is detected or potentially detectable by another observer. Typical causes of objective tinnitus include vascular abnormalities or neuromuscular disorders. For example, in some vascular disorders, sounds generated by turbulent blood flow (e.g., arterial bruits or venous hums) are conducted to the auditory system. Vascular disorders typically produce a pulsatile form of tinnitus.

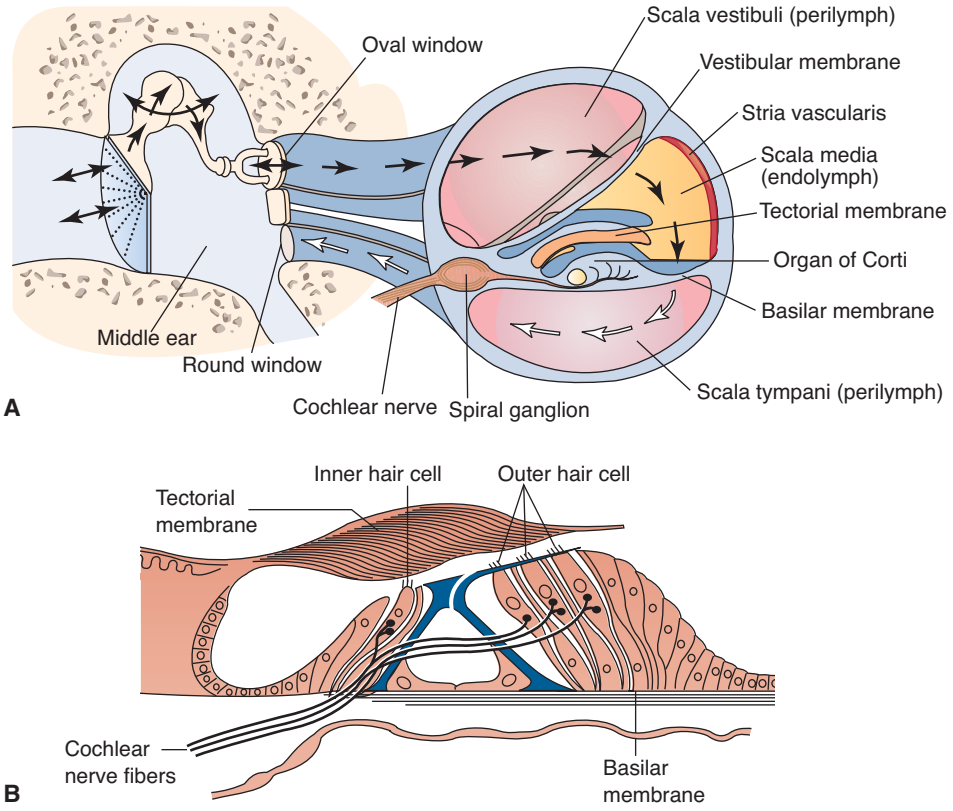


FIGURE 38-21. **(A)** Path taken by sound waves reaching the inner ear. **(B)** Spiral organ of Corti has been removed from the cochlear duct and greatly enlarged to show the inner and outer hair cells, the basilar membrane, and cochlear nerve fibers.

Subjective tinnitus refers to noise perception when there is no noise stimulation of the cochlea. A number of causes and conditions have been associated with subjective tinnitus. Intermittent periods of mild, high-pitched tinnitus lasting for several minutes are common in normal-hearing persons. Impacted cerumen is a benign cause of tinnitus, which resolves after the earwax is removed. Medications such as aspirin and stimulants such as nicotine and caffeine can cause transient tinnitus. Conditions associated with more persistent tinnitus include noise-induced hearing loss, presbycusis (sensorineural hearing loss that occurs with aging), hypertension, atherosclerosis, head injury, and cochlear or labyrinthine infection or inflammation. The physiologic mechanism underlying subjective tinnitus is largely unknown. It seems likely that there are several mechanisms, including abnormal firing of auditory receptors, dysfunction of cochlear neurotransmitter function or ionic balance, and alterations in central processing of the signal.

Treatment measures for tinnitus are designed to treat the symptoms, rather than effect a cure.[56,57] They include elimination of drugs or other substances, such as caffeine, some cheeses, red wine, and foods containing monosodium glutamate, that are suspected of causing tinnitus. Tinnitus retraining therapy, which includes directive counseling and extended use of low-noise generators to facilitate auditory adaptation to the tinnitus, has met with considerable success.

Disorders of the Central Auditory Pathways

The auditory pathways in the brain involve communication between the two sides of the brain at many levels. As a result, strokes, tumors, abscesses, and other focal abnormalities seldom produce more than a mild reduction in auditory acuity on the side opposite the lesion. For intelligibility of auditory language, lateral dominance becomes important. On the dominant side, usually the left side, the more medial and dorsal portion of the auditory association cortex is of crucial importance. This area is called the *Wernicke area,* and damage to it is associated with auditory receptive aphasia. Persons with damage to this area of the brain can speak intelligibly and read normally but are unable to understand the meaning of major aspects of audible speech.

Irritative foci that affect the auditory radiation or the primary auditory cortex can produce roaring or clicking sounds, which appear to come from the auditory environment of the opposite side (i.e., auditory hallucinations). Focal seizures that originate in or near the auditory cortex often are immediately preceded by the perception of ringing or other sounds preceded by a prodrome (i.e., aura). Damage to the auditory association cortex, especially if bilateral, results in deficiencies of sound recognition and memory (i.e., auditory agnosia). If the damage is in the dominant hemisphere, speech recognition can be affected (i.e., sensory or receptive aphasia).

Hearing Loss

Nearly 36 million Americans have some degree of hearing loss.[59] It affects persons of all age groups. Two to 3 of every 1000 children in the United States are born deaf or hard of hearing, and 9 of 10 children who are born deaf are born to parents who can hear.[59] Approximately 30% of adults between the ages of 65 and 75 years old and approximately 47% of those 75 years of age and older have a hearing loss.[59]

The level of hearing is measured in decibels (db), where 0 dB is the threshold for perception of sound at a given frequency in persons with normal hearing. A 10-fold increase in sound pressure level from 0 dB is mea sured as 20 dB. Hearing loss is classified as mild (26 to 40 dB), moderate (41 to 55 dB), severe (71 to 90 dB), or profound (91 dB or greater).[60] "Hard of hearing" is defined as hearing loss greater than 20 to 25 dB in adults and greater than 15 dB in children. Profound deafness is defined as hearing loss greater than 90 dB in adults[61] or 70 dB in children.[62]

There are many causes of hearing loss or deafness. Most fit into the categories of conductive, sensorineural, or mixed deficiencies that involve a combination of conductive and sensorineural function deficiencies of the same ear.[60,61] Chart 38-1 summarizes common causes of hearing loss. Hearing loss may be genetic or acquired, sudden or progressive, unilateral or bilateral, partial or complete, reversible or irreversible. Age and suddenness of onset provide important clues as to the cause of hearing loss.

Hearing Loss

- Hearing is a special sensory function that incorporates the sound-transmitting properties of the external ear canal, the eardrum that separates the external and middle ear, the bony ossicles of the middle ear, the sensory receptors of the cochlea in the inner ear, the neural pathways of the vestibulocochlear or auditory nerve, and the primary auditory and auditory association cortices.
- Hearing loss represents impairment of the ability to detect and perceive sound.
- It can range from mild, affecting sounds of different tones and intensities, to moderate or profound.
- Hearing loss can be caused by conductive disorders, in which auditory stimuli are not transmitted through the structures of the outer and middle ears to the sensory receptors in the inner ear; by sensorineural disorders that affect the inner ear, auditory nerve, or auditory pathways; or by a combination of conductive and sensorineural disorders.

Conductive Hearing Loss

Conductive hearing loss occurs when auditory stimuli are not adequately transmitted through the auditory canal, tympanic membrane, middle ear, or ossicle chain

CHART 38-1 Common Causes of Conductive and Sensorineural Hearing Loss

Conductive Hearing Loss

- External ear conditions
  - Impacted earwax or foreign body
  - Otitis externa
- Middle ear conditions
  - Trauma
  - Otitis media (acute and with effusion)
  - Otosclerosis
  - Tumors

Sensorineural Hearing Loss

- Trauma
  - Head injury
  - Noise
- Central nervous system infections (e.g., meningitis)
- Degenerative conditions
  - Presbycusis
- Vascular
  - Atherosclerosis
  - Sudden deafness
- Ototoxic drugs (e.g., aminoglycosides, salicylates, loop diuretics)
- Tumors
  - Vestibular schwannoma (acoustic neuroma)
  - Meningioma
  - Metastatic tumors
- Idiopathic
  - Ménière disease

Mixed Conductive and Sensorineural Hearing Loss

- Middle ear conditions
  - Barotrauma
  - Cholesteatoma
  - Otosclerosis
- Temporal bone fractures

to the inner ear. Temporary hearing loss can occur as the result of impacted cerumen in the outer ear or fluid in the middle ear. Foreign bodies, including pieces of cotton and insects, may impair hearing. More permanent causes of hearing loss are thickening or damage of the tympanic membrane or involvement of the bony structures (ossicles and oval window) of the middle ear caused by otosclerosis or Paget disease.

Sensorineural Hearing Loss

Sensorineural, or perceptive, hearing loss occurs with disorders that affect the inner ear, auditory nerve, or auditory pathways of the brain. With this type of deafness, sound waves are conducted to the inner ear, but abnormalities of the cochlear apparatus or auditory nerve decrease or distort the transfer of information to the brain. Tinnitus often accompanies cochlear nerve irritation. Abnormal function resulting from damage or malformation of the central auditory pathways and circuitry is included in this category.

Sensorineural hearing loss may have a genetic cause or may result from intrauterine infections, such as maternal rubella, or developmental malformations of the inner ear. Genetic hearing loss may result from mutation in a single gene (monogenetic) or from a combination of mutations in different genes and environmental factors (multifactorial). It has been estimated that 50% of profound deafness in children has a monogenetic basis.[59,60] The inheritance pattern for monogenetic hearing loss is autosomal recessive in approximately 75% of cases.[62] Hearing loss may begin before development of speech (prelingual) or after speech development (postlingual). Most prelingual forms are present at birth. Genetic forms of hearing loss also can be classified as being part of a syndrome in which other abnormalities are present, or as nonsyndromic, in which deafness is the only abnormality.

Sensorineural hearing loss also can result from trauma to the inner ear, tumors that encroach on the inner ear or sensory neurons, vascular disorders with hemorrhage, or thrombosis of vessels that supply the inner ear. Other causes of sensorineural deafness are infections and drugs. Sudden sensorineural hearing loss represents an abrupt loss of hearing that occurs instantaneously or on awakening. It most commonly is caused by viral infections or circulatory disorders. Hypothyroidism is a potential cause of sensorineural hearing loss in older persons.

Environmentally induced deafness can occur through direct exposure to excessively intense sound, as in the workplace or at a concert. This is a particular problem in older adults who were working in noisy environments before the mid-1960s, when there were no laws mandating use of devices for hearing protection. Sustained or repeated exposure to noise pollution at sound intensities greater than 100 to 120 dB can cause corresponding mechanical damage to the organ of Corti. Severe damage can result in permanent sensorineural deafness to the affected sound frequencies. Wearing earplugs or ear protection is important under many industrial conditions and for musicians and music listeners exposed to high sound amplification.

A number of infections can cause sensorineural hearing loss. Deafness or some degree of hearing impairment is the most common serious complication of bacterial meningitis in infants and children, reportedly resulting in sensorineural hearing loss in 5% to 35% of persons who survive the infection.[60] The mechanism causing hearing impairment is thought to be a suppurative labyrinthitis or neuritis resulting in the loss of hair cells and damage to the auditory nerve. Untreated suppurative OM also can extend into the inner ear and cause sensorineural hearing loss through the same mechanisms.

Among the neoplasms that impair hearing are *acoustic neuromas*. Acoustic neuromas are benign Schwann cell tumors affecting CN VIII. These tumors usually are unilateral and cause hearing loss by compressing the cochlear nerve or interfering with blood supply to the nerve and cochlea. Other neoplasms that can affect hearing include meningiomas and metastatic brain tumors. The temporal bone is a common site of metastases.

Drugs that damage inner ear structures are labeled *ototoxic*. Vestibular symptoms of ototoxicity include lightheadedness, giddiness, and dizziness; if toxicity is severe, cochlear symptoms consisting of tinnitus or hearing loss

occur. Hearing loss is sensorineural and may be bilateral or unilateral, transient or permanent. Several classes of drugs, in particular, have been identified as having ototoxic potential, including the aminoglycoside antimicrobials and some other basic antimicrobials, antimalarial drugs, some chemotherapeutic drugs, loop diuretics, and salicylates (aspirin). The symptoms of drug-induced hearing loss may be transient, as often is the case with salicylates and diuretics, or they may be permanent. The risk of ototoxicity depends on the total dose of the drug and its concentration in the bloodstream. It is increased in persons with impaired kidney functioning and in those previously or currently treated with another potentially ototoxic drug.

Diagnosis and Treatment of Hearing Loss

Diagnosis of hearing loss is aided by careful history of associated otologic factors such as otalgia, otorrhea, tinnitus, and self-described hearing difficulties; physical examination to detect the presence of conditions such as otorrhea, impacted cerumen, or injury to the tympanic membrane; and hearing tests. Testing for hearing loss includes a number of methods, including a person's reported ability to hear an observer's voice, use of a tuning fork to test air and bone conduction, audioscopes, and auditory brain stem evoked responses (ABRs).[60]

Tuning forks are used to differentiate conductive and sensorineural hearing loss. Audioscopes can be used to assess a person's ability to hear pure tones at 1000 to 2000 Hz (usual speech frequencies). The ABR uses electroencephalographic (EEG) electrodes and high-gain amplifiers to produce a record of brain wave activity elicited during repeated acoustic stimulations of either or both ears. It involves subjecting the ear to loud clicks and using a computer to analyze nerve impulses as they are processed in the midbrain. Imaging studies such as computed tomography (CT) scans and magnetic resonance imaging (MRI) can be done to determine the site of a lesion and the extent of damage.[63]

Untreated hearing loss can have many consequences. Social isolation and depressive disorders are common in the hearing-impaired elderly. Hearing-impaired people may avoid social situations where background noise makes conversation difficult to hear. Safety issues, both in and out of the home, may become significant. Treatment measures for hearing loss range from simple removal of impacted cerumen in the external auditory canal to surgical procedures, such as those used to reconstruct the tympanic membrane. For other people, particularly the frail elderly, hearing aids remain an option. Cochlear implants also are an option for some people.

Hearing aids remain the mainstay of treatment for many persons with conductive and sensorineural hearing loss. With the advent of microcircuitry, hearing aids are now being designed with computer chips that allow multiple programs to be placed in a single hearing aid. The various programs allow the user to select a specific setting for different listening situations. The development of microcircuitry has also made it possible for hearing aids to be miniaturized to the point that, in many cases, they can be placed deep in the ear where they take advantage of the normal shape of the external ear and ear canal. Although modern hearing aids have improved greatly, they cannot replicate the hearing person's ability to hear both soft and loud noises. They also fail consistently to filter out distorted or background noise.[64] Other aids for the hearing impaired include alert and signal devices, assisted-listening devices from telephone companies, and dogs trained to respond to various sounds.

Surgically implantable cochlear prostheses for the profoundly deaf have been developed and are available for use in adults and children.[65] These prostheses are inserted into the scala tympani of the cochlea and work by providing direct stimulation to the auditory nerve, bypassing the stimulation that typically is provided by transducer cells but that is absent or nonfunctional in a deaf cochlea. For the implant to work, the auditory nerve must be functional. Although early implants used a single electrode, current implants use multielectrode placement, enhancing speech perception. Much of the progress in implant performance has been achieved through improvements in the speech processors that convert sound into electrical stimuli. Advances in the development of the multichannel implant have improved performance such that cochlear implants have been established as an effective option for adults and children with profound hearing impairment.[65,66] Most persons who are deafened after learning speech derive substantial benefit when cochlear implants are used in conjunction with lip reading; some are able to understand some speech without lip reading; and some are able to communicate by telephone.

Hearing Loss in Infants and Children

Even mild or unilateral hearing loss can have a detrimental effect on the language development and hearing-associated learning of the young child.[67,68] The cause of hearing impairment in children depends on whether the hearing loss is conductive or sensorineural. Most conductive hearing loss is caused by middle ear infections. Causes of sensorineural hearing impairment include genetic, infectious, traumatic, and ototoxic factors.

Genetic causes are probably responsible for as much as 50% of sensorineural hearing loss in children. The most common infectious cause of congenital sensorineural hearing loss is cytomegalovirus (CMV), which infects 1 of 100 newborns in the United States each year; of these, about 1200 to 2000 have sensorineural hearing loss.[68] Of particular concern is the fact that congenital CMV infection can cause both symptomatic and asymptomatic hearing loss in the newborn. Some children with congenital CMV infection, who were asymptomatic as newborns, have suddenly lost residual hearing at 4 to 5 years of age. Postnatal causes of sensorineural hearing loss include β-hemolytic streptococcal sepsis in the newborn and bacterial meningitis. *S. pneumoniae* is the most common cause of bacterial meningitis that results in sensorineural hearing loss after the neonatal period; this cause may become less frequent with the routine administration of the conjugate pneumococcal vaccine. Other causes of

sensorineural hearing loss are toxins and trauma. Early in pregnancy, the embryo is particularly sensitive to toxic substances, including ototoxic drugs such as the aminoglycosides and loop diuretics. Trauma, particularly head trauma, may cause sensorineural hearing loss.

Hearing impairment can have a major impact on the development of a child; therefore, early identification through screening programs is strongly advocated.[68–70] The currently recommended screening techniques are either the transient evoked otoacoustic emissions (TEOAEs) or the ABR. Both methodologies are noninvasive, relatively quick (<5 minutes), and easy to perform. The TEOAE measures sound waves generated in the inner ear (cochlea) in response to clicks or tone bursts emitted and recorded by a minute microphone placed in the external ear canals of the infant. The ABR uses three electrodes pasted to the infant's scalp to measure the EEG waves generated by clicks. Because many children become hearing impaired after the neonatal period and are not identified by neonatal screening programs, the American Academy of Pediatricians and the Joint Commission of Infant Hearing recommend that all infants with risk factors for delayed onset of progressive hearing loss receive ongoing audiologic and medical monitoring for 3 years and at appropriate intervals thereafter.

Once hearing loss has been identified, a full developmental and speech and language evaluation is needed. Parental involvement and counseling are essential. Children with sensorineural hearing loss should be evaluated for possible hearing aid use by a pediatric audiologist. Hearing aids may be fitted for infants as young as 2 months of age.[68] Infants and young children with profound congenital or prelingual deafness have benefited from multichannel cochlear implants.[68] Because of the increased risk of pneumococcal meningitis, children who receive implants should receive age-appropriate immunization against pneumococcal disease.

Hearing Loss in the Elderly

The term *presbycusis* is used to describe degenerative hearing loss that occurs with advancing age.[71,72] The degenerative changes that impair hearing may begin in the fifth decade of life and may not be clinically apparent until later. The hearing loss is typically gradual, bilateral, and characterized by high-frequency hearing loss. It is further characterized by reduced hearing sensitivity and speech understanding in noisy environments, slowed central processing of acoustic information, and impaired localization of sound sources. The disorder first reduces the ability to understand speech and, later, the ability to detect, identify, and localize sounds. The most common complaint of persons with presbycusis is not that they cannot hear, but rather that they cannot understand what is being said. For example, they often confuse words like *mash* with *math, map* with *mat,* and *Sunday* with *some day.* High-frequency warning sounds, such as beepers, turn signals, and escaping steam, are not heard and localized, with potentially dangerous results.

Given the high prevalence of hearing loss in people of retirement age and its adverse effects on well-being, screening for hearing loss should be performed at annual health care visits. Clinical measures for hearing loss such as whispered voice tests and finger friction tests are reportedly imprecise and are not reliable methods for screening. Screening audiometry administered by someone trained in its use is a practical and cost-effective method for detecting significant hearing loss.

The majority of hearing loss in the elderly is sensorineural. In mild to severe loss, the most effective treatment is hearing amplification with hearing aids, speech reading, and assistive listening devices (e.g., hearing aids with the telephone, captioning on televised programs, flashing alarms). Cochlear implants are indicated at any age for people with bilateral hearing losses not materially helped by hearing aids.

In summary, disorders of the auditory system include infections of the external and middle ear, otosclerosis, tinnitus, and conduction and sensorineural deafness. Otitis externa is an inflammatory process of the external ear. Otitis media refers to inflammation of the middle ear. Acute otitis media refers to an acute middle ear infection; and otitis media with effusion, the presence of fluid in the middle ear that is not due to infection and does not usually require treatment with antimicrobial agents. Otosclerosis is a familial disorder of the otic capsule that results in hearing loss due to immobilization of the stapes and conduction deafness.

Disorders of the inner ear, which contains the receptors for hearing, can lead to tinnitus (ringing of the ears) or sensorineural hearing loss. Tinnitus can be subjective, in which the sound is perceived by the individual but is not evident to the observer, or it can be objective, in which case the sound, often due to vascular disorders, can be detected by an observer. Disorders of the central auditory pathways, due to conditions such as a stroke, produce a sensorineural hearing loss on the side opposite the lesion.

Deafness, or hearing loss, can develop as the result of a number of auditory disorders. It can be conductive, sensorineural, or mixed. Conduction deafness occurs when transmission of sound waves from the external ear to the inner ear is impaired. Sensorineural deafness can involve cochlear structures of the inner ear or the neural pathways that transmit auditory stimuli. Sensorineural hearing loss can result from genetic or congenital disorders, trauma, infections, vascular disorders, tumors, or ototoxic drugs. Hearing loss that occurs in young children and the elderly can have special implications. Even mild or unilateral hearing loss can affect the development and hearing-associated learning of the young child. The age-related degenerative changes that impair hearing may begin in the fifth decade and not be clinically apparent until later. Treatment of hearing loss includes the use of hearing aids and, in some cases of profound deafness, implantation of a cochlear implant.

The Vestibular System and Disorders of Equilibrium

The equilibrium sense is not easy to describe. Although a mechanism of perception, it does not provide a sensation such as sight, hearing, or touch. Instead, it serves to maintain a stable body position through the control of postural reflexes. The vestibular receptive organs, which are located in the inner ear, and their CNS connections provide for the sense of equilibrium and orientation in space. Because the vestibular apparatus is part of the inner ear and located in the head, it is head position and acceleration that are sensed. The equilibrium sense, which is also dependent on vision and input from stretch receptors in muscles and tendons, serves to maintain and assist recovery of a stable body and head position through control of postural reflexes, and it serves to maintain a stable visual field despite marked changes in head position.

The Vestibular System

The vestibular system is contained in the bony labyrinth of the inner ear next to and continuous with the cochlea of the auditory system. Like the cochlea, the vestibular system consists of two fluid-filled compartments—an outer bony labyrinth that is filled with perilymph and an inner membranous labyrinth that is filled with endolymph[2,14] (Fig. 38-22A). The bony labyrinth is divided into three semicircular canals and a central vestibule or egg-shaped cavity that lies posterior to the cochlea and anterior to the semicircular canals. Suspended in the perilymph and united by a duct are two membranous labyrinth sacs, the saccule and utricle. The specialized sensory regions of the vestibular system consist of sensory hair cells and accessory supporting cells. These regions project from the wall of the membranous labyrinth into the endolymph space in each inner ear.

Located in each semicircular canal is a corresponding semicircular duct, which communicates with the utricle. Each of these ducts has an enlarged swelling at one end called an *ampulla*. The ampulla of each of the semicircular canals contains a ridge that is covered by a sensory epithelium with tufts of hair cells that are covered by a flexible gelatinous cap called the *cupula* (see Fig. 38-22B). These hair cells are sensitive to angular and rotary movements of the head rather than straight-line movement. The cavities of the three semicircular canals, the lateral, anterior, and posterior canals, are oriented in one of three planes of space. The lateral (horizontal) canals are in the same plane, whereas the anterior (superior) canal of one side is parallel with the posterior (inferior) canal on the other side, and the two function as a pair. Thus, regardless of which plane one moves in, there will be receptors to detect movement. Impulses from the semicircular ducts are particularly important in reflex movement of the eyes. Vestibular nystagmus (to be discussed) is a complex phenomenon that occurs during and immediately after rotational motion. During head rotation the eyes slowly drift in the opposite direction and then jump rapidly back toward the direction of rotation to establish a new fixation point.

The saccule and utricle house equilibrium receptors called *maculae* that respond to our sense of static equilibrium (see Fig. 38-22C). The maculae report on changes in space with respect to the pull of gravity when the body is not moving. Because they provide information on which way is up or down, they help to keep the head erect. Each macula is a small, flat epithelial patch containing supporting cells and sensory hair cells, the sides and bases of which synapse with sensory endings of the vestibular nerve. The hair cells of the macula in both the utricular and saccular maculae are embedded in a flattened gelatinous mass, the *otolithic membrane,* which is studded with tiny stones (calcium carbonate crystals) called *otoliths*. Although they are small, the density of the otoliths increases the membrane's weight and its resistance to change in motion. When the head is tilted, the gelatinous mass shifts its position because of the pull of the gravitational field, bending the cilia of the macular hair cells (see Fig. 38-22D). In a condition called *benign paroxysmal positional vertigo* (sensation of whirling or spinning motion), the otoliths become dislodged from their gelatinous base, causing a vertigo that is precipitated by changes in the recumbent head position (to be discussed).

The response to body imbalance, such as stumbling, must be fast and reflexive. Hence, information from the vestibular system goes directly to reflex centers in the brain stem, rather than to the cerebral cortex. Impulses

Disorders of the Vestibular System

- The receptors concerned with the sense of balance and position in space are located in fluid (endolymph)-filled semicircular canals of the vestibular system of the inner ear.
- The vestibular system has extensive interconnections with neural pathways controlling vision, hearing, and autonomic nervous system function. Disorders of the vestibular system are characterized by vertigo, nystagmus, tinnitus, nausea and vomiting, and autonomic nervous system manifestations.
- Disorders of vestibular function can result from repeated stimulation of the vestibular system such as during car, air, and boat travel (motion sickness); acute infection of the vestibular pathways (acute vestibular neuritis); dislodgement of otoliths that participate in the receptor function of the vestibular system (benign paroxysmal positional vertigo); or distention of the endolymphatic compartment of the inner ear (Ménière disease).

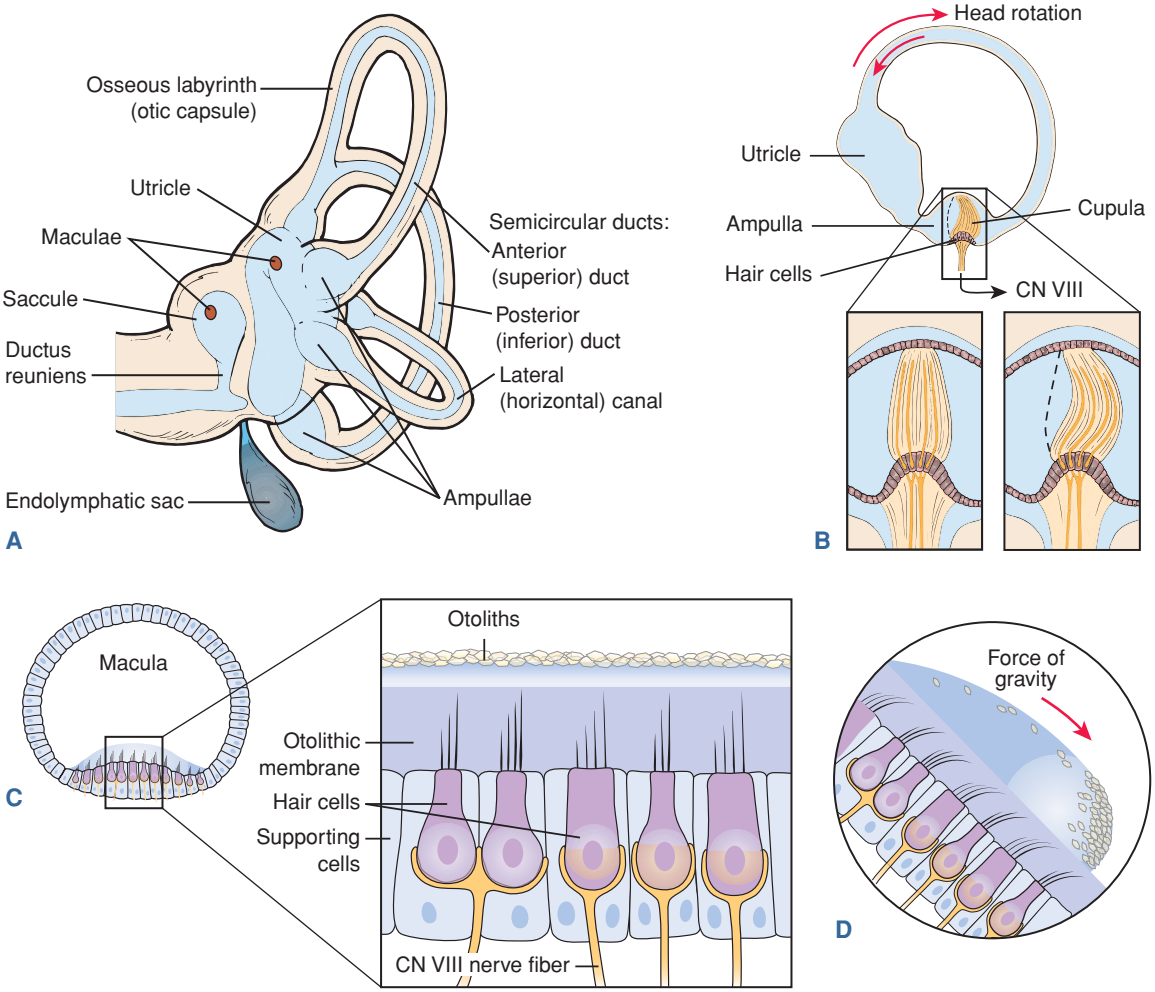


FIGURE 38-22. Vestibular labyrinth. **(A)** Osseous and membranous vestibular labyrinth of the middle ear showing the utricle and saccule with their maculae and three semicircular canals and their ampullae. **(B)** Diagram of the crista ampullaris within the semicircular canal and location of the cupula and movement of the hair cells with head movement. **(C)** Relationship of the otoliths to the sensory hair cells, which synapse with the sensory endings of the vestibular nerve (CN VIII) in the maculae of the utricle and saccule. **(D)** Movement of the otoliths and bending of the macular hair cells when the head is tilted due to the forces of gravity.

from the vestibular nerves initially pass to one of two destinations: the vestibular nuclear complex in the brain stem or the cerebellum. The vestibular nuclei, which form the main integrative center for balance, also receive input from visual and somatic receptors, particularly from stretch receptors in the neck muscles that report the angle or inclination of the head. The vestibular nuclei integrate this information and then send impulses to the brain stem centers that control the extraocular eye movements and reflex movements of the neck, limb, and trunk muscles. These reflex movements include the vestibulo-ocular reflexes that keep the eyes still as the head moves and the vestibulospinal reflexes that enable the skeletomotor system to make the quick adjustments needed to maintain or regain balance.

Neurons of the vestibular nuclei also project to the thalamus, the temporal cortex, the somesthetic area of the parietal cortex, and the chemoreceptor trigger zone. The thalamic and cortical projections provide the basis for the subjective experiences of position in space and of rotation. Connections with the chemoreceptor trigger zone stimulate the vomiting center, accounting for the nausea and vomiting that often are associated with motion sickness and vestibular disorders.

Nystagmus

The term *nystagmus* refers to the involuntary rhythmic and oscillatory eye movements that preserve eye fixation on stable objects in the visual field during angular and rotational movements of the head.[14] The vestibulo-ocular reflexes produce slow compensatory conjugate eye rotations that occur in the direction precisely opposite to ongoing head rotation and provide for continuous, ongoing reflex stabilization of the binocular fixation point. When compensatory vestibulo-ocular reflexes carry the conjugate eye

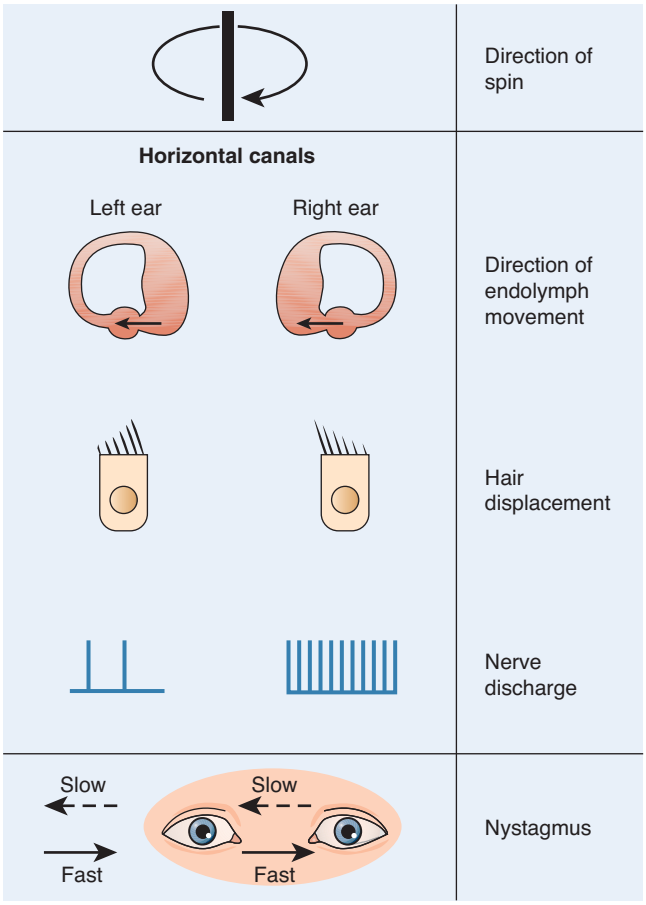


FIGURE 38-23. Effect of spinning a subject clockwise. On acceleration, the endolymph in the horizontal canals will lag behind with respect to movement of the canal wall. The hairs of cristae will be displaced to the left. In the left semicircular canal, hair displacement is away from the kinocilium, leading to decreased nerve discharges below the resting level. On the right, hair displacement is toward the kinocilium, leading to an increase in nerve discharge above the resting level. (From Sekurt F.E. [1982]. *Basic physiology for the health professions* [2nd ed., p. 140]. Boston: Little, Brown.)

rotations to their physical limit, a very rapid conjugate movement moves the eyes in the direction of head rotation to a new fixation point, followed by a slow vestibulo-ocular reflex as the head continues to rotate past the new fixation point. This pattern of slow–fast–slow movements is called *nystagmus* (Fig. 38-23). Clinically, the direction of nystagmus is named for the fast phase of nystagmus.

Spontaneous nystagmus that occurs without head movement or visual stimuli is always pathologic. It seems to appear more readily and more severely with fatigue and to some extent can be influenced by psychological factors. Nystagmus due to a CNS pathologic process, in contrast to vestibular end-organ or vestibulocochlear nerve sources, seldom is accompanied by vertigo. If present, the vertigo is mild. Nystagmus eye movements can be tested by caloric stimulation or rotation (to be discussed).

Vertigo

Disorders of vestibular function are characterized by a condition called *vertigo,* in which an illusion of motion occurs. With vertigo, the person may be stationary and the environment in motion (i.e., objective vertigo) or the person may be in motion and the environment stationary (i.e., subjective vertigo). Persons with vertigo frequently describe a sensation of spinning, "to-and-fro" motion, or falling.

Vertigo should be differentiated from light-headedness, faintness, or syncope.[73–75] Presyncope, which is characterized by a feeling of light-headedness or "blacking out," is commonly caused by postural hypotension (see Chapter 18) or a stenotic lesion in the cerebral circulation that limits blood flow. An inability to maintain normal gait may be described as dizziness despite the absence of objective vertigo. The unstable gait may be caused by disorders of sensory input (e.g., proprioception), peripheral neuropathy, gait problems, or disorders other than vestibular function and usually is corrected by touching a stationary object such as a wall or table.

Vertigo can result from central or peripheral vestibular disorders. Vertigo due to peripheral vestibular disorders tends to be severe in intensity and episodic or brief in duration. In contrast, vertigo due to central vestibular causes tends to be mild and constant and chronic in duration.

Motion Sickness. Motion sickness is a form of normal physiologic vertigo. It is caused by repeated rhythmic stimulation of the vestibular system, such as that encountered in car, air, or boat travel. Vertigo, malaise, nausea, and vomiting are the principal symptoms. Autonomic signs, including lowered blood pressure, tachycardia, and excessive sweating, may occur. Hyperventilation, which commonly accompanies motion sickness, produces changes in blood volume and pooling of blood in the lower extremities, leading to postural hypotension and sometimes to syncope. Some persons experience a variant of motion sickness, complaining of sensing the rocking motion of the boat after returning to ground. This usually resolves after the vestibular system becomes accustomed to the stationary influence of being back on land.

Disorders of Peripheral Vestibular Function

Disorders of peripheral vestibular function occur when signals from the vestibular apparatus are distorted, as in benign paroxysmal positional vertigo, or are unbalanced by unilateral involvement of one of the vestibular organs, as in Ménière disease. The inner ear is vulnerable to injury caused by fracture of the petrous portion of the temporal bones; by infection of nearby structures, including the middle ear and meninges; and by blood-borne toxins and infections. Damage to the vestibular system can occur as an adverse effect of certain drugs or from allergic reactions to foods. The aminoglycosides (e.g., streptomycin, gentamicin) have a specific toxic affinity for the vestibular

portion of the inner ear. Alcohol can cause transient episodes of vertigo. The cause of peripheral vertigo remains unknown in approximately half of the cases.

Severe irritation or damage of the vestibular end-organs or nerves results in severe balance disorders reflected by instability of posture, ataxia, and falling accompanied by vertigo. With irritation, falling is away from the affected side; with destruction, it is toward the affected side. Adaptation to asymmetric stimulation occurs within a few days, after which the signs and symptoms diminish and eventually are lost. After recovery, there usually is a slightly reduced acuity for tilt, and the person walks with a somewhat broadened base to improve postural stability. After adaptation to the loss of vestibular input from one side, the loss of function of the opposite vestibular apparatus produces signs and symptoms identical to those resulting from unilateral rather than bilateral loss. Within weeks, adaptation is again sufficient for locomotion and even for driving a car. Such a person relies heavily on visual and proprioceptive input from muscle and joint sensors and has severe orientation difficulty in the dark, particularly when traversing uneven terrain.

Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional vertigo (BPPV) is the most common cause of pathologic vertigo and usually develops after the fourth decade of life. It is characterized by brief periods of vertigo, usually lasting less than 1 minute, that are precipitated by a change in head position.[76] The most prominent symptom of BPPV is vertigo that occurs in bed when the person rolls into a lateral position. It also commonly occurs when the person is getting in and out of bed, bending over and straightening up, or extending the head to look up. It also can be triggered by amusement rides that feature turns and twists.

Benign paroxysmal positional vertigo is thought to result from damage to the delicate sensory organs of the inner ear, the semicircular ducts, and otoliths (see Fig. 38-22). In persons with BPPV, the calcium carbonate particles (otoliths) from the utricle become dislodged and become free-floating debris within the endolymph of a semicircular canal, most commonly the posterior canal, which is the most dependent part of the inner ear. Movement of the free-floating debris causes this portion of the vestibular system to become more sensitive, such that any movement of the head in the plane parallel to the posterior duct may cause vertigo and nystagmus. There usually is a several-second delay between head movement and onset of vertigo, representing the time it takes to generate the exaggerated endolymph activity. Symptoms usually subside with continued movement, probably because the movement causes the debris to be redistributed throughout the endolymph system and away from the posterior semicircular canal.

Diagnosis is based on tests that involve the use of a change in head position to elicit vertigo and nystagmus. BPPV often is successfully treated with drug therapy to control vertigo-induced nausea. Nondrug therapies using habituation exercises and canalith repositioning are successful in many people. Canalith repositioning involves a series of maneuvers in which the head is moved to different positions in an effort to reposition the free-floating debris in the endolymph of the semicircular canals.

Acute Vestibular Neuronitis

Acute vestibular neuronitis represents an inflammation of the vestibular nerve and is characterized by an acute onset (usually hours) of vertigo, nausea, and vomiting lasting several days and not associated with auditory or other neurologic manifestations. Most persons experience gradual improvement over 1 to 2 weeks, but some develop recurrent episodes.[77,78] A large percentage report an upper respiratory tract illness 1 to 2 weeks before onset of symptoms, suggesting a viral origin. The condition also can occur in persons with herpes zoster oticus. In some persons, attacks of acute vestibulopathy recur over months or years. There is no way to determine whether a person who experiences a first attack will have repeated attacks.

Ménière Disease

Ménière disease is a disorder of the inner ear due to distention of the endolymphatic compartment of the inner ear, causing a triad of hearing loss, vertigo, and tinnitus.[79–81] A number of mechanisms have been postulated, including an increased production of endolymph, decreased production of perilymph accompanied by a compensatory increase in volume of the endolymphatic sac, and decreased absorption of endolymph caused by malfunction of the endolymphatic sac or blockage of endolymphatic pathways.

The cause of Ménière disease is unknown. A number of conditions, such as trauma, infection (e.g., syphilis), and immunologic, endocrine (i.e., adrenal-pituitary insufficiency and hypothyroidism), and vascular disorders have been proposed as possible causes of Ménière disease. The most common form of the disease is an idiopathic form thought to be caused by a single viral injury to the fluid transport system of the inner ear. One area of investigation has been the relation between autoimmune disorders and Ménière disease.

Ménière disease is characterized by fluctuating episodes of tinnitus, feelings of ear fullness, and violent rotary vertigo that often renders the person unable to sit or walk. There is a need to lie quietly with the head fixed in a comfortable position, avoiding all head movements that aggravate the vertigo. Symptoms referable to the autonomic nervous system, including pallor, sweating, nausea, and vomiting, usually are present. The more severe the attack, the more prominent are the autonomic manifestations. A fluctuating hearing loss occurs with a return to normal after the episode subsides. Initially the symptoms tend to be unilateral, resulting in rotary nystagmus caused by an imbalance in vestibular control of eye movements. Because initial involvement usually is unilateral and because the sense of hearing is bilateral, many persons with the disorder are not aware of the full extent

of their hearing loss. However, as the disease progresses, the hearing loss stops fluctuating and progressively worsens, with both ears tending to be affected so that the prime disability becomes one of deafness.[63] The episodes of vertigo diminish and then disappear, although the person may be unsteady, especially in the dark.

Methods used in the diagnosis of Ménière disease include audiograms, vestibular testing by electronystagmography, and petrous pyramid radiographs. The administration of hyperosmolar substances, such as glycerin and urea, often produces acute temporary hearing improvement in persons with Ménière disease and sometimes is used as a diagnostic measure of endolymphatic hydrops. The diuretic furosemide also may be used for this purpose.

The management of Ménière disease focuses on attempts to reduce the distention of the endolymphatic space, and can be medical or surgical. Pharmacologic management consists of suppressant drugs (e.g., prochlorperazine, promethazine, diazepam), which act centrally to decrease the activity of the vestibular system. Diuretics are used to reduce endolymph fluid volume. A low-sodium diet is recommended in addition to these medications. The steroid hormone prednisone may be used to maintain satisfactory hearing and resolve dizziness. Intratympanic gentamicin therapy has been used for ablation of the vestibular system.[81] This treatment is mainly effective in controlling vertigo and does not alter the underlying pathologic process. Surgical methods include the creation of an endolymphatic shunt in which excess endolymph from the inner ear is diverted into the subarachnoid space or the mastoid (endolymphatic sac surgery), and vestibular nerve section. Advances in vestibular nerve section have facilitated the monitoring of CN VII and CN VIII potentials as a means of preventing hearing damage.

Disorders of Central Vestibular Function

Abnormal nystagmus and vertigo can occur as a result of CNS lesions involving the cerebellum and lower brain stem. Central causes of vertigo include brain stem ischemia, tumors, and the demyelinating effects of multiple sclerosis. When brain stem ischemia is the cause of vertigo, it usually is associated with other brain stem signs, such as diplopia, ataxia, dysarthria, or facial weakness. Compression of the vestibular nuclei by cerebellar tumors invading the fourth ventricle results in progressively severe signs and symptoms. In addition to abnormal nystagmus and vertigo, vomiting and a broad-based and dystaxic gait become progressively more evident.

In contrast to peripherally generated nystagmus, CNS-derived nystagmus is relatively constant rather than episodic, can occur in any direction rather than being primarily in the horizontal or torsional (rotatory) dimensions, often changes direction through time, and cannot be suppressed by visual fixation. Repeated induction of nystagmus results in rapid diminution or "fatigue" of the reflex with peripheral abnormalities, but fatigue is not characteristic of central lesions.

Diagnosis and Treatment

Tests of Vestibular Function

Diagnosis of vestibular disorders is based on a description of the symptoms, a history of trauma or exposure to agents that are destructive to vestibular structures, and physical examination. Tests of eye movements (i.e., nystagmus) and muscle control of balance and equilibrium often are used.

Electronystagmography (ENG) is a precise and objective diagnostic method of evaluating nystagmic eye movements. Electrodes are placed lateral to the outer canthus of each eye and above and below each eye, and a ground electrode is placed on the forehead. With ENG, the velocity, frequency, and amplitude of spontaneous or induced nystagmus and the changes in these measurements brought by a loss of fixation, with the eyes open or closed, can be quantified. *Caloric testing* involves elevating the head 30 degrees and irrigating each external auditory canal separately with 30 to 50 mL of ice water. The resulting changes in temperature, which are conducted through the petrous portion of the temporal bone, set up convection currents in the otic fluid that mimic the effects of angular acceleration. In an unconscious person with a functional brain stem and intact vestibulo-ocular reflexes, the eyes exhibit a jerk nystagmus lasting 2 to 3 minutes, with the slow component toward the irrigated ear followed by rapid movement away from the ear. With impairment of brain stem function, the response becomes perverted and eventually disappears. An advantage of the caloric stimulation method is the ability to test the vestibular apparatus on one side at a time. The test is never done on a person who does not have an intact ear drum or those who have blood or fluid collected behind the ear drum.

Rotational testing involves the use of a motor-driven revolving chair or platform. Unlike caloric testing, rotational testing depends only on the inner ear and is unrelated to conditions of the external ear or temporal bone. A major disadvantage of the method is that both ears are tested simultaneously. Motor-driven chairs or platforms can be precisely controlled, and multiple graded stimuli can be delivered in a relatively short period. Testing usually is performed in the dark without visual influence and with selected light stimuli. Eye movements are usually monitored using ENG.

The *Romberg test* is used to demonstrate disorders of static vestibular function. The person being tested is requested to stand with feet together and arms extended forward so that the degree of sway and arm stability can be observed. The person then is asked to close his or her eyes. When visual clues are removed, postural stability is based on proprioceptive sensation from the joints, muscles, and tendons and from static vestibular reception. Deficiency in vestibular static input is indicated by greatly increased sway and a tendency for the arms to drift toward the side of

deficiency. If vestibular input is severely deficient, the subject falls toward the deficient side.

Treatment of Vestibular Disorders

Pharmacologic Treatment. Depending on the cause, vertigo may be treated pharmacologically.[82] There are two types of drugs used in the treatment of vertigo. First are the drugs used to suppress the illusion of motion. These include drugs such as antihistamines (e.g., meclizine, cyclizine, dimenhydrinate, and promethazine) and anticholinergic drugs (e.g., scopolamine, atropine) that suppress the vestibular system. Although the antihistamines have long been used in treating vertigo, little is known about their mechanism of action. The second type includes drugs used to relieve the nausea and vomiting that commonly accompany the condition. Antidopaminergic drugs (e.g., phenothiazines) and benzodiazepines commonly are used for this purpose.

Vestibular Rehabilitation. Vestibular rehabilitation, a relatively new treatment modality for peripheral vestibular disorders, has met with considerable success.[83,84] It commonly is done by physical therapists and uses a home exercise program that incorporates habituation exercises, balance retraining exercises, and a general conditioning program. The habituation exercises take advantage of physiologic fatigue of the neurovegetative response to repetitive movement or positional stimulation and are done to decrease motion-provoked vertigo, light-headedness, and unsteadiness. The exercises are selected to provoke the vestibular symptoms. The person moves quickly into the position that causes symptoms, holds the position until the symptoms subside, relaxes, and then repeats the exercise for a prescribed number of times. The exercises usually are repeated twice daily. The habituation effect is characterized by decreased sensitivity and duration of symptoms. It may occur in as little as 2 weeks or take as long as 6 months.

Balance retraining exercises consist of activities directed toward improving individual components of balance that may be abnormal. General conditioning exercises, a vital part of the rehabilitation process, are individualized to the person's preferences and lifestyle. They should consist of motion-oriented activity that the person is interested in and should be done on a regular basis, usually four to five times per week.

In summary, the vestibular system plays an essential role in the equilibrium sense, which is closely integrated with the visual and proprioceptive (position) senses. Receptors for the vestibular system, in the semicircular ducts of the inner ear, respond to changes in linear and angular acceleration of the head. The vestibular nerve fibers travel in CN VIII to the vestibular nuclei at the junction of the medulla and pons; some fibers pass through the nuclei to the cerebellum.

Disorders of peripheral vestibular function, which involve the inner ear sensory organs, include Ménière disease and BPPV. Ménière disease, which is caused by an overaccumulation of endolymph, is characterized by severe, disabling episodes of tinnitus, feelings of ear fullness, and violent rotary vertigo. BPPV is thought to be caused by free-floating particles in the posterior semicircular canal. It presents as a sudden onset of dizziness or vertigo that is provoked by certain changes in head position. Among the methods used in treatment of the vertigo that accompanies vestibular disorders are habituation exercises (for BPPV) and antivertigo drugs.

REVIEW EXERCISES

1. The mother of a 3-year-old boy notices that his left eye is red and watering when she picks him up from day care. He keeps rubbing his eye as though it itches. The next morning, however, she notices that both eyes are red, swollen, and watering. Being concerned, she takes him to the pediatrician in the morning and is told that he has "pink eye." She is told that the infection should go away by itself.

A. What part of the eye is involved?
B. What type of conjunctivitis do you think this child has (bacterial, viral, or allergic)?
C. Why didn't the pediatrician order an antimicrobial drug?
D. Is the condition contagious? What measures should she take to prevent its spread?

2. During a routine eye examination to get new glasses because she had been having difficulty with her distant vision, a 75-year-old woman is told that she is developing cataracts.

A. What types of visual changes occur as the result of a cataract?
B. What can the woman do to prevent the cataracts from getting worse?
C. What treatment may she eventually need?

3. A 50-year-old woman is told by her eye doctor that her intraocular pressure is slightly elevated and that although there is no evidence of damage to her eyes at this time, she is at risk for developing glaucoma and should have regular eye examinations.

A. Describe the physiologic mechanisms involved in the regulation of intraocular pressure.
B. Differentiate between open-angle and angle-closure glaucoma in terms of their pathology, manifestations, and treatment.
C. Use Figure 38-7 to relate the "optic disk cupping" that occurs with glaucoma to the visual field loss that occurs with the disorder.

4. The parents of a newborn infant have been told that their son has congenital cataracts and will require cataract surgery to prevent losing his sight.

A. Explain why the infant is at risk for losing his sight if the cataracts are not removed.
B. When should this procedure be done to prevent loss of vision?

5. A mother notices that her 13-month-old child is fussy and tugging at his ear and refuses to eat his breakfast. When she takes his temperature, it is 100°F. Although the child attends day care, his mother has kept him home and made an appointment with the child's pediatrician. In the physician's office, his temperature is 100.2°F, he is somewhat irritable, and he has a clear nasal drainage. His left tympanic membrane shows normal landmarks and motility on pneumatic otoscopy. His right tympanic membrane is erythematous and there is decreased motility on pneumatic otoscopy.

A. What risk factors are present that predispose this child to the development of acute otitis media?
B. Are his signs and symptoms typical of otitis media in a child of this age?
C. What are the most likely pathogens? What treatment would be indicated?
D. Later in the week, the mother notices that the child does not seem to hear as well as he did before developing the infection. Is this a common occurrence, and should the mother be concerned about transient hearing loss in a child of this age?

6. A granddaughter is worried that her grandfather is "losing his hearing." Lately, he has been staying away from social gatherings that he always enjoyed, saying everybody mumbles. He is defiant in maintaining that there is nothing wrong with his hearing. However, he does complain that his ears have been ringing a lot lately.

A. What are common manifestations of hearing loss in the elderly?
B. What type of evaluation would be appropriate for determining if this man has a hearing loss, and the extent of his hearing loss?
C. What are some things the granddaughter might do so that her grandfather could hear her better when she is talking to him?

7. A 70-year-old man complains that he gets this terrible feeling "like the room is moving around" and becomes nauseated when he rolls over in bed or bends over suddenly. It usually goes away once he has been up for a while. He has been told that his symptoms are consistent with benign paroxysmal positional vertigo.

A. What is the pathophysiology associated with this man's vertigo?
B. Why do the symptoms subside once he has been up for a while?
C. What methods are available for treatment of the disorder?

REFERENCES

1. Lighthouse International. *About us*. [Online] Available: http://www.lighthouse.org. Accessed October 31, 2009.
2. Ross M.H., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 834–856, 866–883). Philadelphia: Lippincott Williams & Wilkins.
3. Garcia-Ferrier F., Schwab J.R., Shetlar D.J. (2008). Conjunctivitis. In Riordan-Eva P., Whitcher J.P. (Eds.), *Vaughan & Ashbury's general ophthalmology* (17th ed., pp. 98–125). New York: Lange Medical Books/McGraw-Hill.
4. Pasternak A., Irish B. (2004). Ophthalmologic infections in primary care. *Clinics in Family Practice* 6(1), 19–33.
5. Leibowitz H.M. (2000). The red eye. *New England Journal of Medicine* 343(5), 345–351.
6. Rubin E., Strayer D.S. (Eds.). (2008). *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 335–336, 1247–1266). Philadelphia: Lippincott Williams & Wilkins.
7. Ono S.J., Abelson M.B. (2006). Allergic conjunctivitis: Update on pathophysiology and prospects for future treatment. *Journal of Allergy and Clinical Immunology* 115(1), 118–122.
8. Biswell R. (2008). Cornea. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (17th ed., pp. 126–150). New York: Lange Medical Books/McGraw-Hill.
9. Pepose J.S., Keadle T.L., Morrison L.A. (2006). Ocular herpes simplex: Changing epidemiology, emerging disease patterns, and potential of vaccine prevention and therapy. *American Journal of Ophthalmology* 141, 547–557.
10. Shaikh S., Ta C. (2002). Evaluation and management of herpes zoster ophthalmicus. *American Family Physician* 66, 1723–1732.
11. Dart J.K.G., Saw V.P.L., Kilvington S. (2009). Acanthamoeba keratitis: Diagnosis and treatment update 2009. *American Journal of Ophthalmology* 148(4), 487–499.
12. Albiani D.A., Campbell R.J., Hodge W.G. (2008). Corneal graft rejections. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (16th ed., pp. 346–348). New York: Lange Medical Books/McGraw-Hill.
13. Harper R.A., Shock J.P. (2004). Lens. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (16th ed., pp. 212–229). New York: Lange Medical Books/McGraw-Hill.
14. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp, 613–650, 651–662, 692–697). Philadelphia: Elsevier Saunders.
15. Packer M., Fine H., Hoffman R.S. (2006). Refractive lens surgery. *Ophthalmology Clinics of North America* 19, 77–88.
16. Abraham A.G., Condon N.G., Gower E.W. (2006). The new epidemiology of cataract. *Ophthalmology Clinics of North America* 19, 415–425.
17. Asbell P.A., Dualan I., Mindel J., et al. (2005). Age-related cataract. *Lancet* 365, 599–609.
18. Jobling A.J., Augusteyn R.C. (2002). What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. *Clinical and Experimental Optometry* 852, 61–75.
19. Kandel E.R., Schwartz J.H., Jessell T.M. (2000). *Principles of neural science* (4th ed., pp. 523–547, 591–624, 801–815). New York: McGraw-Hill.

20. Fletcher E.C., Chong G.V., Shetler D.J. (2008). Retina. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (17th ed., pp. 186–209). New York: Lange Medical Books/McGraw-Hill.
21. Riordan-Eva P. (2008). Neuro-ophthalmology. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (16th ed., pp. 259–304). New York: Lange Medical Books/McGraw-Hill.
22. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1345–1368). Philadelphia: Saunders Elsevier.
23. Frank R.N. (2004). Diabetic retinopathy. *New England Journal of Medicine* 350(1), 48–58.
24. Fong D.S., Aiello L., Ferris F.L., et al. (2004). Diabetic retinopathy. *Diabetes Care* 27(10), 2540–2553.
25. Cuilla T.A., Amador A.G., Zinman B. (2003). Diabetic retinopathy and diabetic macular edema. *Diabetes Care* 26, 2653–2664.
26. Wong T.Y., Mitchell P. (2004). Hypertensive retinopathy. *New England Journal of Medicine* 351(22), 2310–2317.
27. Gariano R.F., Chang-Hee K. (2004). Evaluation and management of suspected retinal detachment. *American Family Physician* 69(7), 1691–1698.
28. Gottlieb J.L. (2002). Age-related macular degeneration. *JAMA* 288(18), 2233–2236.
29. Coleman H.R., Chan C-C., Ferris F.L. III., et al. (2008). Age-related macular degeneration. *Lancet* 372, 1835–1845.
30. Nowak J.Z. (2006). Age-related macular degeneration (AMD): Pathogenesis and therapy. *Pharmacological Reports* 58, 353–363.
31. Salmon J.F. (2008). Glaucoma. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (17th ed., pp. 212–228). New York: Lange Medical Books/McGraw-Hill.
32. Kwon Y.H., Fingert J.H., Kuehn M.H., et al. (2009). Primary open-angle glaucoma. *New England Journal of Medicine* 360(11), 1113–1124.
33. Distellhorst J.S., Hughes G.M. (2003). Open-angle glaucoma. *American Family Physician* 67, 1937–1950.
34. Singh A. (2005). Medical therapy of glaucoma. *Ophthalmology Clinics of North America* 18, 397–408.
35. Kipp M.A. (2003). Childhood glaucoma. *Pediatric Clinics of North America* 50, 89–104.
36. West C.E., Asbury T. (2008). Strabismus. In Riordan-Eva P. (Ed.), *Vaughan & Ashbury's general ophthalmology* (17th ed., pp. 229–248). New York: Lange Medical Books/McGraw-Hill.
37. Donahue S.P. (2007). Pediatric strabismus. *New England Journal of Medicine* 356(10), 1040–1047.
38. Ticho B.H. (2003). Strabismus. *Pediatric Clinics of North America* 50, 173–188.
39. Mittelman D. (2003). Amblyopia. *Pediatric Clinics of North America* 50, 189–196.
40. Doshi N.R., Rodriguez M.L (2007). Amblyopia. *American Family Physician* 73, 361–367.
41. Wu C., Hunter D.G. (2006). Amblyopia: Diagnostic and therapeutic options. *American Journal of Ophthalmology* 141(1), 175–184.
42. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine Section of Ophthalmology. (2003). Eye examination in infants, children, and young adults by pediatrician. *Pediatrics* 111(4), 902–907.
43. InfantSEE. (2007). *The infantSEE assessment explained*. [Online] Available: http://www.infantsee.org. Accessed June 27, 2010.
44. Moore K.L., Dallen A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 1022–1043). Philadelphia: Lippincott Williams & Wilkins.
45. McCarter D.F., Pollart S.M. (2007). Cerumen impaction. *American Family Physician* 75(10), 1523–1530.
46. Lustig L.R., Schindler J. (2009). Ear, nose & throat. In Tierney L.M., McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (49th ed., pp. 173–186). New York: McGraw-Hill Medical.
47. Danner C.J. (2006). Eustachian tube function and the middle ear. *Otolaryngologic Clinics of North America* 39, 1221–1235.
48. Kerschner J.E. (2007). Otitis media. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2632–2646). Philadelphia: Saunders Elsevier.
49. Kalyanakrishnan R., Sparks R.A., Berryhill W.E. (2007). Diagnosis and treatment of otitis media. *American Family Physician* 76, 1650–1660.
50. Bhetwal N., McConaghy J.R. (2007). The evaluation and treatment of children with acute otitis media. *Primary Care Clinics in Office Practice* 34, 59–70.
51. American Academy of Pediatrics and American Academy of Family Physicians. (2004). Diagnosis and management of acute otitis media. *Pediatrics* 113, 1451–1465.
52. American Academy of Pediatrics and American Academy of Family Physicians. (2004). Otitis media with effusion. *Pediatrics* 113, 1412–1429.
53. Semann M.T., Mergerian C.A. (2006). The pathophysiology of cholesteatoma. *Otolaryngologic Clinics of North America* 39, 1143–1159.
54. Holt J.J. (2003). Cholesteatoma and otosclerosis. *Clinical Medicine & Research* 1(2), 151–154.
55. Siddig M.A. (2006). Otosclerosis: A review of aetiology, management and outcomes. *British Journal Hospital Medicine* 67(9), 472–476.
56. Lockwood A.H. (2005). Tinnitus. *Neurologic Clinics* 23, 893–900.
57. Noell C.A., Meyerhoff W.L. (2003). Tinnitus: Diagnosis and treatment of this elusive symptom. *Geriatrics* 58(2), 28–34.
58. Møller A.R. (2003. Pathophysiology of tinnitus. *Otolaryngologic Clinics of North America* 36, 246–266.
59. National Institute on Deafness and Other Communication Disorders. (2008). *Statistics about hearing disorders, ear infections, and deafness*. [Online] Available: http://www.nidcd.nih.gov/health/statistics/hearing.asp. Accessed November 1, 2009.
60. Nadol J.G. (1993). Hearing loss. *New England Journal of Medicine* 329, 1092–1101.
61. Kozak A.T. (2009). Hearing loss. *Otolaryngology Clinics of North America* 42, 79–85.
62. Willems P.J. (2000). Genetic causes of hearing loss. *New England Journal of Medicine* 342, 1101–1109.
63. Isaacson J.E., Vora N.M. (2003). Differential diagnosis and treatment of hearing loss. *American Family Physician* 68(5), 1125–1132.
64. Palmer C.V., Ortmann A. (2005). Hearing loss and hearing aids. *Neurologic Clinics* 23, 901–918.
65. National Institute of Deafness and Other Communicative Disorders. (2009). *Cochlear implants*. [Online] Available: http://www.nidcd.nih.gov/health/hearing/coch.htm#c. Accessed November 2, 2009.
66. Papsin B.C., Gordon K.A. (2007). Cochlear implants for children with severe-to-profound hearing loss. *New England Journal of Medicine* 357(23), 2380–2387.
67. Katbamna B., Patel D.R. (2008). Hearing impairment in children. *Pediatric Clinics of North America* 55, 1175–1188.
68. Haddad J. (2007). Hearing loss. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2632–2646). Philadelphia: Saunders Elsevier.
69. Wrightson A.S. (2007). Universal newborn hearing screening. *American Family Physician* 75(9), 1349–1352.
70. Joint Committee on Infant Hearing. (2007). Year 2007 position statement: Principles and guidelines for early hearing detection and intervention program. *Pediatrics* 120(4), 898–921.
71. Gates G.A., Mills J.H. (2005). Presbycusis. *Lancet* 366, 1111–1119.

72. Bance M. (2007). Hearing and aging. *Canadian Medical Association Journal* 176(7), 925–927.
73. Chawla N., Olshaker J.S. (2006). Diagnosis and management of dizziness and vertigo. *Medical Clinics of North America* 90, 291–304.
74. Labuguen R.H. (2006). Initial evaluation of vertigo. *American Family Physician* 73(2), 244–254.
75. Schwartz R., Longwell B. (2005). Treatment of vertigo. *American Family Physician* 71(6), 1115–1130.
76. Parnes L.S., Agrawal S.K., Atlas J. (2003). Diagnosis and management of benign paroxysmal positional vertigo (BPPV). *Canadian Medical Association Journal* 169(7), 681–693.
77. Hotson J.R., Baloh R.W. (1998). Acute vestibular syndrome. *New England Journal of Medicine* 339, 680–685.
78. Baloh R.W. (2003). Vestibular neuritis. *New England Journal of Medicine* 348(11), 1027–1032.
79. da Costa S.S., de Sousa L.C., de Toledo Piza M.R. (2002). Ménière's disease: Overview, epidemiology, and natural history. *Otolaryngology Clinics of North America* 35, 455–495.
80. Paparella M.M., Djalilian H.R. (2002). Etiology, pathophysiology of symptoms and pathogenesis of Ménière's disease. *Otolaryngology Clinics of North America* 35, 529–545.
81. Hollis L., Bottrill I. (1999). Ménière's disease. *Hospital Medicine (London)* 60, 574–578.
82. Hain T.C., Yacovino D. (2005). Pharmacologic treatment of persons with vertigo. *Neurologic Clinics* 23, 831–853.
83. Wrisley D.M., Pavlou M. (2005). Physical therapy for balance disorders. *Neurologic Clinics* 23, 855–874.
84. Hall C. (2009). The role of vestibular rehabilitation in the balance disorder patient. *Otolaryngology Clinics of North America* 42, 161–169.

UNIT 11

Genitourinary and Reproductive Function

Physiologic Basis of Male Reproductive Function
- *Testicular Function*
  - Hormone Production
  - Spermatogenesis and Semen Production
  - Hypothalamic/Pituitary Control of Testicular Function
- *Neural Control of Male Sexual Function*
  - Erectile Dysfunction

Disorders of the Penis, the Scrotum and Testes, and the Prostate
- *Disorders of the Penis*
  - Inflammation and Infection
  - Peyronie Disease
  - Priapism
  - Neoplasms of the Penis
- *Disorders of the Scrotum and Testes*
  - Disorders of the Testicular Tunica
  - Testicular Torsion
  - Epididymitis and Orchitis
  - Neoplasms of the Scrotum and Testes
- *Disorders of the Prostate*
  - Prostatitis
  - Benign Prostatic Hyperplasia
  - Cancer of the Prostate

Disorders in Childhood and Aging Changes
- *Disorders of Childhood*
  - Hypospadias and Epispadias
  - Phimosis and Paraphimosis
  - Cryptorchidism
- *Aging Changes*

Chapter 39

Disorders of the Male Genitourinary System

The male genitourinary system is subject to a number of structural and functional disorders, all of which can affect urine elimination, sexual function, and fertility. This chapter is divided into three parts: (1) the physiologic basis of male reproductive function, including hormone production, spermatogenesis, and neural control of sexual function; (2) disorders of the male genitourinary structures, including the penis, scrotum and testes, and prostate gland; and (3) disorders of childhood and changes that occur as a result of the aging process.

Physiologic Basis of Male Reproductive Function

The male genitourinary system is composed of the paired gonads, or testes; genital ducts; accessory genital organs; and penis (Fig. 39-1). The testes function in the production of androgens or male sex hormones and spermatozoa; the ductile system aids in the storage and transport of spermatozoa; and the accessory genital organs produce the fluid constituents of semen. The penis functions in both urine elimination and sexual function.

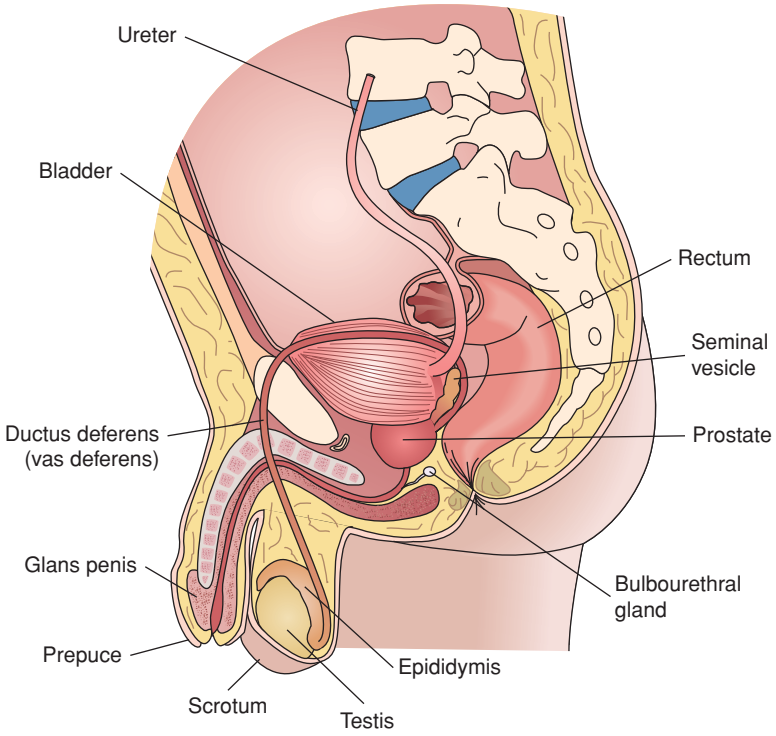


FIGURE 39-1. Structures of the male reproductive system, including the testes, the scrotum, and the excretory ducts.

Testicular Function

The two primary functions of the testes or male gonads are *steroidogenesis*, or synthesis of androgens or male sex hormones, and *spermatogenesis*, or sperm production.[1–3] The testes are paired ovoid organs that lie within the scrotum, which hangs outside the abdominal cavity. The testes are surrounded by two tunics. The outer tunic is the two-layered tunica vaginalis derived from the peritoneum. Deep to this is the *tunica albuginea*, the dense connective tissue capsule of the testes (Fig. 39-2). Septal extensions of the tunica albuginea divide the testes into 200 to 300 wedge-shaped compartments or lobules. Each lobule contains one to four tightly coiled *seminiferous tubules*, in which sperm are produced, and a connective tissue stroma, in which the androgen-producing *Leydig* or *interstitial cells* are located.

Male Reproductive System

- The male genitourinary system functions in both urine elimination and reproduction.
- The testes function in both production of male germ cells (spermatogenesis) and secretion of the male sex hormone, testosterone.
- The ductile system (epididymides, vas deferens, and ejaculatory ducts) transports and stores sperm, and assists in their maturation; and the accessory glands (seminal vesicles, prostate gland, and bulbourethral glands) prepare the sperm for ejaculation.
- Sperm production requires temperatures that are 2°C to 3°C below body temperature. The position of the testes in the scrotum and the unique blood flow cooling mechanisms provide this environment.
- The urethra, which is enclosed in the penis, is the terminal portion of the male genitourinary system. Because it conveys both urine and semen, it serves both urinary and reproductive functions.

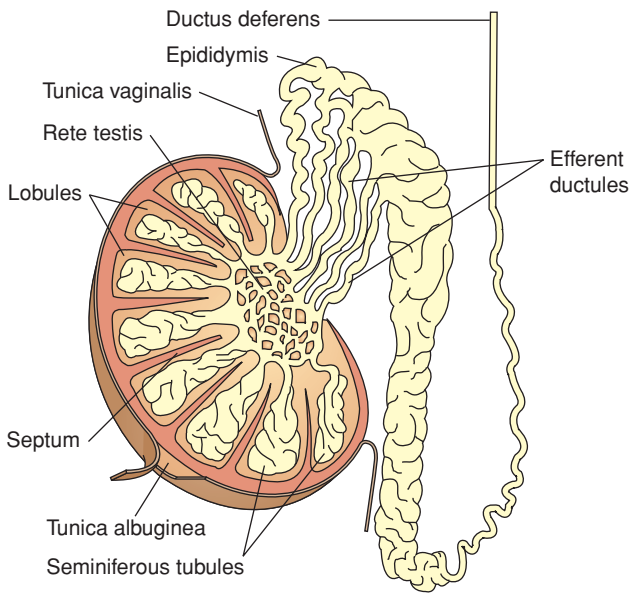


FIGURE 39-2. The parts of the testes and epididymis.

Hormone Production

The testes produce several male sex hormones, including *testosterone, dihydrotestosterone,* and *androstenedione.*[1–3] Testosterone, which is the most abundant of these hormones, is considered the main testicular hormone. The adrenal cortex also produces androgens, albeit in much smaller quantities (<5% of the total male androgens) than the testes. Larger amounts of testosterone are formed from dihydrotestosterone and androstenedione in other tissues of the body, especially the liver.[1] In addition to testosterone, small amounts of estrogens are formed in the male. Some of this estrogen, thought to be formed from testosterone, plays an important role in spermatogenesis.

Testosterone is metabolized in the liver and excreted by the kidneys. In the bloodstream, testosterone exists in an unbound (free) or a bound form. The bound form is attached to plasma proteins, including albumin and the sex hormone–binding protein produced by the liver. Only approximately 3% of circulating testosterone is unbound and therefore able to enter the cell and exert its metabolic effects.[1] Much of the testosterone that becomes fixed to the tissues is converted to dihydrotestosterone, especially in certain target tissues such as the prostate gland. Some of the actions of testosterone depend on this conversion, whereas others do not.

Testosterone exerts a number of biologic effects in the male (Chart 39-1). In the male embryo, testosterone is essential for appropriate differentiation of the internal and external genitalia, and it is necessary for descent of the testes in the fetus. Testosterone is essential to the development of primary and secondary male sex characteristics during puberty and for the maintenance of these characteristics during adult life. It causes growth of pubic, chest, and facial hair; it produces changes in the larynx that result in the male bass voice; and it increases the thickness of the skin and the activity of the sebaceous glands, predisposing to acne.

Most of the actions of testosterone and other androgens result from increased protein synthesis in target tissues.

CHART 39-1 Main Actions of Testosterone

- Induces differentiation of the male genital tract during fetal development
- Induces development of primary and secondary sex characteristics
  - Gonadal function
  - External genitalia and accessory organs
  - Male voice timbre
  - Male skin characteristics
  - Male hair distribution
- Anabolic effects
  - Promotes protein metabolism
  - Promotes musculoskeletal growth
  - Influences subcutaneous fat distribution
- Promotes spermatogenesis (in FSH-primed tubules) and maturation of sperm
- Stimulates erythropoiesis

Androgens function as anabolic agents in males and females to promote metabolism and musculoskeletal growth. Testosterone and the androgens have a great effect on the development of increasing musculature during puberty, with boys averaging approximately 50% more of an increase in muscle mass than girls.[1]

Spermatogenesis and Semen Production

Spermatogenesis, which occurs in the seminiferous tubules of the testes, is the sequence of events that leads to the formation of male germ cells or spermatozoa. The process begins shortly before puberty and continues throughout a man's life.

The seminiferous tubules are composed of two types of cells: Sertoli cells and spermatogenic cells[1–3] (Fig. 39-3A). Sertoli cells are tall columnar cells with extensive

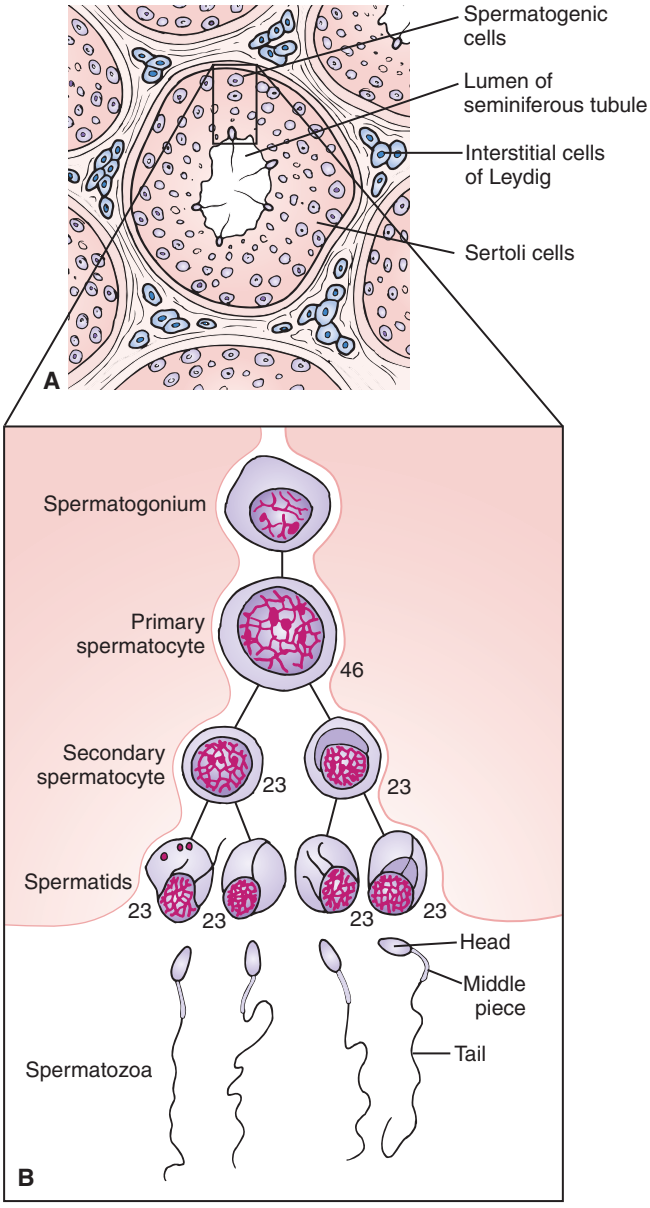


FIGURE 39-3. **(A)** Cross-section of seminiferous tubule and **(B)** stages of development of spermatozoa. (46, 23 = number of chromosomes.)

cytoplasmic processes that surround the spermatogenic cells and form tight junctions with other Sertoli cells. Also known as *supporting* or *sustentacular cells*, Sertoli cells provide structural organization for the tubules; they supply both physical and nutritional support for the developing germ cells; and their tight junctions prevent the passage of proteins from the interstitial space into the lumen of the seminiferous tubules, thus forming a blood-testis barrier.[2,3] In addition, these cells have been shown to be responsible for the movement of spermatozoa from the base of the tubule toward the lumen and for the release of mature sperm into the lumen. They also phagocytose damaged germ cells and residual bodies formed during the last stage of spermatogenesis. Finally, in response to follicle-stimulating hormone (FSH) or testosterone, the Sertoli cells secrete androgen-binding protein. This substance, which has a high affinity for androgens, provides high concentrations of testosterone to the developing germ cells during spermatogenesis.

Spermatogenic cells, the source of spermatozoa, are organized in poorly defined layers of progressive development between adjacent Sertoli cells. Both spermatogenesis and oogenesis, its counterpart in the female, involve a unique kind of nuclear division in which the chromosome number is reduced from 46 to 23 (see Chapter 5). The process of spermatogenesis begins with the spermatogonial phase, during which the spermatogonia undergo mitotic division to form more spermatogonia as well as primary spermatocytes (Fig. 39-3B). During the next phase of spermatogenesis, the primary spermatocyte undergoes meiotic division during which its 46 chromosomes (23 pairs) are divided so that 23 chromosomes go to one secondary spermatocyte and the other 23 to another secondary spermatocyte. During the final stage of spermatogenesis, the secondary spermatocytes divide to form spermatids, which develop into mature spermatozoa or sperm cells.

Ductile Transport. After their development in the seminiferous tubules, the spermatozoa move into a highly convoluted network of ducts called the *rete testis* (Fig. 39-2). The spermatozoa are then transported through the efferent ductules and into a single duct called the *epididymis*, which is the final site for sperm maturation.[1,2] The epididymis also serves as a reservoir for sperm. Sperm can be stored in the epididymis for several months. If held longer they are eventually phagocytized by the epithelial cells of the epididymis. When the male is sexually stimulated and ejaculates, the smooth muscle in the wall of the epididymis contracts vigorously, moving sperm into the next segment of the ductal system, the *ductus deferens*, also called the *vas deferens* (Fig. 39-4). The ductus deferens ascends along the posterior border of the testes and then enters the abdomen in the spermatic cord, which serves as a conduit for all of the structures passing to and from the testes. After leaving the spermatic cord, the ductus deferens descends in the pelvis to the level of the bladder, where its distal end enlarges to form the *ampulla*. Surgical disconnection of the vas deferens in the scrotal area (i.e., vasectomy) serves as an effective method of male contraception. Because sperm are stored in the ampulla, men can remain fertile for 4 to 5 weeks after performance of a vasectomy.

Accessory Genital Glands. The accessory genital glands include the paired seminal vesicles and bulbourethral glands and the single prostate gland (Fig. 39-1).[1,2] These glands secrete fluids that form the bulk of the ejaculatory fluid or semen.

The seminal vesicles, which lie on the posterior wall of the bladder, consist of highly tortuous tubes that secrete

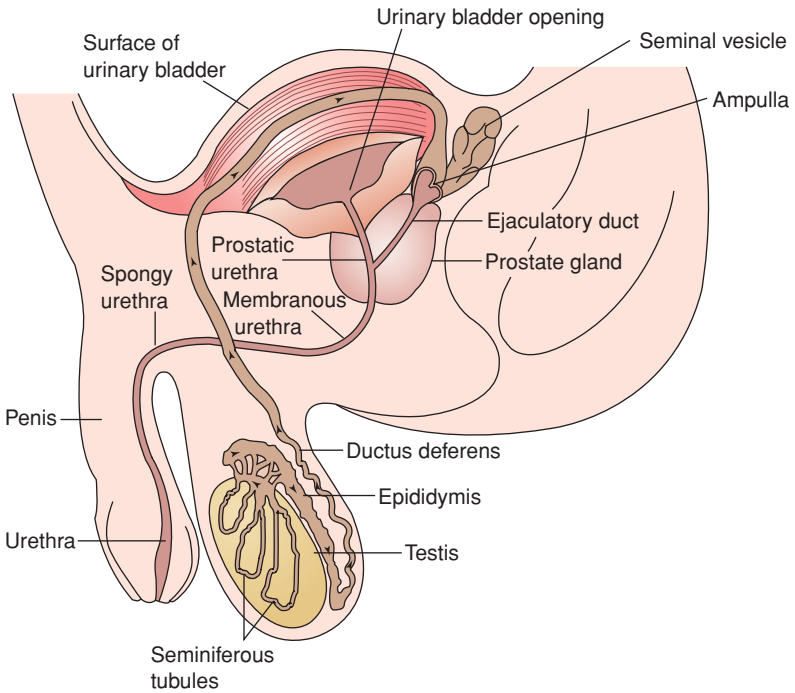


FIGURE 39-4. The excretory ducts of the male reproductive system and the path that sperm follows as it leaves the testis and travels to the urethra.

fluid for the semen. Each of the paired seminal vesicles is lined with secretory epithelium containing an abundance of fructose, prostaglandins, and several other proteins. The fructose secreted by the seminal vesicles provides the energy for sperm motility. The prostaglandins are thought to assist in fertilization by making the cervical mucus more receptive to sperm and by causing reverse peristaltic contractions in the uterus and fallopian tubes to move the sperm toward the ovaries. A short excretory duct from the each seminal vesicle combines with the ampulla of the ductus deferens to form the ejaculatory duct, which enters the posterior part of the prostate and continues through until it ends in the prostatic portion of the urethra. Contraction of the smooth muscle coat of the seminal vesicles during ejaculation discharges their secretion into the ejaculatory ducts and helps to flush sperm out of the urethra.

The prostate, which is the largest of the accessory glands, is located in the pelvis, inferior to the bladder, where it surrounds the prostatic portion of the urethra. The prostate gland secretes a thin, milky, alkaline fluid containing citric acid, calcium, acid phosphate, a clotting enzyme, and a profibrinolysin.[2] During ejaculation, the capsule of the prostate contracts, and the added fluid increases the bulk of the semen. Both vaginal secretions and the fluid from the vas deferens are strongly acidic. Because sperm mobilization occurs at a pH of 6.0 to 6.5, the alkaline nature of the prostatic secretions is essential for successful fertilization of the ovum.

The bulbourethral glands are peanut-sized glands located on either side of the membranous urethra. A duct of each gland joins the initial portion of the penile urethra. The glands, which structurally resemble mucus-secreting glands, produce a clear mucuslike secretion.[2] Sexual stimulation causes release of the secretion, which constitutes the major portion of the preseminal fluid and serves to lubricate the penile urethra.

Hypothalamic/Pituitary Control of Testicular Function

The hypothalamus and the anterior pituitary gland play an essential role in promoting spermatogenesis in the testes and maintaining the endocrine function of the testes by means of the gonadotropic hormones (i.e., anterior pituitary hormones that promote the function and growth of the testes in the male).[1,3] The synthesis and release of the gonadotropic hormones from the pituitary gland are regulated by gonadotropin-releasing hormone (GnRH), which is synthesized by the hypothalamus and secreted into the hypothalamohypophysial portal circulation (Fig. 39-5).

Two gonadotropic hormones are secreted by the pituitary gland: FSH and luteinizing hormone (LH). In the male, LH also is called *interstitial cell–stimulating hormone*. The production of testosterone by the interstitial cells of Leydig is regulated by LH. FSH binds selectively to Sertoli cells surrounding the seminiferous tubules, where it functions in the initiation of spermatogenesis. Under the influence of FSH, Sertoli cells produce androgen-binding protein, plasminogen activator, and inhibin.

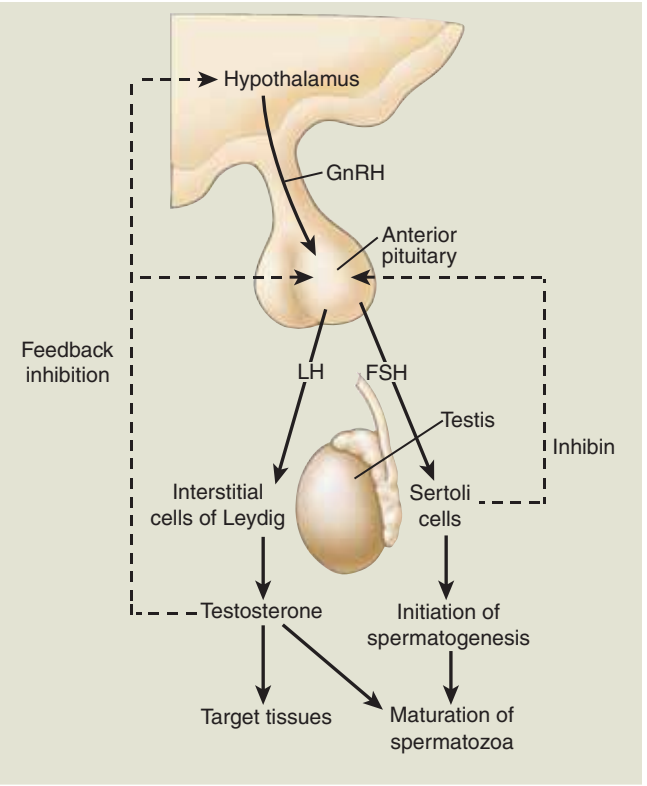


FIGURE 39-5. Hypothalamic-pituitary feedback control of spermatogenesis and testosterone levels in the male. The *dashed line* represents negative feedback. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Androgen-binding protein binds testosterone and serves as a carrier and storage site for testosterone in Sertoli cells. Although FSH is necessary for the initiation of spermatogenesis, full maturation of the spermatozoa requires testosterone. Androgen-binding protein also serves as a carrier of testosterone from the testes to the epididymis. Plasminogen activator, which converts plasminogen to plasmin, functions in the final detachment of mature spermatozoa from Sertoli cells.

Circulating levels of the gonadotropic hormones are regulated in a negative feedback manner by testosterone.[1,3] High levels of testosterone suppress LH secretion through a direct action on the pituitary and an inhibitory effect on the hypothalamus. FSH is thought to be inhibited by a substance called *inhibin,* produced by Sertoli cells. Although two forms of inhibin have been identified, only inhibin B has been found in males.[3] Inhibin suppresses FSH release from the pituitary gland without effecting LH release. The pituitary gonadotropic hormones and Sertoli cells in the testes form a classic negative feedback loop in which FSH stimulates inhibin secretion and increased inhibin levels suppress FSH release from the hypothalamus. Unlike the cyclic hormonal pattern in the woman, in the man, FSH, LH, and testosterone secretion and spermatogenesis occur at relatively unchanging rates during adulthood.

Neural Control of Male Sexual Function

The penis is the male external genital organ through which the urethra passes. It functions both as a sexual organ and as an organ of urine elimination. Anatomically, the external penis consists of a shaft that ends in a tip called the *glans* (Fig. 39-1). The loose skin of the penis shaft folds to cover the glans, forming what is called the *prepuce*, or *foreskin*. It is the foreskin that is removed during circumcision. The glans of the penis contains many sensory nerves, making this the most sensitive portion of the penile shaft. The cylindrical body or shaft of the penis is composed of three masses of erectile tissue held together by fibrous strands and covered with a thin layer of skin (Fig. 39-6B). The two dorsal masses of tissue are called the *corpora cavernosa* and the third ventral mass, in which the spongy part of the urethra is enclosed, is called the *corpus spongiosum*.[2] The corpora cavernosa and corpus spongiosum are cavernous sinuses that normally are relatively empty but become engorged with blood during penile erection.

The physiology of the male sex act involves a complex interaction between autonomic nervous system–mediated spinal cord reflexes, higher neural centers, and the vascular system[1,2] (Fig. 39-6A). It involves erection, emission, ejaculation, and detumescence. *Erection* involves increased inflow of blood into the corpora cavernosa and penile rigidity, *emission* is the contraction of the vas deferens and ampulla with expulsion of sperm into the internal urethra, and *ejaculation* is the expulsion of semen from the urethra. *Detumescence*, or penile relaxation, results from outflow of blood from the corpora cavernosa.

The penis is innervated by both the autonomic and somatic nervous systems. In the pelvis, the sympathetic and parasympathetic components of the autonomic nervous system merge to form what are called the *cavernous nerves*.[4] Erection is under the control of the parasympathetic nervous system, and ejaculation and detumescence are under the control of the sympathetic nervous system. Somatic innervation, which occurs through the pudendal nerve, is responsible for penile sensation and contraction and relaxation of the extracorporeal striated bulbocavernosus and ischiocavernous muscles.

Erection is a neurovascular process involving the autonomic nervous system, neurotransmitters and endothelial relaxing factors, the vascular smooth muscle of the arteries and veins supplying the penile tissue, and the trabecular smooth muscle of the sinusoids of the corpora cavernosa.[4] It involves increased inflow of blood into the corpora cavernosa due to relaxation of the trabecular smooth muscle that surrounds the sinusoidal spaces and compression of the veins controlling outflow of blood from the venous plexus. Erection is mediated by parasympathetic impulses that pass from the sacral segments of the spinal cord through the pelvic nerves to the penis. Parasympathetic stimulation results in release of nitric oxide, a nonadrenergic-noncholinergic neurotransmitter,

Disorders of Penile Erection

- Erection is a neurovascular process involving the autonomic nervous system, the somatic nervous system by way of the pudendal nerve, the vascular system, and the sinusoidal spaces of the corpora cavernosa.
- Parasympathetic innervation through the pelvic nerves initiates relaxation of the trabecular smooth muscle of the corpora cavernosa through the action of nitric oxide, the inflow of arterial blood, and cessation of venous outflow.
- Erectile failure can result from disorders in one or a combination of the neural, vascular, or chemical mediator aspects of the erectile process.
- Priapism is an abnormal, painful, sustained erection that can lead to ischemic damage of penile structures. It can occur at any age and is one of the possible complications of sickle cell disease.

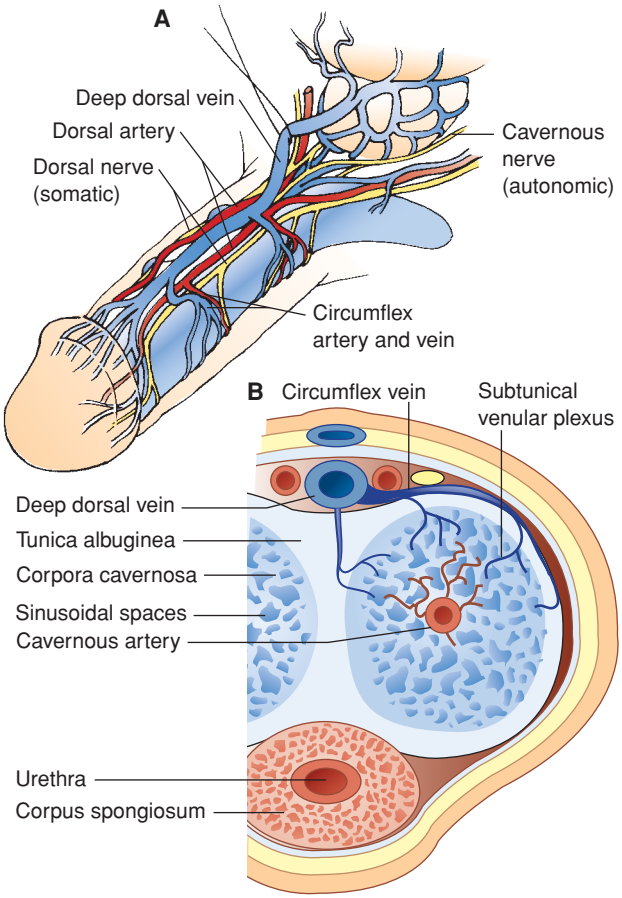


FIGURE 39-6. Anatomy and mechanism of penile erection. **(A)** Innervation and arterial and venous blood supply to penis. **(B)** Cross-section of penis, showing the corpus spongiosum and the sinusoidal system of the corpora cavernosa.

which causes relaxation of the trabecular smooth muscle of the corpora cavernosa. This relaxation permits the inflow of blood into the sinuses of the cavernosa at pressures approaching those of the arterial blood pressure. Because the erectile tissues of the cavernosa are surrounded by a nonelastic fibrous covering, high pressure in the sinusoids causes ballooning of the erectile tissue to such an extent that the penis becomes hard and elongated. At the same time, contraction of the somatic-innervated ischiocavernous muscles forcefully compresses the blood-filled corpora cavernosa, producing a further increase in intercavernous pressures. During this phase of erection, inflow and outflow of blood cease.

Parasympathetic innervation must be intact and nitric oxide synthesis must be active for erection to occur. Nitric oxide activates guanyl cyclase, an enzyme that increases the concentration of cyclic guanosine monophosphate (cGMP), which in turn causes smooth muscle relaxation. Other smooth muscle relaxants (e.g., prostaglandin E_1 analogs and α-adrenergic antagonists), if present in high enough concentrations, can independently cause sufficient cavernosal relaxation to result in erection.[4] Many of the drugs that have been developed to treat erectile dysfunction act at the levels of these mediators.[5,6]

Detumescence or penile relaxation is largely a sympathetic nervous system response. It results from a cessation of neurotransmitter release, the breakdown of second messengers such as cGMP, or sympathetic discharge during ejaculation. Contraction of the trabecular smooth muscle opens the venous channels so that the trapped blood can be expelled and penile flaccidity can return.

Erectile Dysfunction

Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse.[7] It has been estimated that the disorder affects about 150 million men worldwide.[6] Erectile dysfunction is commonly classified as psychogenic, organic, or mixed psychogenic and organic.[5,6,8] Organic etiologies are the most common.

Psychogenic causes of erectile dysfunction include performance anxiety, a strained relationship with a sexual partner, depression, and overt psychotic disorders such as schizophrenia. Depression is a common cause of erectile dysfunction.[5,8] Psychogenic factors can be further exacerbated by the side effects of many of the therapies used to treat these disorders, which can themselves cause erectile dysfunction.

Organic causes span a wide range of pathologic processes. They include neurogenic, hormonal, vascular, drug-induced, and penile-related etiologies. Neurogenic disorders such as Parkinson disease, stroke, and cerebral trauma often contribute to erectile dysfunction by decreasing libido or preventing the initiation of erection. In spinal cord injury, the extent of neural impairment depends on the level, location, and extent of the lesion. Somatosensory innervation of the genitalia is essential to the reflex mechanisms involved in erection; this becomes important with aging and conditions such as diabetes that impair peripheral nerve function. Extensive pelvis surgery, especially radical prostatectomy (even so-called "nerve-sparing" procedures), are common causes of erectile dysfunction due to both direct and indirect nerve damage.

Hormonal causes of erectile dysfunction include a decrease in androgen levels because of both primary and secondary hypogonadism. Androgen levels may be decreased because of aging (andropause). Hyperprolactinemia from any cause interferes with both reproduction and erectile function. This is because prolactin acts centrally to inhibit the release of the hypothalamic GnRH that controls the release of the pituitary gonadotropic hormones, LH and FSH. Elevated prolactin levels may also interfere with normal functioning at the level of the gonad.

Common risk factors for generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation.[8] In hypertension, erectile function is impaired not so much by the increased blood pressure as by the associated stenotic arterial lesions. Focal stenosis of the common penile artery most often occurs in men who sustained blunt pelvic or perineal trauma (e.g., from bicycling accidents). Failure of the veins to close completely during an erection (veno-occlusive dysfunction) may occur in men with large venous channels that drain the corpora cavernosa. Other disorders that impair venous occlusion are degenerative changes involving the tunica albuginea, as in Peyronie disease.

Many drugs are reported to cause erectile dysfunction, including antidepressant, antipsychotic, antiandrogen, and antihypertensive medications.[5,6,8] Cigarette smoking can induce vasoconstriction and penile venous leakage because of its effects on cavernous smooth muscle and can double the risk of erectile dysfunction.[8] Alcohol in small amounts may increase libido and improve erection; however, in large amounts it can cause central sedation, decreased libido, and transient erectile dysfunction.

Aging is known to increase the risk of erectile dysfunction.[9] After 50 years of age, the overall prevalence of erectile dysfunction is reported to be greater than 50%.[10] Many of the pathologic processes that contribute to erectile dysfunction are more common in older men, including diabetes, hyperlipidemia, vascular disease, and the long-term effects of cigarette smoking. Age-related declines in testosterone may also play a role (andropause). Psychosocial problems such as depression, esteem issues, partner relationships, history of substance abuse, and anxiety and fear of performance failure also may contribute to erectile dysfunction in older men.[10]

A diagnosis of erectile dysfunction requires careful history (medical, sexual, and psychosocial), physical examination, and laboratory tests aimed at determining what other tests are needed to rule out organic causes of the disorder. Because many medications, including prescribed, over-the-counter, and illicit drugs, can cause erectile dysfunction, a careful drug history is indicated.

Erectile dysfunction is now recognized as a marker for cardiovascular disease, and is now considered a component of the metabolic syndrome (a collection of cardiovascular risk factors; see Chapter 33).[5,6,11,12] The association between erectile dysfunction and the metabolic syndrome

may be related to the underlying endothelial dysfunction seen in both conditions (see Chapter 18). Men with erectile dysfunction should be evaluated for coexisting vascular disease and cardiovascular risk factors should be modified or treated (e.g., smoking, diabetes, hypertension, and hyperlipidemia).[5,6,11]

Treatment methods include psychosexual counseling, androgen replacement therapy (when androgen deficiency is confirmed), oral and intracavernous drug therapy, vacuum constriction devices, and surgical treatment (prosthesis and vascular surgery).[5,6,8] Among the commonly prescribed drugs used for the treatment of erectile dysfunction are the selective inhibitors of phosphodiesterase type 5 (PDE-5), the enzyme that inactivates cGMP (sildenafil, vardenafil, and tadalafil). These drugs act by facilitating corporeal smooth muscle relaxation in response to sexual stimulation. The concomitant use of PDE-5 inhibitors and nitrates (used, for example, in ischemic heart disease) is absolutely contraindicated because of the risk of profound hypotension.[11] The PDE-5 inhibitors are taken orally. Alprostadil, a prostaglandin E_1 analog, acts by producing relaxation of cavernous smooth muscle. It is either injected directly into the cavernosa (with diffusion into the opposite cavernosa) or placed in the urethra as a minisuppository. Phentolamine (α_2-adrenergic receptor antagonist) and papaverine (smooth muscle relaxant) are also administered by intracavernous injection.

In summary, the male genitourinary system consists of the testes, genital ducts, accessory genital organs, and penis. The testes or male gonads are divided into lobules that consist of *seminiferous tubules,* in which sperm are produced, and the *Leydig* or *interstitial cells* that produce male sex hormones, mainly testosterone. Testosterone is essential for differentiation of the internal and external genitalia in the male embryo, descent of the testes in the fetus, development of primary and secondary male sex characteristics during puberty, and maintenance of these characteristics during adult life.

Spermatogenesis, which occurs in the seminiferous tubules of the testes, is the sequence of events that leads to the production of spermatozoa or male germ cells. The seminiferous tubules are composed of two types of cells: Sertoli cells, which surround and provide physical and nutritional support for the developing germ cells, and the spermatogenic cells, which develop into mature male germ cells or spermatozoa. After formation in seminiferous tubules, the spermatozoa travel through the efferent tubules to the epididymis, then to the ductus deferens, and on to the ampulla, where they are stored until released through the penis during ejaculation. The seminal vesicles, bulbourethral glands, and prostate gland are accessory genital glands that secrete fluids that form the bulk of the male ejaculate or semen.

The function of the male reproductive system is under the negative feedback control of the hypothalamus and the anterior pituitary gonadotropic hormones—FSH and LH. Spermatogenesis is initiated by FSH, and the production of testosterone is regulated by LH.

The male sex act involves erection, emission, ejaculation, and detumescence. The physiology of these functions involves a complex interaction between autonomic-mediated spinal cord reflexes, higher neural centers, and the vascular system. Erection is mediated by the parasympathetic nervous system and emission and ejaculation by the sympathetic nervous system. Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse. It can be due to psychogenic factors, organic disorders, or mixed psychogenic and organic conditions. Erectile dysfunction is now recognized as a marker for cardiovascular disease and men with the disorder should be evaluated for coexisting vascular disease.

Disorders of the Penis, the Scrotum and Testes, and the Prostate

Disorders of the Penis

Disorders of the penis include congenital defects (discussed in the section on disorders of childhood), acute and chronic inflammatory conditions, Peyronie disease, priapism, and neoplasms.

Inflammation and Infection

The term *balanitis* refers to local inflammation of the glans penis and *balanoposthitis* to inflammation of the glans penis and overlying prepuce.[13–15] The condition may result from trauma, irritation, or infection caused by a wide array of organisms. Among the most common infectious agents are *Candida albicans*, anaerobic bacteria, and pyogenic bacteria. A significant number of inflammatory conditions are caused by sexually transmitted infections (see Chapter 41). Balanitis due to *C. albicans* infection may be a presenting feature or result from poorly controlled diabetes mellitus.

Acute superficial balanoposthitis is characterized by erythema of the glans and prepuce. An exudate in the form of malodorous discharge may be present. It usually is encountered in males with phimosis (a tight foreskin) or a large, redundant prepuce that interferes with cleanliness and predisposes to bacterial growth in the accumulated secretions and smegma (i.e., debris from the desquamated epithelia). Extension of the erythema and edema may lead to extensive scarring and a condition called *phimosis*, in which the prepuce cannot be retracted easily over the glans prepuce. When the stenotic prepuce is forcibly retracted over the glans prepuce, the circulation can be compromised causing congestion, swelling, and pain, a condition known as *paraphimosis*.

Balanitis xerotica obliterans is a chronic, sclerosing, atrophic process of the glans penis that occurs in uncircumcised men. It is clinically and histologically similar

to the lichen sclerosus that is seen in women[15] (see Chapter 40). Typically, the lesions consist of grayish-white plaques on the surface of the glans penis and the prepuce. The foreskin is thickened and fibrous and is not retractable. Although balanitis xerotica obliterans was once considered a benign condition, it has been associated with several reports of penile cancer and is now recognized as a precancerous state.[16] Treatment measures include circumcision and topical or intralesional injections of corticosteroids.[13]

Peyronie Disease

Peyronie disease involves a localized and progressive fibrosis of unknown origin that affects the tunica albuginea (i.e., the tough, fibrous sheath that surrounds the corpora cavernosa) of the penis. It is named after Francois de la Peyronie, who in 1743 described a patient who had "rosary beads of scar tissue to cause upward curvature of the penis during erection."[17,18] The disorder is characterized initially by an inflammatory process that results in dense fibrous plaque formation. The plaque usually is on the dorsal midline of the shaft, causing upward bowing of the shaft during erection (Fig. 39-7). Some men may develop scarring on both the dorsal and ventral aspects of the shaft, causing the penis to be straight but shortened or have a lateral bend. The fibrous tissue prevents lengthening of the involved area during erection, making intercourse difficult and painful. The disease usually occurs in middle-aged or elderly men.

The manifestations of Peyronie disease include painful erection, bent erection, and the presence of a hard mass at the site of fibrosis. Approximately two thirds of men complain of pain as a symptom. The pain is thought to be generated by inflammation of the adjacent fascial tissue and usually disappears as the inflammation resolves. During the first year or so after formation of the plaque, while the scar tissue is undergoing the process of remodeling, penile distortion may increase, remain static, or resolve and disappear completely. In some cases, the scar tissue may progress to calcification and formation of bonelike tissue.

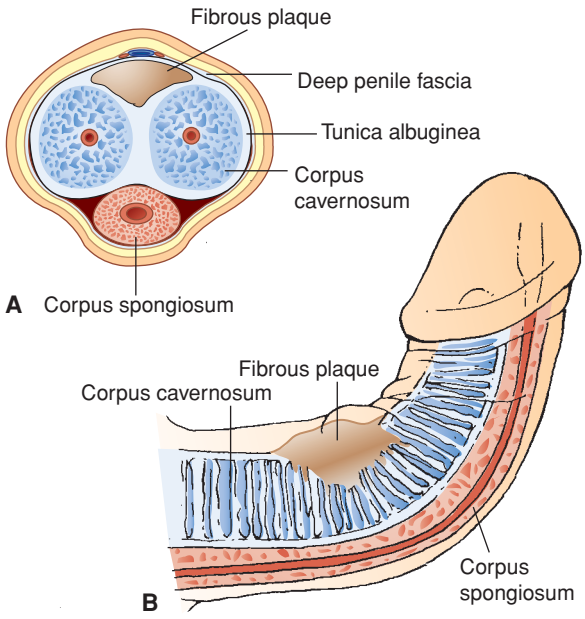


FIGURE 39-7. Peyronie disease. **(A)** Penile cross-section showing plaque between the corpora. **(B)** Penile curvature.

Diagnosis is based on history and physical examination. Doppler ultrasonography may be used to assess the cause of the disorder. Although surgical intervention can be used to correct the disorder, it often is delayed because in many cases the disorder is self-limiting. Less invasive treatments include the administration of oral agents with antioxidant properties (e.g., vitamin E, colchicine) and intralesional treatments, including corticosteroids.

Priapism

Priapism is an involuntary, prolonged (>4 hours), abnormal and painful erection that continues beyond, or is unrelated to, sexual stimulation.[19,20] Priapism is a true urologic emergency because the prolonged erection can result in ischemia and fibrosis of the erectile tissue with significant risk of subsequent impotence. Priapism can occur at any age, in the newborn as well as other age groups. Sickle cell disease or neoplasms are the most common cause in boys between 5 and 10 years of age.[21]

Priapism is caused by impaired blood flow in the corpora cavernosa of the penis. Priapism is classified as primary (idiopathic) or secondary to a disease or drug effect. Secondary causes include hematologic conditions (e.g., leukemia, sickle cell disease, polycythemia), neurologic conditions (e.g., stroke, spinal cord injury), and renal failure. Between 6% and 42% of males with sickle cell disease are affected at some stage by priapism.[21] The relative deoxygenation and stasis of cavernosal blood during erection is thought to increase sickling. Various medications, such as erectile dysfunction drugs, antihypertensive drugs, anticoagulant drugs, antidepressant agents, alcohol, and marijuana, can contribute to the development of priapism. Currently, intracavernous injection therapy for erectile dysfunction is one of the more common causes of priapism.

The diagnosis of priapism usually is based on clinical findings. Color Doppler studies of penile blood flow, penile ultrasonography, and computed tomography (CT) scans may be used to determine intrapelvic pathology. Initial treatment measures include analgesics, sedation, and hydration. Urinary retention may necessitate catheterization. Local measures include ice packs and cold saline enemas, aspiration and irrigation of the corpus cavernosum with plain or heparinized saline, or instillation of α-adrenergic drugs. If less aggressive treatment does not produce detumescence, a temporary surgical shunt may be established between the corpus cavernosum and the corpus spongiosum.

The prognosis for whether fibrosis or erectile failure will occur is determined by the severity and duration of blood stasis. Persistent stasis priapism is known to result in impaired erectile function and tissue fibrosis unless resolved within 24 to 48 hours of onset.[20]

Neoplasms of the Penis

Although relatively rare (<1% of male genital tumors) in developed countries of the world, cancer of the penis may account for 10% to 20% of all genital malignancies in areas such as Africa and South America.[22] When it is diagnosed early, penile cancer is highly curable. The greatest hindrance to early diagnosis is a delay in seeking medical attention.

The cause of penile cancer is unknown.[16,22,23] Several risk factors have been proposed, including poor genital hygiene, human papillomavirus (HPV) infection, ultraviolet radiation exposure, increasing age, and immunodeficiency states. Circumcision confers protection, and hence cancer of the penis is extremely rare in men circumcised at birth.[14,15] It is thought that circumcision is associated with better genital hygiene, which, in turn, reduces exposure to carcinogens that may accumulate in smegma and decreases the likelihood of potentially oncogenic strains of HPV. Ultraviolet radiation is thought have a carcinogenic effect on the penis.[23] Men who were treated for psoriasis with ultraviolet A radiation (i.e., PUVA) have had a reported increased incidence of genital squamous cell carcinomas. Because of this observation, it is suggested that men should shield their genital area when using tanning salons. Immunodeficiency states (e.g., acquired immunodeficiency syndrome [AIDS]) also may play a role in the pathogenesis of penile cancer.[16,23] Dermatologic lesions with precancerous potential include balanitis xerotica obliterans (discussed under penile inflammatory conditions) and giant condylomata acuminata.[22] Giant condylomata acuminata, or genital warts, are cauliflower-like lesions arising on the prepuce or glans as a result of HPV infection (see Chapter 41).

Most penile cancers are of squamous epithelial cell origin and include carcinoma in situ, which is restricted to the epithelium and does not infiltrate the underlying dermis, and invasive carcinomas.[14–16] In situ carcinomas of the penis are known as *Bowen disease* and *erythroplasia of Queyrat*.[15] *Bowen disease* appears as a sharply demarcated, erythematous or grayish-white plaque on the shaft of the penis. Erythroplasia of Queyrat manifests as single or multiple shiny red, sometimes velvety plaques on the glans or foreskin. In approximately 10% of men, these lesions may transform into infiltrating squamous cell cancer.[14,15]

Invasive squamous cell carcinoma of the penis usually begins as a small lump or ulcer on the glans or inner surface of the prepuce. The lesions are usually slow growing and have often been present for a year or more before being brought to medical attention. The lesions are usually nonpainful until they undergo secondary ulceration and infection.[14–16,22] If phimosis is present, there may be painful swelling, purulent drainage, or difficulty urinating. Metastasis to the inguinal lymph is characteristic of early-stage disease, but widespread dissemination is uncommon until the lesion is far advanced.

Diagnosis usually is based on physical examination and biopsy results. CT scans, penile ultrasonographic studies, and magnetic resonance imaging (MRI) may be used in the diagnostic workup. Treatment options vary according to stage, size, location, and invasiveness of the tumor. Carcinoma in situ may be treated conservatively with fluorouracil cream application or laser treatment.[22] Conservative treatment requires frequent follow-up examinations. Surgery remains the mainstay of treatment for invasive carcinoma.

Disorders of the Scrotum and Testes

The testes, or male gonads, are two egg-shaped structures located outside the abdominal cavity in the scrotum. Embryologically, the testes develop in the abdominal cavity and then descend through the inguinal canal into a pouch of peritoneum (which becomes the tunica vaginalis) in the scrotum during the seventh to ninth months of fetal life.[23] As they descend, the testes pull their arteries, veins, lymphatics, nerves, and conducting excretory ducts with them. These structures are encased by the cremaster muscle and layers of fascia that constitute the spermatic cord (Fig. 39-8A). The descent

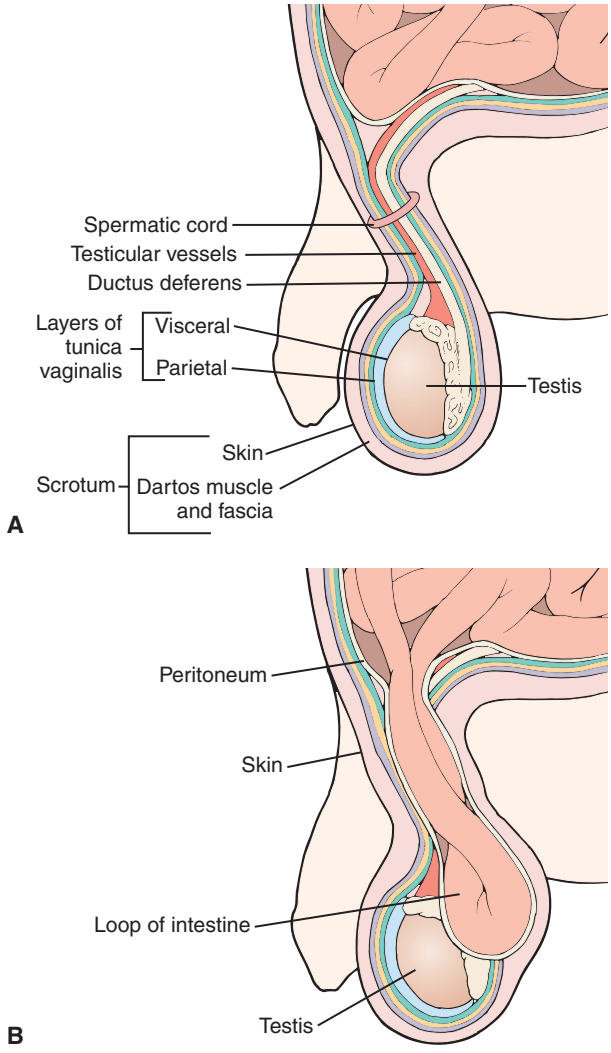


FIGURE 39-8. **(A)** Anterior view of the spermatic cord and inguinal canal and coverings of the spermatic cord and testes. **(B)** Indirect inguinal hernia. (Adapted from Moore K.L., Agur A.M. [2002]. *Essentials of clinical anatomy* [2nd ed., pp. 130, 138]). Philadelphia: Lippincott Williams & Wilkins.)

of the testes is thought to be mediated by testosterone, which is active during this stage of fetal development.

After descent of the testes, the inguinal canal closes almost completely. Failure of this canal to close predisposes to the development of an inguinal hernia later in life (Fig. 39-8B). An inguinal hernia or "rupture" is a protrusion of the parietal peritoneum and part of the intestine through an abnormal opening from the abdominal cavity. A loop of small bowel may become incarcerated in an inguinal hernia (strangulated hernia), in which case the lumen of the bowel may become obstructed and its vascular supply compromised.

The testes and epididymis are completely surrounded by the tunica vaginalis, a serous pouch derived from the peritoneum during fetal descent of the testes into the scrotum. The tunica vaginalis has an outer parietal layer and a deeper visceral layer that adheres to the dense fibrous covering of the testes, the tunica albuginea. The tunica albuginea protects the testes and gives them their ovoid shape. A space exists between these two layers that typically contains a few milliliters of clear fluid. The cremaster muscles, which are bands of skeletal muscle arising from the internal oblique muscles of the trunk, elevate the testes. The testes receive their arterial blood supply from the long testicular arteries, which branch from the aorta. The testicular veins, which drain the testes, arise from a venous network called the *pampiniform plexus* that surrounds the spermatic artery. The testes are innervated by fibers from both divisions of the autonomic nervous system. Associated sensory nerves transmit pain impulses, resulting in excruciating pain, especially when the testes are hit forcibly.

The scrotum, which houses the testes, is made up of a thin outer layer of darkly pigmented skin that is continuous with the outer skin of the groin. Under the outer skin lies the closely related dartos fascia, a fat-free fascial layer with smooth muscle fibers (i.e., dartos muscle) that is responsible for the wrinkled appearance of the scrotum. This layer contains a septum that separates the two testes. Because the dartos muscle attaches to the skin, its contraction causes the scrotum to wrinkle when cold, reducing the surface area of the scrotum and assisting the cremaster muscles in holding the testes closer to the body.

The location of the testes in the scrotum is important for sperm production, which is optimal at 2°C to 3°C (35°C to 37.4°C) below body temperature. Two mechanisms maintain the temperature of the testes at a level consistent with sperm production. One is the pampiniform plexus of testicular veins that surround the testicular artery. This plexus absorbs heat from the arterial blood, cooling it as it enters the testes. The other is the dartos and cremaster muscles, which respond to decreases in testicular temperature by moving the testes closer to the body. Prolonged exposure to elevated temperatures, as a result of prolonged fever or the dysfunction of thermoregulatory mechanisms, can impair spermatogenesis. Some tight-fitting undergarments hold the testes against the body and are thought to contribute to a decrease in sperm counts and infertility by interfering with the thermoregulatory function of the scrotum.

Disorders of the Testicular Tunica

Disorders of the testicular tunica represent scrotal swelling or enlargement due to an accumulation of fluid (hydroceles), blood (hematocele), or sperm (spermatocele) between the layers of the tunica vaginalis, or to dilation of the testicular veins (varicocele) (Fig. 39-9).

Hydrocele. A hydrocele forms when excess fluid collects between the layers of the tunica vaginalis[15,23] (Fig. 39-9B). It may be unilateral or bilateral and can develop as a primary congenital defect or as a secondary condition. Acute hydrocele may develop after local injury, epididymitis or orchitis, gonorrhea, lymph obstruction, or germ cell testicular tumor, or as a side effect of radiation therapy. Chronic hydrocele is more common. Fluid collects about the testis, and the mass grows gradually. Its cause is unknown, and it usually develops in men older than 40 years.

Most cases of hydrocele in male infants and children are caused by a patent processus vaginalis, which is continuous with the peritoneal cavity. There usually are reports that the mass increases in size during the day and decreases at night if the hydrocele communicates with the peritoneal cavity. In many cases they are associated with an indirect inguinal hernia.[24] Most hydroceles of infancy close spontaneously; therefore, they are not repaired before 1 year of age. If the hydrocele persists beyond 2 years of age, surgical treatment usually is indicated.

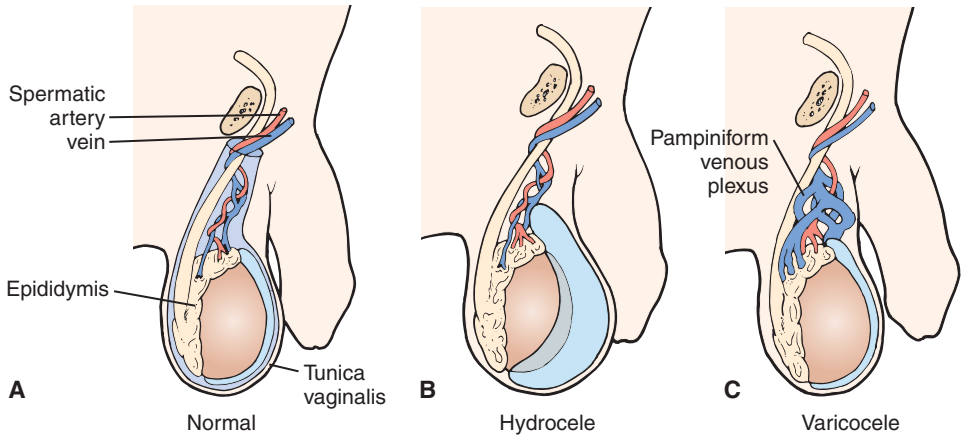


FIGURE 39-9. **(A)** Normal testis and appendages, **(B)** hydrocele, and **(C)** varicocele.

Hydroceles are palpated as cystic masses that may attain massive proportions. If there is enough fluid, the mass may be mistaken for a solid tumor. Transillumination of the scrotum (i.e., shining a light through the scrotum to visualize its internal structures) or ultrasonography can help to determine whether the mass is solid or cystic and whether the testicle is normal. A dense hydrocele that does not illuminate should be differentiated from a testicular tumor. If a hydrocele develops in a young man without apparent cause, careful evaluation is needed to exclude cancer or infection.

In an adult male, a hydrocele is a relatively benign condition. The condition often is asymptomatic, and no treatment is necessary. When symptoms do occur, the feeling may be that of heaviness in the scrotum or pain in the lower back. In cases of secondary hydrocele, the primary condition is treated. If the hydrocele is painful or cosmetically undesirable, surgical correction is indicated.

Hematocele. A hematocele is an accumulation of blood in the tunica vaginalis, which causes the scrotal skin to become dark red or purple.[15] It may develop as a result of an abdominal surgical procedure, scrotal trauma, a bleeding disorder, or a testicular tumor.

Spermatocele. A spermatocele is a painless, sperm-containing cyst that forms at the end of the epididymis.[15] It is located above and posterior to the testis, is attached to the epididymis, and is separate from the testes. Spermatoceles may be solitary or multiple and usually are less than 1 cm in diameter. They are freely movable and should transilluminate. Spermatoceles rarely cause problems, but a large one may become painful and require excision.

Varicocele. A varicocele is characterized by varicosities of the pampiniform plexus, a network of veins supplying the testes[25] (see Fig. 39-9C). The left side is more commonly affected because the left internal spermatic vein inserts into the left renal vein at a right angle, whereas the right spermatic vein has a more oblique insertion into the inferior vena cava. In the standing male, this particular anatomy may cause higher pressures to be transmitted to the left scrotal veins and result in retrograde reflux into veins of the pampiniform plexus. If the condition persists, there may be damage to the elastic fibers and hypertrophy of the vein walls, as occurs in formation of varicose veins in the leg. Sperm concentration and motility are decreased in men with varicoceles.

Varicoceles rarely are found before puberty, and the incidence is highest in males between 15 and 35 years of age. Symptoms of varicocele include an abnormal feeling of heaviness in the left scrotum, although many are asymptomatic. Usually, a varicocele is readily diagnosed on physical examination with the man in the standing and recumbent positions. Typically, the varicocele disappears in the lying position because of venous decompression into the renal vein. Scrotal palpation of a varicocele has been compared to feeling a "bag of worms." Additional diagnostic methods include ultrasonography, radioisotope scanning, and spermatic venography.

Treatment options for varicocele include surgical ligation or sclerosis using a percutaneous transvenous catheter under fluoroscopic guidance. It has been suggested that men with abnormalities in their semen and a varicocele show some degree of improvement in fertility after obliteration of the dilated veins.[25] However, the effectiveness of varicocele treatment in men from subfertile couples is still debated, especially when other assisted reproductive techniques (e.g., intracytoplasmic sperm injection [ICSI]) may be effective with as few as 20 sperm.[25] Aside from improving fertility, other reasons for surgery include the relief of the sensation of "heaviness" and cosmetic improvement.

Testicular Torsion

Testicular torsion is a twisting of the spermatic cord that suspends the testis.[26,27] Testicular torsion can be divided into two distinct types, extravaginal or intravaginal, depending on the level of spermatic cord involvement (Fig. 39-10).

Extravaginal torsion, which occurs in fetuses or neonates, is the less common form of testicular torsion.[28] It occurs when the testicle and the fascial tunicae that surround it rotate around the spermatic cord at a level well above the tunica vaginalis. The torsion probably occurs during fetal or neonatal descent of the testes before the tunica adheres to the scrotal wall. When the torsion occurs in utero, the baby is born with a large firm, nontender testis. Usually the ipsilateral testis is ecchymotic. In these cases the torsed testis is rarely viable because of the time that has elapsed. In other cases the initial examination is normal, and acute scrotal swelling is recognized subsequently. In these cases, the torsed testis may occasionally be saved. The use of surgical treatment (orchiopexy [attachment of the testes to the scrotum] and orchiectomy [removal of the testis]) is controversial. There are multiple animal studies indicating that failure to remove the torsed testis may produce an autoimmune response that affects the normal testis.[28]

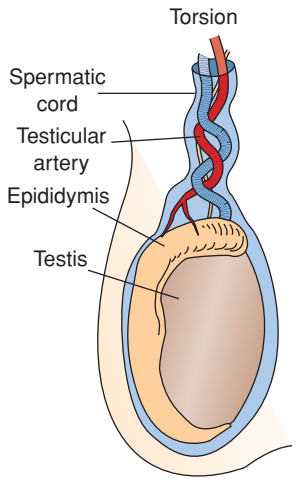


FIGURE 39-10. Testicular torsion with twisting of the spermatic cord that suspends the testis and the spermatic vessels that supply the testis with blood.

Intravaginal torsion involves twisting of the spermatic cord within the tunica vaginalis. It is a true surgical emergency, and early recognition and treatment are necessary if the testicle is to be saved.[26–28] Intravaginal testicular torsion can occur at any age, but is more common during adolescence. Torsion usually occurs in the absence of any precipitating event and is thought to be due to abnormal fixation of the testis within the tunica vaginalis, allowing the testis to twist, especially during periods of testicular growth such as puberty. The torsion obstructs venous drainage, with resultant edema and hemorrhage, and subsequent arterial obstruction. Males usually present in severe distress within hours of onset and often have nausea, vomiting, and tachycardia. The affected testis is large and tender, with pain radiating to the inguinal area.

Testicular torsion must be differentiated from epididymitis, orchitis, and trauma to the testis. On physical examination, the testicle often is high in the scrotum and in an abnormal orientation. These changes are caused by the twisting and shortening of the spermatic cord. The degree of scrotal swelling and redness depends on the duration of symptoms. The cremasteric reflex, normally elicited by stroking the medial aspect of the thigh and observing testicular retraction, frequently is absent. Color Doppler ultrasonography is increasingly used in the evaluation of suspected testicular torsion.

Treatment includes surgical detorsion and orchiectomy. Orchiectomy is carried out when the testis is deemed nonviable after surgical detorsion. Testicular salvage rates are directly related to the duration of torsion. Because the opposite testicle usually is affected by the same abnormal attachments, prophylactic fixation of that testis often is performed.

Epididymitis and Orchitis

Epididymitis. Epididymitis is an inflammation of the epididymis, the elongated cordlike structure that is located along the posterior border of the testis and functions in the transport and storage of sperm[29,30] (Fig. 39-4). The cause of epididymitis varies with age. Most cases of epididymitis in men younger than 35 years are due to sexually transmitted infections such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. In men older than 35, epididymitis is generally caused by infection with common urinary tract pathogens, such as *Escherichia coli* and *Pseudomonas*. In prepubertal children, the disorder usually is associated with congenital urinary tract abnormalities and infection with gram-negative rods.

Infections may reach the epididymis through the vas deferens, in which case the pressure associated with voiding or physical strain may force pathogen-containing urine from the urethra or prostate up the ejaculatory duct and through the vas deferens into the epididymis. Infections may also reach the epididymis through the lymphatics of the spermatic cord. Risk factors for epididymitis in all men include sexual activity, heavy physical exertion, and bicycle or motorcycle riding. Recent urinary tract surgery or instrumentation and anatomic abnormalities such as prostatic obstruction are risk factors in older men.

Epididymitis is characterized by unilateral pain and swelling, accompanied by erythema and edema of the overlying scrotal skin that develops over a period of 24 to 48 hours. Initially, the swelling and induration are limited to the epididymis. The distinction between the testis and epididymis becomes less evident as the inflammation progresses, and the testis and epididymis become one mass. There may be tenderness over the groin (spermatic cord) or in the lower abdomen. Symptoms of lower urinary tract infection, such as fever, frequency, urgency, and dysuria, may be present. Whether urethral discharge is present depends on the organism causing the infection; it usually accompanies gonorrheal infections, is common in chlamydial infections, and is less common in infections caused by gram-negative organisms.

Laboratory findings usually reveal an elevated white blood cell count. Urinalysis and urine culture are important in the diagnosis of epididymitis, with bacteriuria and pyuria suggestive of the disorder; however, the urinalysis may be normal. If the diagnosis remains uncertain, color Doppler ultrasonography may be useful, revealing increased blood flow to the affected testis.

Treatment of epididymitis includes bed rest, scrotal elevation and support, analgesics, nonsteroidal anti-inflammatory agents, and antibiotics. Bed rest with scrotal support improves lymphatic drainage.[29,30] The choice of antibiotics is determined by age, physical findings, urinalysis, Gram stain results, cultures, and sexual history. Sexual activity or physical strain may exacerbate the infection and worsen the symptoms, and should be avoided. If a sexually transmitted disease is suspected, it is important to ensure that the sexual partner receives treatment.

Orchitis. Orchitis is an infection of the testes. It can be precipitated by a primary infection in the genitourinary tract, or the infection can be spread to the testes through the epididymis, bloodstream, or lymphatics.[29] It can develop as a complication of a systemic infection, such as parotitis (i.e., mumps), scarlet fever, or pneumonia. Probably the best known of these complications is orchitis caused by the mumps virus.[31]

Mumps orchitis is now rarely seen in children younger than 10, but is the most common complication of mumps infection in the postpubertal male, occurring in approximately 20% to 30% of adolescent boys and young men with mumps. Although the incidence of mumps orchitis has dramatically declined since the introduction of childhood vaccination programs, a sharp increase in mumps and mumps orchitis has recently been reported in both the United States[32] and the United Kingdom.[31] It is also important to note that mumps remains epidemic in many countries throughout the world, and the mumps vaccine is only used in 57% of the World Health Organization member-countries.[31]

The onset of mumps orchitis is sudden; it usually occurs approximately 3 to 4 days after the onset of the parotitis and is characterized by fever, painful enlargement of the testes, and small hemorrhages into the tunica albuginea. Unlike epididymitis, the urinary symptoms are absent. The symptoms usually run their course in 7 to 10 days. The residual effects seen after the acute phase of

the infection include hyalinization of the seminiferous tubules and atrophy of the testes (seen in half of affected men). Spermatogenesis is irreversibly impaired in approximately 30% of testes damaged by mumps orchitis. If both testes are involved (which occurs in 10% to 30% of cases), permanent sterility can result, but is rare.[31] Androgenic hormone function is usually maintained in these cases.

Neoplasms of the Scrotum and Testes

Tumors can develop in the scrotum or the testes. Benign scrotal tumors are common and often do not require treatment. Carcinoma of the scrotum is rare and usually is associated with exposure to carcinogenic agents. Almost all solid tumors of the testes are malignant.

Scrotal Cancer. Cancer of the scrotum was the first cancer directly linked to a specific occupation when, in the 1800s, it was associated with chimney sweeps.[33] Studies have linked this cancer to exposure to tar, soot, and oils. Most squamous cell cancers of the scrotum are linked to poor hygiene and chronic inflammation. Exposure to PUVA or HPV also has been associated with the disease. The mean age of presentation with the disease is 60 years, often preceded by 20 to 30 years of chronic irritation.

In the early stages, cancer of the scrotum may appear as a small tumor or wartlike growth that eventually ulcerates. The thin scrotal wall lacks the tissue reactivity needed to block the malignant process; more than one half of the cases seen involve metastasis to the lymph nodes. Because this tumor does not respond well to chemotherapy or irradiation, the treatment includes wide local excision of the tumor with inguinal and femoral node dissection.[34] Prognosis correlates with lymph node involvement.

Testicular Cancer. Testicular cancer accounts for 1% to 2% of all neoplasms in men.[35] Although relatively rare, it is the most common cause of cancer in the 20- to 35-year-old age group.[35] In the past, testicular cancer was a leading cause of death among men entering their most productive years. Since the late 1970s, however, advances in therapy have transformed an almost invariably fatal disease into one that is highly curable.

Although the cause of testicular cancer is unknown, several predisposing influences may be important: cryptorchidism, genetic factors, and disorders of testicular development.[14,15,35] The strongest association has been with cryptorchid or undescended testis. Genetic predisposition also appears to be important. Family clustering of the disorder has been described, although a well-defined pattern of inheritance has not been established. Men with disorders of testicular development, including those with Klinefelter syndrome and testicular feminization, have a higher risk of germ cell tumors.

The majority of testicular tumors are of germ cell origin.[14,15] Germ cell tumors can be classified as seminomas and nonseminomas. *Seminomas* account for approximately 50% of germ cell tumors and are most frequent in the fourth decade of life.[14,15] Seminomas tend to retain the phenotypic features of spermatogonia and are the type of germ cell tumor most likely to produce a uniform population of cells. The *nonseminoma* tumors include embryonal carcinoma, teratoma, choriocarcinoma, and yolk cell carcinoma derivatives. They usually contain more than one cell type and are less differentiated than seminomas. *Embryonal carcinomas* are the least differentiated of the tumors, with the capacity to differentiate into other nonseminomatous cell types. They occur most commonly in the 20- to 30-year-old age group. *Choriocarcinoma* is a rare and highly malignant form of testicular cancer that is identical to tumors that arise in placental tissue. *Yolk sac tumors* mimic the embryonic yolk sac histologically. They are the most common type of testicular tumors in infants and children up to 3 years of age, and in this age group have a very good prognosis. Teratomas are composed of somatic cell types from two or more germline layers (ectoderm, mesoderm, or endoderm). They constitute less than 2% to 3% of germ cell tumors and can occur at any age from infancy to old age. They usually behave as benign tumors in children, but contain minute foci of cancer cells in adults.

Often the first sign of testicular cancer is a slight enlargement of the testicle that may be accompanied by some degree of discomfort. This may be an ache in the abdomen or groin or a sensation of dragging or heaviness in the scrotum. Frank pain may be experienced in the later stages, when the tumor is growing rapidly and hemorrhaging occurs. Testicular cancer can spread when the tumor may be barely palpable. Approximately 10% of men present with symptoms related to metastatic disease.[35] Signs of metastatic spread include swelling of the lower extremities, back pain, neck mass, cough, hemoptysis, or dizziness. Gynecomastia (breast enlargement) may result from human chorionic gonadotropin (hCG)-producing tumors and occurs in about 5% of men with germ cell tumors. Although routine screening and monthly self-examination in young men has been recommended, studies have not shown that they improve outcomes.[35] However, men with suggestive signs and symptoms should be carefully evaluated to avoid delayed diagnosis or misdiagnosis.

The diagnosis of testicular cancer requires a thorough urologic history and physical examination. A painless testicular mass may be cancer. Conditions that produce an intrascrotal mass similar to testicular cancer include epididymitis, orchitis, hydrocele, or hematocele. The examination for masses should include palpation of the testes and surrounding structures, transillumination of the scrotum, and abdominal palpation. Testicular ultrasonography can be used to differentiate testicular masses. CT scans and MRI are used in assessing metastatic spread.

Tumor markers that measure protein antigens produced by malignant cells may provide information about the existence of a tumor and the type of tumor present. Three tumor markers are of importance in the diagnosis and management of testicular cancer: α-fetoprotein (AFP), β-hCG, and lactic acid dehydrogenase (LDH).[14,35] AFP is normally present in fetal serum in high levels, but should be present in only trace amounts beyond the age of 1 year. β-hCG is a hormone produced by the placenta in pregnant women, and should not be present in significant

levels in the normal male. Elevated serum LDH levels, a cellular enzyme found in muscle, liver, kidneys, and brain, has been shown to correlate with the mass of tumor cells. LDH is often elevated in widespread, metastatic testicular cancer.

The basic treatment of all testicular cancers includes orchiectomy, which is done at the time of diagnostic exploration. Depending on the histologic characteristics of the tumor and the clinical stage of disease, radiation or chemotherapy may be used after orchiectomy. Rigorous follow-up in all men with testicular cancer is necessary to detect recurrences, most of which occur within 2 years of the end of treatment.[35,36] Testicular cancer is a disease in which even recurrence is highly treatable. With appropriate treatment, the prognosis for men with testicular cancer is excellent. Even patients with more advanced disease have excellent chances for long-term survival.

Disorders of the Prostate

The prostate gland is a walnut-sized fibromuscular and glandular organ that encircles the urethra just inferior to the bladder (see Fig. 39-1). The segment of urethra that travels through the prostate gland is called the *prostatic urethra*. The prostatic urethra is lined by a thin layer of smooth muscle that is continuous with the bladder wall. This smooth muscle represents the true involuntary sphincter of the male posterior urethra. Because the prostate surrounds the urethra, it can produce urinary obstruction when it becomes enlarged.

The prostate gland is made up of many secretory glands arranged in three concentric areas surrounding the prostatic urethra, into which they open. The component glands of the prostate include the (1) small mucosal glands associated with the urethral mucosa, (2) intermediate submucosal glands that lie peripheral to the mucosal glands, and (3) large main prostatic glands that are situated toward the outside of the gland. It is the overgrowth of the mucosal glands that causes benign prostatic hyperplasia in older men.

Prostatitis

Prostatitis refers to a variety of inflammatory disorders of the prostate gland, some bacterial and some not. It may occur spontaneously, as a result of catheterization or instrumentation, or secondary to other diseases of the male genitourinary system. As an outcome of two consensus conferences, the National Institutes of Health has established a classification system with four categories of prostatitis syndromes: acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/pelvic pain syndrome, and asymptomatic inflammatory prostatitis.[37] Men with *asymptomatic inflammatory prostatitis* have no subjective symptoms and are detected incidentally on biopsy or examination of prostatic fluid.

Acute Bacterial Prostatitis. Acute bacterial prostatitis often is considered a subtype of urinary tract infection.[38,39] The most likely etiology of acute bacterial prostatitis is an ascending urethral infection or reflux of infected urine into the prostatic ducts. *E. coli*, other gram-negative rods, and enterococci, organisms known to cause urethritis, are the most common infectious agents. Risk of infection is increased in persons with impaired host defenses (e.g., due to diabetes or human immunodeficiency [HIV] infection), recent catheterization or instrumentation of the urinary tract, or urethral strictures.

The manifestations of acute bacterial prostatitis include fever and chills, malaise, myalgia, arthralgia, frequent and urgent urination, dysuria, and urethral discharge. Dull, aching pain often is present in the perineum, rectum, or sacrococcygeal region. The urine may be cloudy and malodorous because of urinary tract infection. Rectal examination reveals a swollen, tender, warm prostate with scattered soft areas. Prostatic massage produces a thick discharge with white blood cells that grows large numbers of pathogens on culture.

Acute prostatitis usually responds to appropriate antimicrobial therapy chosen in accordance with the sensitivity of the causative agents in the urethral discharge. Depending on the urine culture results, antibiotic therapy usually is continued for at least 4 weeks. Because acute prostatitis often is associated with anatomic abnormalities, a thorough urologic examination usually is performed after treatment is completed.

A persistent fever indicates the need for further investigation for an additional site of infection or a prostatic abscess. CT scans and transrectal ultrasonography of the prostate are useful in the diagnosis of prostatic abscesses. Prostatic abscesses, which are relatively uncommon since the advent of effective antibiotic therapy, are found more commonly in men with diabetes mellitus.

Chronic Bacterial Prostatitis. In contrast to acute bacterial prostatitis, chronic bacterial prostatitis is a subtle disorder that is difficult to treat. Men with the disorder typically present with recurrent urinary tract infections with persistence of the same strain of pathogenic bacteria in the prostatic fluid and urine.[39–41] Organisms responsible for chronic bacterial prostatitis usually are the gram-negative enterobacteria (*E. coli, Proteus,* or *Klebsiella*) or *Pseudomonas*.

The symptoms are variable and include frequent and urgent urination, dysuria, perineal discomfort, and low back pain. Occasionally, myalgia and arthralgia accompany the other symptoms. Secondary epididymitis sometimes is associated with the disorder. Most men are afebrile but have a history of recurrent or relapsing urinary tract infections. Others may be asymptomatic and the diagnosis made after investigation of bacteriuria.

The most accurate method of establishing a diagnosis is by urine cultures. Even after an accurate diagnosis has been established, treatment of chronic prostatitis often is difficult and frustrating.[39–41] Long-term therapy with an appropriate oral antimicrobial agent is the mainstay of treatment. Selection of an appropriate agent is important since antimicrobial drugs penetrate poorly into the chronically inflamed prostate.

Chronic Prostatitis/Chronic Pelvic Pain Syndrome. Chronic prostatitis/pelvic pain syndrome is both the most

common and least understood of the prostatitis syndromes.[42] The category is divided into two types, inflammatory and noninflammatory, based on the presence of leukocytes in the prostatic fluid. The inflammatory type was previously referred to as *nonbacterial prostatitis,* and the noninflammatory type as *prostatodynia.*

A large group of men with prostatitis have pain along the penis, testicles, and scrotum; painful ejaculation; low back pain; rectal pain radiating to the inner thighs; urinary symptoms; decreased libido; and impotence, but they have no bacteria in the urinary system. Men with nonbacterial prostatitis often have inflammation of the prostate with an elevated leukocyte count and abnormal inflammatory cells in their prostatic secretions. The cause of the disorder is unknown, and efforts to prove the presence of unusual pathogens (e.g., mycoplasmas, *Chlamydia,* trichomonads, viruses) have been largely unsuccessful. It also is thought that nonbacterial prostatitis may be an autoimmune disorder.

Men with noninflammatory prostatitis have symptoms resembling those of nonbacterial prostatitis but have negative urine culture results and no evidence of prostatic inflammation (i.e., normal leukocyte count). The cause of noninflammatory prostatitis is unknown, but because of the absence of inflammation, the search for the cause of symptoms has been directed toward extraprostatic sources. In some cases, there is an apparent functional obstruction of the bladder neck near the external urethral sphincter; during voiding, this results in higher-than-normal pressures in the prostatic urethra that cause intraprostatic urine reflux and chemical irritation of the prostate by urine. In other cases, there is an apparent myalgia (i.e., muscle pain) associated with prolonged tension of the pelvic floor muscles. Emotional stress also may play a role.

Treatment methods for chronic prostatitis/pelvic pain syndrome are highly variable and require further study. Antibiotic therapy is used when an occult infection is suspected. Treatment often is directed toward symptom control. In men with irritative urination symptoms, α-adrenergic blocking agents may be beneficial. Noncentered treatment methods such as physical therapy, myofascial trigger point release therapy, and relaxation techniques may provide some symptom relief.[43]

Benign Prostatic Hyperplasia

Nodular hyperplasia of the prostate, also termed benign prostatic hyperplasia (BPH), is an age-related, nonmalignant enlargement of the prostate gland[14,15,44–46] (Fig. 39-11). BPH is one of the most common diseases of aging men. It has been reported that more than 50% of men older than 60 years of age have BPH.[44] The disorder is seen most frequently in Europe and the United States, and is seen least commonly in Asia.[15] The prevalence of the disorder in the United States is higher among blacks than among whites.

The pathogenesis of BPH is not completely understood, but appears to involve an imbalance between cell proliferation and cell death. There is an increased number of epithelial cells and stromal components of the periurethral area of the prostate, but no clear evidence of increased epithelial cell proliferation. Instead, it has been proposed that the cause of the hyperplastic process is decreased cell death, resulting in an accumulation of senescent cells.[14] The main androgen in the prostate is dihydrotestosterone (DHT), which is formed in the prostate from the conversion of testosterone by the enzyme 5α-reductase. It is thought that DHT-induced growth factors contribute to the development of BPH by increasing the proliferation of prostatic stromal cells and

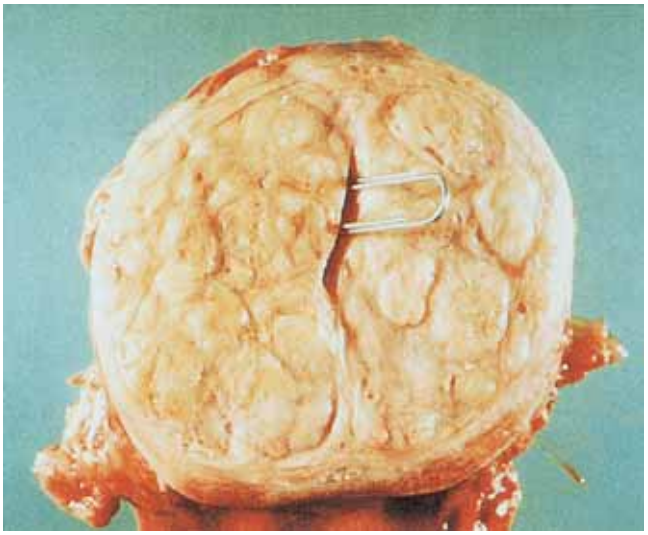


FIGURE 39-11. Nodular hyperplasia of the prostate. Cut surface of a prostate enlarged by nodular hyperplasia shows numerous, well-circumscribed nodules of prostatic tissue. The prostatic urethra (*paper clip*) has been compressed to a narrow slit. (From Damjanov I. [2008]. The lower urinary tract and male reproductive system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 774]. Philadelphia: Lippincott Williams & Wilkins.)

Hyperplasia and Cancer of the Prostate

- The prostate gland surrounds the urethra and periurethral enlargement causes manifestations of urinary obstruction.
- Benign prostatic hyperplasia is an age-related enlargement of the prostate gland with formation of large, discrete lesions in the periurethral region of the prostate. These lesions compress the urethra and produce symptoms of dysuria or difficulty urinating.
- Prostate cancer begins in the peripheral zones of the prostate gland and usually is asymptomatic until the disease is far advanced and the tumor has eroded the outer prostatic capsule and spread to adjacent pelvic tissues or metastasized.

decreasing the death of the epithelial cells. The discovery that DHT is the active factor in BPH provides the rationale for the use of 5α-reductase inhibitors in the treatment of the disorder.

BPH is characterized by the formation of large, discrete lesions in the periurethral region of the prostate rather than the peripheral zones, which commonly are affected by prostate cancer (Fig. 39-12). The anatomic location of the prostate at the bladder neck contributes to the pathophysiology and symptomatology of BPH. There are two prostatic components to the obstructive properties of BPH and development of lower urinary tract symptoms: dynamic and static.[44,45] The static component of BPH is related to an increase in prostatic size and gives rise to symptoms such as a weak urinary stream, postvoid dribbling, frequency of urination, and nocturia. The dynamic component of BPH is related to prostatic smooth muscle tone, which is mediated by α_1-adrenergic receptors. The recognition of the role of α_1-adrenergic receptors on neuromuscular function in the prostate is the basis for use of α_1-adrenergic receptor blockers in treating BPH. A third component, detrusor instability and impaired bladder contractility, may contribute to the symptoms of BPH independent of the outlet obstruction created by an enlarged prostate (see Chapter 27). It has been suggested that some of the symptoms of BPH might be related to a decompensating or aging bladder rather than being primarily related to outflow obstruction. An example is the involuntary contraction that results in urgency and an attempt to void that occurs because of small bladder volume.[45]

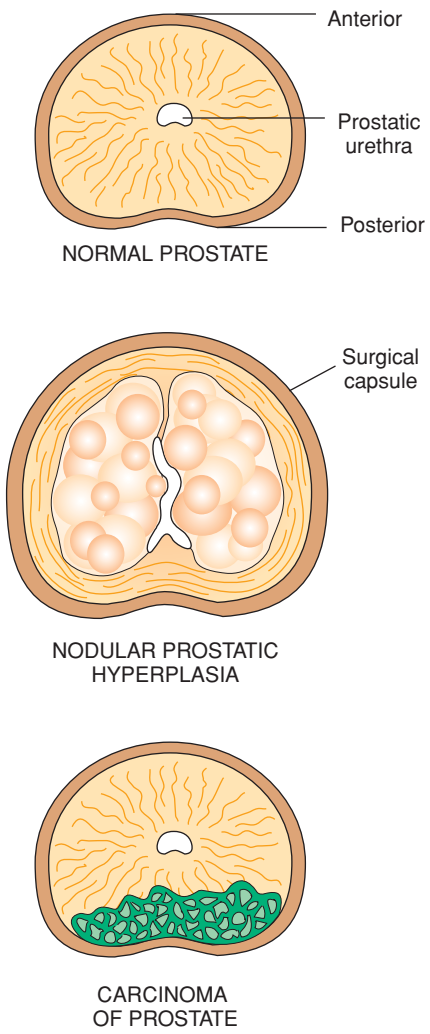


FIGURE 39-12. Normal prostate, nodular benign prostatic hyperplasia, and cancer of the prostate. In prostatic hyperplasia, which involves predominantly the periurethral part of the gland, the nodules compress and distort the urethra. The expansion of the central prostatic glands leads to compression of the peripheral parts and fibrosis, resulting in the formation of the so-called surgical capsule. Prostatic cancer usually arises from the peripheral glands and compression of the urethra is a late clinical event. (From Damjanov I. [2008]. The lower urinary tract and male reproductive system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 774]. Philadelphia: Lippincott Williams & Wilkins.)

Clinical Course. The clinical significance of BPH resides in its tendency to compress the urethra and cause partial or complete obstruction of urinary outflow. As the obstruction increases, acute retention of urine may occur with overdistention of the bladder. The residual urine in the bladder causes increased frequency of urination and a constant desire to empty the bladder, which becomes worse at night. With marked bladder distention, overflow incontinence may occur with the slightest increase in intra-abdominal pressure. The resulting obstruction to urinary flow can give rise to urinary tract infection, destructive changes of the bladder wall, hydroureter, and hydronephrosis. Hypertrophy and changes in bladder wall structure develop in stages. Initially, the hypertrophied fibers form trabeculations and then herniations, or sacculations; finally, diverticula develop as the herniations extend through the bladder wall (see Chapter 27, Fig. 27-4). Because urine seldom is completely emptied from them, these diverticula are readily infected. Back-pressure on the ureters and collecting system of the kidneys promotes hydroureter, hydronephrosis, and danger of eventual renal failure.

Current practice suggests that the single most important factor in the evaluation and treatment of BPH is the man's own experiences related to the disorder. The American Urological Association Symptom Index consists of seven questions about symptoms regarding incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia.[46]

The diagnosis of BPH is based on history, physical examination, digital rectal examination, urinalysis, blood tests for serum creatinine and prostate-specific antigen (PSA), and urine flow rate. The digital rectal examination is used to examine the external surface and size of the prostate. An enlarged prostate found during a digital rectal examination does not always correlate with the degree of urinary obstruction. Some men can have greatly enlarged prostate glands with no urinary obstruction, but others may have severe symptoms without a palpable enlargement of the prostate. Urinalysis is done to detect bacteria, white blood cells, or microscopic hematuria in the presence of infection and inflammation.

The serum creatinine test is used as an estimate of the glomerular filtration rate and renal function. The PSA test is used to screen for prostate cancer. These evaluation measures, along with the symptom index, are used to describe the extent of obstruction, determine if other diagnostic tests are needed, and establish the need for treatment.

Treatment of BPH is determined by the degree of symptoms that the condition produces and complications due to obstruction. When a man develops mild symptoms related to BPH, a "watchful waiting" stance often is taken.[44–46] The condition does not always run a predictable course; it may remain stable or even improve. Until the 1980s, surgery was the mainstay of treatment to alleviate urinary obstruction due to BPH. Currently, there is an emphasis on less invasive methods of treatment, including use of pharmacologic agents. However, when more severe signs of obstruction develop, surgical treatment is indicated to provide comfort and avoid serious kidney damage.

Pharmacologic management includes the use of 5α-reductase inhibitors, α_1-adrenergic blocking drugs, or a combination of the two drugs.[44,45] The 5α-reductase inhibitors such as finasteride reduce prostate size by blocking the effect of androgens on the prostate. Finasteride causes atrophy of the prostate glandular epithelial cells, which results in a 20% to 30% reduction in volume. The onset is slow (3 to 6 months), but long-lasting. The presence of α-adrenergic receptors in prostatic smooth muscle has prompted the use of α_1-adrenergic blocking drugs (e.g., prazosin, terazosin) to relieve prostatic obstruction and increase urine flow.

Herbal therapies have been used for many years by men for the treatment of BPH and lower urinary tract symptoms.[44–46] Several studies have looked at the effects of these agents, including the extract of the saw palmetto berry. Improvements in peak urine flow rates and nocturia can occur compared with placebo, but the durability of these effects is unproven. The long-term toxicity and mechanism of action of these agents remain unclear. Standardization of these products is also worrisome (as with all herbal therapies).

The surgical removal of an enlarged prostate can be accomplished by the transurethral, suprapubic, or perineal approach.[44–46] Currently, transurethral prostatectomy (TURP) is the most commonly used technique. With this approach, an instrument is introduced through the urethra, and prostate tissue is removed using a resectoscope and electrocautery. Late complications of TURP include sexual dysfunction, incontinence, and bladder neck constriction. Many new and experimental techniques have also been used to treat BPH including transurethral incision of the prostate, laser surgery, transurethral vaporization, transurethral microwave therapy, and transurethral needle ablation. For men who have heart or lung disease or a condition that precludes major surgery, a stent may be used to widen and maintain the patency of the urethra. A stent is a device made of tubular mesh that is inserted under local or regional anesthesia. Within several months, the lining of the urethra grows to cover the inside of the stent.

Cancer of the Prostate

Globally, prostate cancer is the second most frequently diagnosed cancer in men. An estimated 782,600 new cases were projected to occur 2007. Nearly three quarters of these cases were expected to be diagnosed in developed countries, with the highest rates being recorded in the United States.[47] The increase in diagnosed cases is thought to reflect earlier diagnosis because of widespread use of PSA testing since the early 1990s. African American men have the highest reported incidence rate for prostate cancer at all ages, and the cancer also tends to be diagnosed at a later stage.[47,48] Asians and Native American men have the lowest rate. Prostate cancer also is a disease of aging. The incidence increases rapidly after 50 years of age; more than 85% of all prostate cancers are diagnosed in men older than 65 years of age.[48]

Etiology and Pathogenesis. The precise cause of prostate cancer is unclear. As with other cancers, it appears that the development of prostate cancer is a multistep process involving genes that control cell differentiation and growth. The incidence of prostate cancer appears to be higher in relatives of men with prostate cancer. It has been estimated that men who have an affected first-degree relative (e.g., father, brother) and an affected second-degree relative (e.g., grandfather, uncle) have an eightfold increase in risk.[14,15,49] It has been suggested that dietary patterns, including increased dietary fats, may alter the production of sex hormones and growth factors and increase the risk of prostate cancer. Supporting the role of dietary fats as a risk factor for prostate cancer has been the observation that the diet of Japanese men, who have a low rate of prostate cancer, is much lower in fat content than that of U.S. men, who have a much higher incidence.

Several factors appear to be protective against the development of prostate cancer. These include dietary factors such as dietary fat reduction and supplementation with vitamins D and E and selenium.[50] Dietary intake of soy, green tea, and tomato-rich products (lycopene) may also be important. Vitamin D is not technically a vitamin, but a steroid hormone that has a variety of antiproliferative and proapoptotic effects in prostatic as well as other cancer cell lines. Vitamin E, selenium, and lycopene are all antioxidants, thought to play an important role in cellular defenses to oxidative stress. The low incidence of prostate cancer in Asia has led to an interest in the study of soy and green tea, which are highly consumed in these nations.

In terms of hormonal influence, androgens are believed to play a role in the pathogenesis of prostate cancer.[14] Evidence favoring a hormonal influence includes the presence of steroid receptors in the prostate, the requirement of sex hormones for normal growth and development of the prostate, and the fact that prostate cancer almost never develops in men who have been castrated. The response of prostate cancer to estrogen administration or androgen deprivation further supports a correlation between the disease and testosterone levels.[14]

Clinical Features. Prostatic adenocarcinomas, which account for most primary prostate cancers, are commonly multicentric and located in the peripheral zones of the prostate[14,15] (see Fig. 39-12). The high frequency of invasion of the prostatic capsule by adenocarcinoma relates to its subcapsular location. Invasion of the urinary bladder is less frequent and occurs later in the clinical course. Metastasis to the lung reflects lymphatic spread through the thoracic duct and dissemination from the prostatic venous plexus to the inferior vena cava. Bony metastases, particularly to the vertebral column, ribs, and pelvis, produce pain that often presents as a first sign of the disease.

Most men with early-stage prostate cancer are asymptomatic.[51] The presence of symptoms often suggests locally advanced or metastatic disease. Depending on the size and location in the prostate of the cancer at the time of diagnosis, there may be changes associated with the voiding pattern similar to those found in BPH. These include urgency, frequency, nocturia, hesitancy, dysuria, hematuria, or blood in the ejaculate.[44] On digital rectal examination, the prostate can be nodular and fixed. Bone metastasis often is characterized by low back pain. Pathologic fractures can occur at the site of metastasis. Men with metastatic disease may experience weight loss, anemia, or shortness of breath.

Screening. Whether screening for prostate cancer results in a decrease in prostate cancer deaths is a subject of much debate.[52,53] The screening tests currently available are digital rectal examination, PSA testing, and transrectal ultrasonography. Depending on the population studied, detection using digital rectal examination varies from 1.5% to 7%, with most cancers being far advanced when they are detected.[53] PSA is a glycoprotein secreted into the cytoplasm of benign and malignant prostatic cells that is not found in other normal tissues or tumors. However, a positive PSA test indicates only the possible presence of prostate cancer. It also can be positive in cases of BPH and prostatitis. Thus, the test can result in a large number of men undergoing biopsy and being treated unnecessarily. Transrectal ultrasonography is not used for first-line detection because of its expense, but may benefit men who are at high risk for development of prostate cancer.

The U.S. Preventative Services Task Force (USPSTF) Recommendation states that for men younger than 75 years, there is no quality evidence to show that finding prostate cancer by PSA screening rather than waiting for symptoms to develop leads to fewer men dying of prostate cancer. For men older than 75 years, the benefits of finding prostate cancer by screening are small to none.[52] These recommendations apply to men at average risk for prostate cancer and not to men at high risk, such as those with a father or brother with prostate cancer. The USPSTF and American Cancer Society advocate that men younger than 75 years who are interested in PSA screening should discuss it with their health care provider.[52,53] Before screening, they should understand the benefits and limitations of screening.

Diagnosis. The diagnosis of prostate cancer is based on history and physical examination and confirmed through biopsy methods.[44,51] Transrectal ultrasonography is used to guide a biopsy needle and document the exact location of the sampled tissue. It also is used for providing staging information. Newly developed small probes for transrectal MRI have been shown to be effective in detecting the presence of cancer in the prostate. Radiologic examination of the bones of the skull, ribs, spine, and pelvis can be used to reveal metastases, although radionuclide bone scans are more sensitive.

Prostatic cancer, like other forms of cancer, is graded and staged[14,15] (see Chapter 7). PSA levels are important in the staging and management of prostate cancer. In untreated cases, the level of PSA correlates with the volume and stage of disease. A rising PSA after treatment is consistent with progressive disease, whether it is locally recurring or metastatic. Measurement of PSA is used to detect recurrence after total prostatectomy. Because the prostate is the source of PSA, levels should drop to zero after surgery; a rising PSA indicates recurring disease.

Treatment. Cancer of the prostate is treated by surgery, radiation therapy, and hormonal manipulations.[44,51] Chemotherapy has shown limited effectiveness in the treatment of prostate cancer. Treatment decisions are based on tumor grade and stage and on the age and health of the man. Expectant therapy (watchful waiting) may be used if the tumor is not producing symptoms, is expected to grow slowly, and is small and contained in one area of the prostate. This approach is particularly suited for men who are elderly or have other health problems.

Radical prostatectomy involves complete removal of the seminal vesicles, prostate, and ampullae of the vas deferens. Refinements in surgical techniques ("nerve-sparing" prostatectomy) have allowed maintenance of continence in most men and erectile function in selected cases. Radiation therapy can be delivered by a variety of techniques, including external-beam radiation therapy and transperineal implantation of radioisotopes (brachytherapy).

Metastatic disease often is treated with androgen deprivation therapy. Androgen deprivation may be induced at several levels along the hypothalamic-pituitary-gonadal axis using a variety of methods or agents.[44,51] Orchiectomy or surgical removal of the testes eliminates the source of testosterone. The use of luteinizing hormone–releasing hormone (LHRH) agonists (e.g., leuprolide, goserelin), which act at the hypothalamic-pituitary level to achieve androgen deprivation without orchiectomy or administration of diethylstilbestrol (a synthetic estrogenic compound), currently is the most common method of reducing testosterone levels. Although testosterone is the main circulating androgen, the adrenal gland also secretes androgens. Inhibitors of adrenal androgen synthesis (i.e., ketoconazole and aminoglutethimide) block the synthesis of adrenal androgens. Complete androgen blockade can be achieved by combining an antiandrogen with use of an LHRH agonist or orchiectomy. The nonsteroidal antiandrogens (e.g., flutamide, bicalutamide) block the uptake and actions of androgens in the prostate cells.

In summary, disorders of the penis include balanitis, an acute or chronic inflammation of the glans penis, and balanoposthitis, an inflammation of the glans and prepuce. Peyronie disease is characterized by the growth of a band of fibrous tissue on top of the penile shaft. Priapism is prolonged, painful, and nonsexual erection that can lead to thrombosis with ischemia and necrosis of penile tissue. Cancer of the penis is relatively rare, accounting for less than 1% of genital cancer in developed countries of the world. Although the tumor is slow growing and highly curable when diagnosed early, the greatest hindrance to successful treatment is a delay in seeking medical attention.

Disorders of the scrotum and testes include collection of fluid (hydrocele), blood (hematocele), or sperm (spermatocele) in the tunica vaginalis; varicosities of the veins in the pampiniform venous plexus (varicocele); and twisting of the spermatic cord with a resulting compromise of the blood supply to the testis (testicular torsion). Inflammatory conditions can involve the scrotal sac, epididymis, or testes. Tumors can arise in the scrotum or the testes. Scrotal cancers usually are associated with exposure to petroleum products such as tar, pitch, and soot. Testicular cancer, which accounts for only 1% to 2% of all cancers in men, is the most common cause of cancer in the 20- to 35-year-old age group. With current treatment methods, a large percentage of men with these tumors can be cured.

The prostate gland is a firm walnut-sized structure that surrounds the urethra. Inflammation of the prostate occurs as an acute or a chronic process. Chronic prostatitis probably is the most common cause of relapsing urinary tract infections in men. Chronic prostatitis/pelvic pain syndrome is both the most common and least understood of the prostatitis syndromes. It is manifest by pain along the penis, testicles, and scrotum; painful ejaculation; low back and rectal pain; urinary symptoms; and impotence. BPH is a common disorder in men older than 50 years. Because the prostate encircles the urethra, BPH exerts its effect through obstruction of urinary outflow from the bladder. Advances in the treatment of BPH include pharmacologic treatment with 5α-reductase inhibitors and α-adrenergic blocking agents, laser surgery, and prostatic stents.

Globally, prostate cancer is the second most frequently diagnosed cancer in men. Nearly three quarters of these cases were expected to be diagnosed in developed countries in 2007, with the highest rates being recorded in the United States. Most prostate cancers are asymptomatic and are incidentally discovered on rectal examination. Cancer of the prostate, like other forms of cancer, is graded according to the histologic characteristics of the tumor and staged clinically. Treatment, which is based on the extent of the disease, includes surgery, radiation therapy, and hormonal manipulation.

Disorders in Childhood and Aging Changes

Disorders of Childhood

Disorders of the male reproductive system that present in childhood include hypospadias, epispadias, phimosis and paraphimosis, and cryptorchidism.

Hypospadias and Epispadias

Hypospadias and epispadias are congenital disorders of the penis resulting from embryologic defects in the development of the urethral groove and penile urethra (Fig. 39-13). In hypospadias, which affects approximately 1 in 250 male infants, the termination of the urethra is on the ventral surface of the penis.[54–57] The testes are undescended in 8% to 10% of boys born with hypospadias and chordee (i.e., ventral bowing of the penis), and inguinal hernia also may accompany the disorder.[54] In the newborn with severe hypospadias and cryptorchidism (undescended testes), the differential diagnosis should consider ambiguous genitalia and masculinization that is seen in female infants with congenital adrenal hyperplasia[58] (see Chapter 32). Because many chromosomal aberrations result in ambiguity of the external genitalia, chromosomal studies often are recommended for male infants with hypospadias and cryptorchidism.[57]

Surgery is the treatment of choice for hypospadias.[57] Circumcision is avoided because the foreskin is used for surgical repair. Factors that influence the timing of surgical repair include anesthetic risk, penile size, and the psychological effects of the surgery on the child. In mild cases, the surgery is done for cosmetic reasons only. In more severe cases, surgical repair becomes essential for normal sexual functioning and to prevent the psychological effects of having malformed genitalia. When

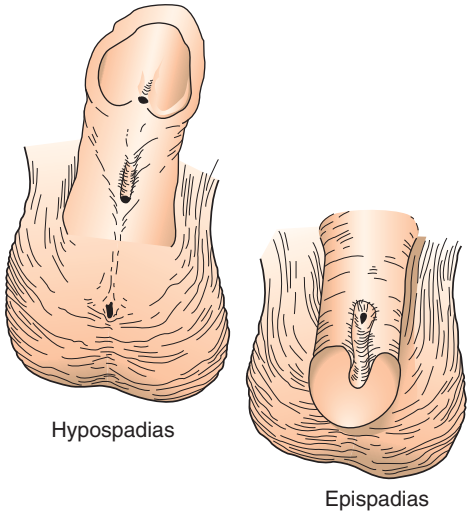


FIGURE 39-13. Hypospadias and epispadias.

indicated, surgical repair is usually done between the ages of 6 and 12 months.[54–57]

Epispadias, in which the opening of the urethra is on the dorsal surface of the penis, is a less common defect. Although epispadias may occur as a separate entity, it often is associated with exstrophy of the bladder, a condition in which the abdominal wall fails to cover the bladder. The treatment depends on the extent of the developmental defect.

Phimosis and Paraphimosis

Phimosis refers to a tightening of the prepuce or penile foreskin that prevents its retraction over the glans.[58] Embryologically, the foreskin begins to develop during the eighth week of gestation as a fold of skin at the distal edge of the penis that eventually grows forward over the base of the glans. By the 16th week of gestation, the prepuce and the glans are adherent. Only a small percentage of newborns have a fully retractable foreskin.[55] With growth, a space develops between the glans and foreskin, and by 3 years of age, approximately 90% of male children have retractable foreskins.

Because the foreskin of many boys cannot be fully retracted in early childhood, it is important that the area be cleaned thoroughly. There is no need to retract the foreskin forcibly because this could lead to infection, scarring, or *paraphimosis*. As the child grows, the foreskin becomes retractable, and the glans and foreskin should be cleaned routinely. If symptomatic phimosis occurs after childhood, it can cause difficulty with voiding or sexual activity. Circumcision is then the treatment of choice.

Cryptorchidism

Cryptorchidism, or undescended testes, occurs when one or both of the testicles fail to move down into the scrotal sac.[59,60] The condition is bilateral in 10% to 20% of cases. The testes develop intra-abdominally in the fetus and usually descend into the scrotum through the inguinal canal during the seventh to ninth months of gestation. The undescended testes may remain in the lower abdomen or at a point of descent in the inguinal canal (Fig. 39-14).

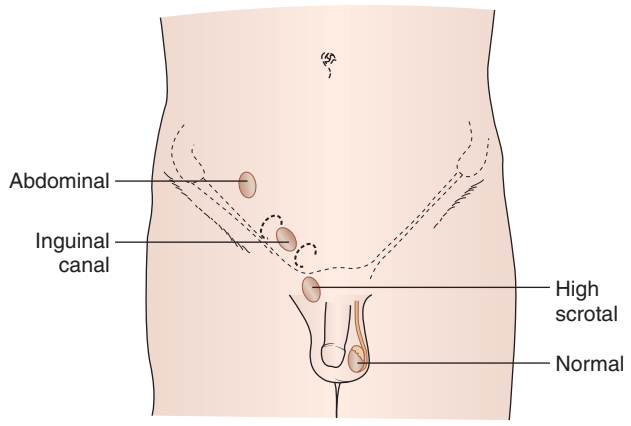


FIGURE 39-14. Possible locations of undescended testicles.

The incidence of cryptorchidism is directly related to birth weight and gestational age; infants who are born prematurely or are small for gestational age have the highest incidence of the disorder. The cause of cryptorchidism in full-term infants is poorly understood. Most cases are idiopathic, but some may result from genetic or hormonal factors.

The major manifestation of cryptorchidism is the absence of one or both of the testes in the scrotum. The testis either is not palpable or can be felt external to the inguinal ring. Spontaneous descent often occurs during the first 3 months of life, and by 6 months of age the incidence decreases to 0.8%.[54] Spontaneous descent rarely occurs after 4 months of age.

In children with cryptorchidism, histologic abnormalities of the testes reflect intrinsic defects in the testicle or adverse effects of the extrascrotal environment. The undescended testicle is normal at birth, but pathologic changes can be demonstrated at 6 to 12 months.[54] There is a delay in germ cell development, changes in the spermatic tubules, and reduced number of Leydig cells. These changes are progressive if the testes remain undescended. When the disorder is unilateral, it also may produce morphologic changes in the contralateral descended testis.

The consequences of cryptorchidism include infertility, testicular torsion, malignancy, and the possible psychological effects of an empty scrotum.[54,59,60] Indirect inguinal hernias usually accompany the undescended testes but rarely are symptomatic. Recognition of the condition and early treatment are important steps in preventing adverse consequences. The risk of malignancy in the undescended testis is 4 to 10 times higher than in the general population.[54] The increased risk of testicular cancer is not significantly affected by orchiopexy, hormonal therapy, or late spontaneous descent after the age of 2 years. However, orchiopexy does allow for earlier detection of a testicular malignancy by positioning the testis in a more easily palpable location.

As a group, men with unilateral or bilateral cryptorchidism usually have decreased sperm counts, poorer-quality sperm, and lower fertility rates than do men whose testicles descend normally. The likelihood of decreased fertility increases when the condition is bilateral. Unlike the risk of testicular cancer, there seems to be some advantage to early orchiopexy for protection of fertility.[60]

Diagnosis is based on careful examination of the genitalia in male infants. Undescended testes due to cryptorchidism should be differentiated from retractable testes that retract into the inguinal canal in response to an exaggerated cremaster muscle reflex. Retractable testes usually are palpable at birth but become nonpalpable later. They can be brought down with careful palpation in a warm room. Retractable testes usually assume a scrotal position during puberty. They have none of the complications associated with undescended testicles due to cryptorchidism.[54] Because imaging has not proven to be 100% reliable, laparoscopy has become standard practice for localization of nonpalpable testes.

The treatment goals for the child with cryptorchidism include measures to enhance future fertility

potential, placement of the gonad in a favorable place for cancer detection, and improved cosmetic appearance. Surgical treatment is the cornerstone of therapy. Current information suggests that placement of the testes in the scrotum should be accomplished by 1 year of age to maximize the potential for fertility. Hormone therapy with hCG or GnRH agonists is used infrequently. Although hormonal treatment has been used in Europe, randomized clinical trials have shown neither hormonal preparation to be effective in stimulating testicular descent.[54]

Treatment of men with undescended testis should include lifelong follow-up, considering the sequelae of testicular cancer and infertility. Parents need to be aware of the potential issues of infertility and increased risk of testicular cancer. On reaching puberty, boys should be instructed in the necessity of testicular self-examination.

Aging Changes

Like other body systems, the male reproductive system undergoes degenerative changes as a result of the aging process; it becomes less efficient with age. The declining physiologic efficiency of male reproductive function occurs gradually and involves the endocrine, circulatory, and neuromuscular systems.[61] Compared with the marked physiologic change in aging women, the changes in the aging man are more gradual and less drastic. Gonadal and reproductive failures usually are not related directly to age because a man remains fertile into advanced age; 80- and 90-year-old men have been known to father children.

As the man ages, his reproductive system becomes measurably different in structure and function from that of the younger man. Male sex hormone levels, particularly testosterone, decrease with age, with the decline starting later on average than in women. The term *andropause* has been used to describe an ill-defined collection of symptoms in aging men, typically those older than 50 years, who may have a low androgen level.[61,62]

The sex hormones play a part in the structure and function of the reproductive system and other body systems from conception to old age; they affect protein synthesis, salt and water balance, bone growth, and cardiovascular function. Decreasing levels of testosterone affect sexual energy, muscle strength, and the genital tissues. The testes become smaller and lose their firmness. The seminiferous tubules, which produce spermatozoa, thicken and begin a degenerative process that finally inhibits sperm production, resulting in a decrease of viable spermatozoa. The prostate gland enlarges, and its contractions become weaker. The force of ejaculation decreases because of a reduction in the volume and viscosity of the seminal fluid. The seminal vesicles change little from childhood to puberty. The pubertal increases in the fluid capacity of the gland remain throughout adulthood and decline after the age of 60 years. After age 60 years, the walls of the seminal vesicles thin, the epithelium decreases, and the muscle layer is replaced by connective tissue. Age-related changes in the penis consist of fibrotic changes in the trabeculae in the corpus spongiosum, with progressive sclerotic changes in arteries and veins. Sclerotic changes also follow in the corpora cavernosa, with the condition becoming generalized in 55- to 60-year-old men.

Erectile dysfunction in the elderly man often is directly related to the general physical condition of the person. Diseases that accompany aging can have direct bearing on male reproductive function. Various cardiovascular, respiratory, hormonal, neurologic, and hematologic disorders can be responsible for secondary impotence. For example, vascular disease affects male potency because it may impair blood flow to the pudendal arteries or their tributaries, resulting in loss of blood volume with subsequent poor distention of the vascular spaces of erectile tissue. Other diseases affecting potency include hypertension, diabetes, cardiac disease, and malignancies of the reproductive organs. In addition, certain medications can have an effect on sexual function.

Testosterone and other synthetic androgens may be used in older men with low androgen levels to improve muscle strength and vigor. Preliminary studies of androgen replacement in aging men with low androgen levels show an increase in lean body mass and a decrease in bone turnover. Before testosterone replacement therapy is initiated, all men should be screened for prostate cancer and other androgen-related diseases. Testosterone is available in an injectable form that is administered every 2 to 4 weeks, as a buccal tablet, or as a transdermal patch or gel. Side effects of replacement therapy may include acne, gynecomastia, and reduced high-density lipoprotein levels. It also may contribute to a worsening of sleep apnea in men who are troubled by this problem.

In summary, childhood disorders of the male reproductive system include congenital disorders in which the urethral opening is located on the ventral surface of the penis (hypospadias) or on the dorsal surface (epispadias). Phimosis is the condition in which the opening of the foreskin is too tight to permit retraction over the glans. Disorders of the scrotum and testes include cryptorchidism or undescended testicles. Early diagnosis and treatment are important because of the risk of malignancy and infertility.

Like other body systems, the male reproductive system undergoes changes as a result of the aging process. The changes occur gradually and involve parallel changes in endocrine, circulatory, and neuromuscular function. Testosterone levels decrease, the size and firmness of the testes decrease, sperm production declines, and the prostate gland enlarges. There often is a decrease in frequency of intercourse or erectile function related to diseases that accompany the aging process.

REVIEW EXERCISES

1. A 64-year-old man presents to his family physician with erectile dysfunction. He is on multiple medications for "his heart disease." An initial physical examination is unremarkable.

A. What additional information should be obtained?
B. Given his medical history, what are possible factors contributing to his problem?

2. A 23-year-old man presents in the emergency department in severe distress. His left testicle is large and tender and he has pain radiating to the inguinal area.

A. What would be a tentative diagnosis for this man?
B. Why would this problem necessitate immediate diagnosis and surgical intervention?

3. A 72-year-old man had a radical prostatectomy for localized prostate cancer. After surgery his PSA level was undetectable. He presents 5 years later having been "lost to follow-up." He complains of pain in his hip and lower back. His PSA level is now markedly elevated.

A. What initial investigations are warranted?
B. What therapies are available for this complication?

REFERENCES

1. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., p. 999). Philadelphia: Elsevier Saunders.
2. Ross M.H., Pawlina W. (2007). *Histology: A text and atlas* (5th ed., pp. 728–771). Philadelphia: Lippincott Williams & Wilkins.
3. Braunstein G.D. (2007). Testes. In Greenspan F.S., Gardner D.G. (Eds.), *Basic and clinical endocrinology* (8th ed., pp. 470–501). New York: McGraw-Hill.
4. Dean R.C., Lue T.F. (2005). Physiology of erectile function and pathophysiology of erectile dysfunction. *Urologic Clinics of North America* 32, 379–395.
5. Matfin G. (2005). Erectile dysfunction as a component of the metabolic syndrome. *Current Diabetes Reports* 5, 64–69.
6. Matfin G., Jawa G., Fonseca V. (2006). Erectile dysfunction in diabetes: An endothelial disorder. In Fonseca V. (Ed.), *Clinical diabetes: Translating research to practice* (pp. 165–178). Philadelphia: Elsevier Saunders.
7. NIH Consensus Development Panel on Impotence. (1993). NIH Consensus Conference: Impotence. *Journal of the American Medical Association* 270, 83–90.
8. AACE Male Sexual Dysfunction Taskforce. (2003). AACE medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: A couple's problem–2003 update. *Endocrine Practice* 9, 77–95.
9. Bacon C.G., Mittleman M.A., Kawachi I., et al. (2003). Sexual function in men older than 50 years of age: Results from the Health Professionals follow-up study. *Annals of Internal Medicine* 139, 161–168.
10. Feldman H.A., Goldstein J., Hatzichristou D.G., et al. (1994). Impotence and its medical and psychosocial effects: Results of the Massachusetts Male Aging Study. *Journal of Urology* 151, 54–61.
11. Rosen R.C., Jackson G., Kostis J.B. (2006). Erectile dysfunction and cardiac disease: Recommendations of the Second Princeton Conference. *Current Urology Reports* 7, 490–496.
12. Minor M.M., Kuritzky L. (2007). Erectile dysfunction: A sentinel marker for cardiovascular disease in primary care. *Cleveland Clinic Journal of Medicine* 74(Suppl 2), 530–537.
13. Edwards S. (1996). Balanitis and balanoposthitis: A review. *Genitourinary Medicine* 72, 155–159.
14. Epstein J.I. (2010). The male genital tract. In Kumar V., Abbas A.K., Fausto N., et al. *Robbins and Cotran pathologic basis of medicine* (8th ed., pp. 982–1002). Philadelphia: Saunders Elsevier.
15. Damajanov I. (2008). The lower urinary tract and male reproductive system. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 758–779). Philadelphia: Lippincott Williams & Wilkins.
16. Micali G., Nasca M.R., Innocenzi D. (2006). Penile cancer. *Journal of the American Academy of Dermatology* 54, 369–391.
17. Chaudary M., Sheikh N., Asterling S., et al. (2005). Peyronie's disease with erectile dysfunction: Modeling over inflatable penile prosthesis. *Urology* 65, 760–764.
18. Taylor F.L., Levine L.A. (2007). Peyronie's disease. *Urologic Clinics of North America* 34, 517–534.
19. Burnett A.L., Bivalacqua T.J. (2007). Priapism: Current principles and practice. *Urologic Clinics of North America* 34, 631–642.
20. American Urological Association. (2003). *Guidelines on the management of priapism.* [Online] Available: http://www.auanet.org. Accessed June 27, 2010.
21. Bruno D., Wigfall D.R., Zimmerman S.A., et al. (2001). Genitourinary complications of sickle cell disease. *Journal of Urology* 166, 803–811.
22. Presti J.C. (2008). Genital tumors. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 375–387). New York: McGraw-Hill.
23. Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 214–231). Philadelphia: Lippincott Williams & Wilkins.
24. Kapur P., Caty M.G., Glick P.L. (1998). Pediatric hernias and hydroceles. *Pediatric Clinics of North America* 45, 773–789.
25. Biyani C.S., Cartledge J., Janetschek G. (2006). Varicocele. *Clinical Evidence Concise* 15, 339–340.
26. Lavallee M.E., Cash J. (2005). Testicular torsion. *Current Sports Medicine Report* 4(2), 102–104.
27. Sessions A.E., Rabinowitz R., Hulbert W.C., et al. (2003). Testicular torsion: Direction, degree, duration, and disinformation. *Journal of Urology* 169, 663–665.
28. Leslie J.A., Cain M.P. (2006). Pediatric urologic emergencies and urgencies. *Pediatric Clinics of North America* 53, 513–527.
29. Tojian T.H., Lishnak T.S., Heiman D. (2009). Epididymitis and orchitis: An overview. *American Family Physician* 79(7), 583–587.
30. Tracy C.R., Steers W.D., Constabile R. (2008). Diagnosis and management of epididymitis. *Urologic Clinics of North America* 35, 101–108.
31. Masarani M., Wazait H., Dinneen M. (2006). Mumps orchitis. *Journal of the Royal Society of Medicine* 99, 573–575.
32. Centers for Disease Control and Prevention. *Prevention of specific infectious disease: Mumps.* [Online] Available: http://wwwn.cdc.gov/travel/yellowbook/ch4/mumps.aspx. Accessed June 19, 2009.
33. Mebcow M.M. (1975). Percivall Pott (1713–1788): 200th anniversary of first report of occupation-induced cancer of the scrotum in chimney sweepers (1745). *Urology* 6, 745.

34. Lowe F.C. (1992). Squamous cell carcinoma of the scrotum. *Urologic Clinics of North America* 19, 297–405.
35. Shaw J. (2008). Diagnosis and treatment of testicular cancer. *American Family Physician* 77(4), 469–476.
36. Vaughn D.J., Gignac G.A., Meadows A.T. (2002). Long-term medical care of testicular cancer survivors. *Annals of Internal Medicine* 136, 463–470.
37. Krieger J.N., Nyberg L., Nickel J.C. (1999). NIH consensus definition and classification of prostatitis. *Journal of the American Medical Association* 282, 721–725.
38. Potts J., Payne R.E. (2007). Prostatitis: Infection, neuromuscular disorder, or pain syndrome? Proper patient classification is key. *Cleveland Clinic Journal of Medicine* 27(Suppl 3), S63–S71.
39. Ngugen H.J. (2008). Bacterial infections of the genitourinary system. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 193–218). New York: McGraw-Hill.
40. Benway B.M., Moon T.D. (2008). Bacterial prostatitis. *Urologic Clinics of North America* 35, 23–32.
41. Erickson B.A., Jang T.L., Ching L., et al. (2006). Chronic prostatitis. *Clinical Evidence Concise* 15, 331–333.
42. Pontari M.A. (2008). Chronic prostatitis/chronic pelvic pain syndrome. *Urologic Clinics of North America* 33, 81–89.
43. Collins M.M., MacDonald R., Wilt T.J. (2000). Diagnosis and treatment of chronic abacterial prostatitis: A systemic review. *Annals of Internal Medicine* 133, 367–381.
44. Presti J.C., Kane C.J., Shinahara K., et al. (2008). Neoplasms of the prostate gland. In Tanagho E.A., McAninch J.W. (Eds.), *Smith's general urology* (17th ed., pp. 348–374). New York: McGraw-Hill.
45. Edwards J.L. (2008). Diagnosis and management of benign prostatic hyperplasia. *American Family Physician* 77(10), 1403–1413.
46. The American Urological Association. (2003). *Guideline on management of prostatic hyperplasia (BPH)*. [Online] Available: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=bph. Accessed June 20, 2009.
47. Garcia M., Jemal A., Ward E., et al. (2007). *Global cancer facts and figures 2007*. [Online] Available: http://www.cancer.org. Accessed June 27, 2010.
48. Crawford E.D. (2009). Understanding the epidemiology, natural history, and key pathways involved in prostate cancer. *Urology* 73(Suppl 5A), 4–10.
49. Nelson W.G., De Manzo A.M., Isaacs W.B. (2003). Prostate cancer. *New England Journal of Medicine* 349, 366–381.
50. Fleshner N., Ziotta A.R. (2007). Prostate cancer prevention: Past, present, and future. *Cancer* 110(9), 1889–1899.
51. Rugo H.S. (2009). Cancer. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (48th ed., pp. 1455–1461). New York: McGraw-Hill.
52. U.S. Preventive Services Task Force. (2008). Screening for prostate cancer: U.S. Preventative Services Task Force recommendations statement. *Annals of Internal Medicine* 149, 185–195.
53. Snowden R.V. (2009). *Prostate cancer screening: Weigh risks, benefits you're your doctor.* American Cancer Society. [Online] Available: http://www.cancer.org. Accessed June 20, 2009.
54. Elder J. (2007). Anomalies of the penis and urethra, and disorders and anomalies of the scrotal contents. In Behrman R., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 2253–2256, 2260–2262). Philadelphia: Elsevier Saunders.
55. Moore K.L., Persaud T.V.N. (2003). *The developing human: Clinically oriented embryology* (7th ed., pp. 304–326). Philadelphia: W.B. Saunders.
56. Hughes I.A., Houk C., Ahmed S.F., et al. (2006). Consensus statement on management of intersex disorders. *Archives of Diseases of Childhood* 91, 554–563.
57. Shukla A.R., Patel R.P. (2004). Hypospadias. *Urologic Clinics of North America* 31, 445–460.
58. Docimo S.G., Silver R.I., Cromie W. (2000). The undescended testicle: Diagnosis and management. *American Family Physician* 62, 2037–2048.
59. Leung A.K.C., Robson W.L.M. (2004). Current status of cryptorchidism. *Advances in Pediatrics* 51, 351–377.
60. Kolon T.F., Patel R.P., Huff D.S. (2004). Cryptorchidism: Diagnosis, treatment, and long-term prognosis. *Urologic Clinics of North America* 31, 469–480.
61. Muller M., Grobbee D.E., Thijssen J.H.H., et al. (2003). Sex hormones and male health: Effects on components of the frailty syndrome. *Trends in Endocrinology and Metabolism* 14, 289–296.
62. Yialamas M.A., Hayes F.J. (2003). Androgens and the aging male. *Endocrine Rounds* 2, 1–6.

Structure and Function of the Female Reproductive System
External Genitalia
Internal Genitalia
Vagina
Uterus and Cervix
Fallopian (Uterine) Tubes
Ovaries
The Menstrual Cycle
The Hypothalamic-Pituitary Axis
Ovarian Hormones
Ovarian Follicle Development and Ovulation
Endometrial Changes
Disorders of the Female Reproductive Organs
Disorders of the External Genitalia
Bartholin Gland Cyst and Abscess
Benign and Malignant Disorders of the Vulva
Vulvodynia
Disorders of the Vagina
Vaginitis
Cancer of the Vagina
Disorders of the Uterine Cervix
Cervicitis
Premalignant Lesions and Cancer of the Cervix
Disorders of the Uterus
Infectious Disorders of the Uterus and Pelvic Structures
Endometriosis
Adenomyosis
Endometrial Cancer
Uterine Leiomyomas
Disorders of Uterine Support
Disorders of the Ovaries
Cystic Lesions of the Ovaries
Polycystic Ovary Syndrome
Benign Ovarian Tumors
Ovarian Cancer
Menstrual Disorders
Dysfunctional Menstrual Cycles
Dysfunctional Bleeding
Amenorrhea
Dysmenorrhea
Premenstrual Syndrome Disorders
Menopause and Aging Changes
Disorders of the Breast
Breast Structures
Benign Disorders
Inflammatory Disorders
Benign Epithelial Disorders
Breast Cancer
Detection
Diagnosis and Classification
Treatment
Paget Disease

Chapter 40

Disorders of the Female Genitourinary System

Disorders of the female reproductive system have widespread effects on physical and psychological function, including general health status, sexuality, and reproductive potential. This chapter provides a review of the structure and function of the female reproductive system and a discussion of disorders of the external and internal female reproductive organs, menstrual disorders, and disorders of the breast.

Structure and Function of the Female Reproductive System

The female reproductive system consists of the external and internal genital structures.[1,2] The external structures, or genitalia, are situated in the anterior part of the perineum, and the internal structures (vagina, uterus, fallopian tubes, and ovaries) are located in the pelvic cavity (Fig. 40-1).

External Genitalia

The external genitalia, which are collectively referred to as the *vulva*, include the mons pubis, labia majora, labia minora, clitoris, and perineal body (Fig. 40-2). Because of their location, the urethra and anus usually are considered in a discussion of the external genitalia.

The *mons pubis* is a rounded, skin-covered fat pad located anterior to the symphysis pubis. Running posteriorly from the mons pubis are two elongated, hair-covered, fatty folds, the *labia majora*. The labia majora enclose the *labia minora*, which are smaller than the labia majora and are composed of skin, fat, and some erectile tissue. The *clitoris* is located below the clitoral hood, which is formed by the joining of the two labia minora. The female clitoris is an erectile organ, rich in vascular and nervous supply. Analogous to the male penis, it is a highly sensitive organ that becomes distended during sexual stimulation.

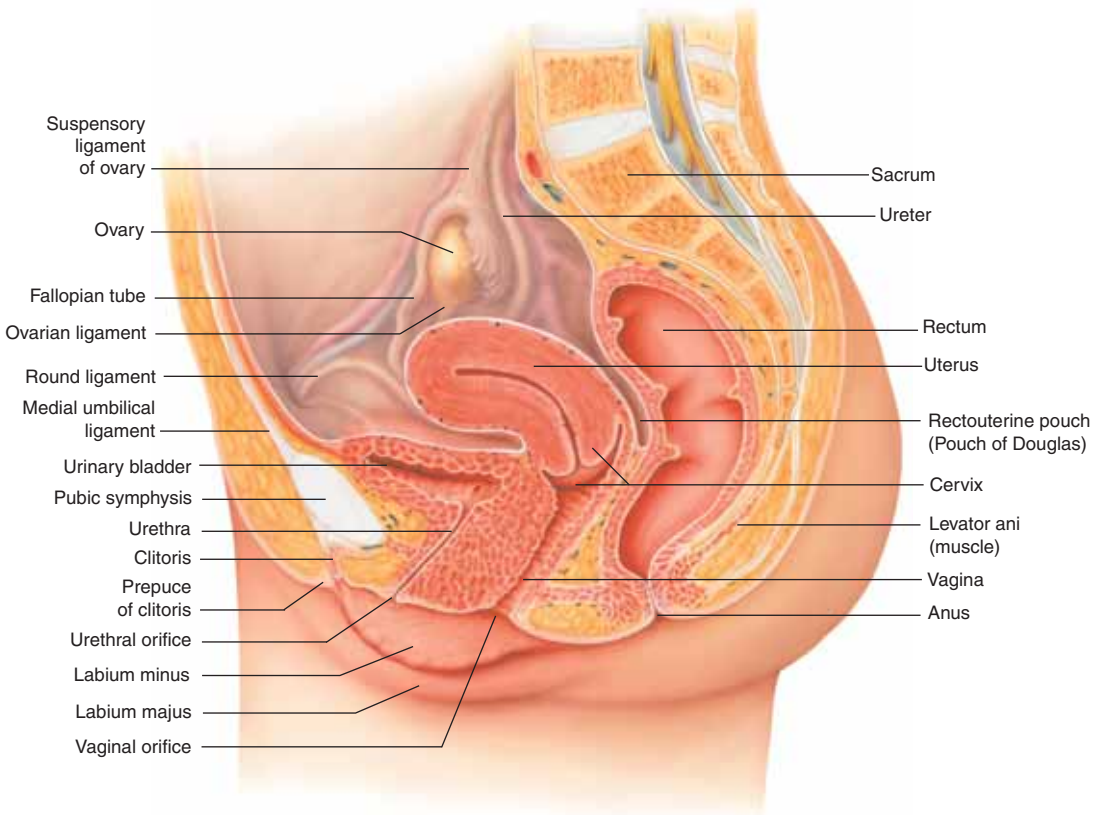


FIGURE 40-1. Female reproductive system as seen in sagittal section. (Adapted from Anatomical Chart Company. [2001]. *Atlas of human anatomy* [p. 253]. Springhouse, PA: Springhouse.)

The area between the labia minora is called the *vestibule*. Located in the vestibule are the urethral and vaginal openings. The urethra is located posterior to the clitoris and usually is closer to the vaginal opening than to the clitoris. The vaginal orifice, commonly known as the *introitus*, is the opening between the external and

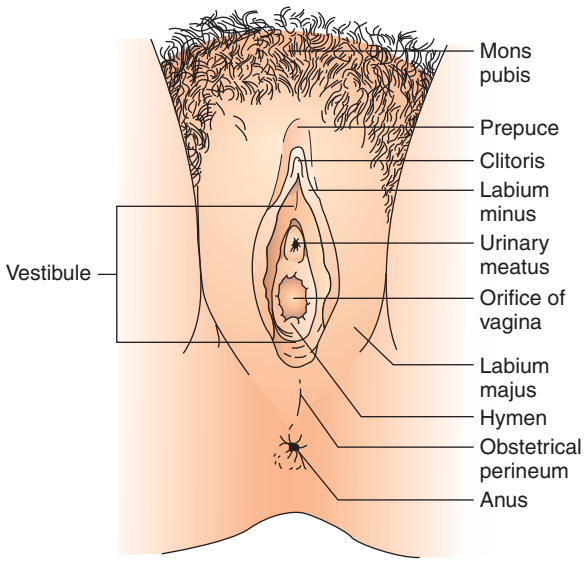


FIGURE 40-2. External genitalia of the female.

The Female Reproductive System

- The female reproductive system, which consists of the external and internal genitalia, has both sexual and reproductive functions.
- The external genitalia (labia majora, labia minora, clitoris, and vestibular glands) surround the openings of the urethra and vagina. Although the female urinary and genital structures are anatomically separate, their close proximity provides a means for cross-contamination and shared symptomatology.
- The internal genitalia of the female reproductive system are specialized to participate in sexual intercourse (the vagina), to produce and maintain the female egg cells (the ovaries), to transport these cells to the site of fertilization (the fallopian tubes), to provide a favorable environment for development of offspring (the uterus), and to produce the female sex hormones (the ovaries).

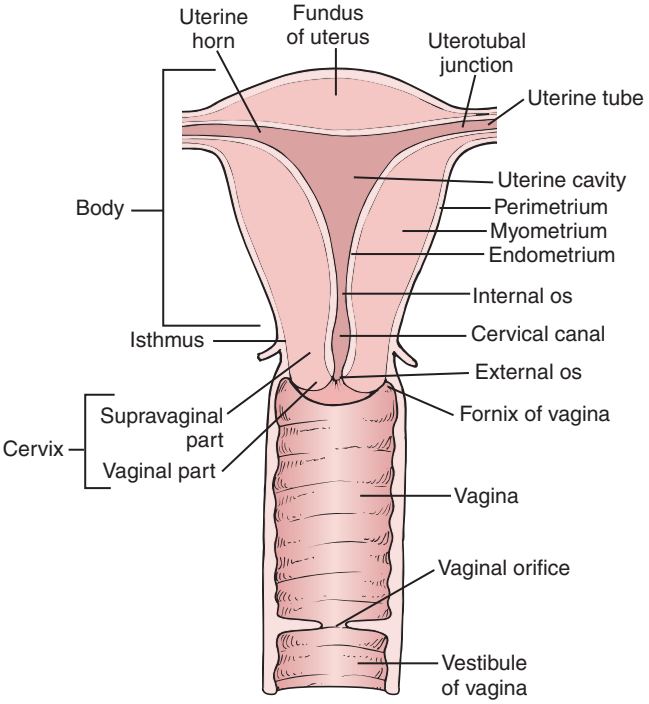


FIGURE 40-3. Median section of the vagina and uterus. (From Moore K.L., Agur A.M.R. [2002]. *Essential clinical anatomy* (2nd ed., p. 238). Philadelphia: Lippincott Williams & Wilkins.)

internal genitalia. The ducts of the Skene (periurethral) and Bartholin glands also open into the vestibule. Secretions from the Bartholin glands are responsible for sexually stimulated vaginal lubrication.

Internal Genitalia

Vagina

The vagina is a fibromuscular tube that connects the external and internal genitalia. The vagina, which is essentially free of sensory nerve fibers, is located behind the urinary bladder and urethra and anterior to the rectum (Fig. 40-3). The uterine cervix projects into the vagina at its upper end, forming recesses called *fornices*. The vagina functions as a route for discharge of menses and other secretions. It also serves as an organ of sexual fulfillment and reproduction.

Uterus and Cervix

The uterus is a thick-walled muscular organ. This pear-shaped, hollow structure is located between the bladder and the rectum. The uterus can be divided into three parts: the upper portion above the insertion of the fallopian tubes, called the *fundus;* the central tapering portion, called the *body;* and the inferior constricted part, called the *cervix*[1,2] (Fig. 40-3). The uterus is supported on both sides by four sets of ligaments: the *broad ligaments,* which run laterally from the body of the uterus to the pelvic side walls; the *round ligaments,* which run from the fundus laterally into each labium majus; the *uterosacral ligaments,* which run from the uterocervical junction to the sacrum; and the *cardinal* or *transverse cervical* ligaments, which are attached to the side of the uterus (Fig. 40-4).

The wall of the uterus is composed of three layers: the perimetrium, the myometrium, and the endometrium.[2] The *perimetrium* is the outer serous covering that is derived from the abdominal peritoneum. This outer layer merges with the peritoneum that covers the broad ligaments. Anteriorly, the perimetrium is reflected over the bladder wall, forming the *vesicouterine pouch*; posteriorly, it extends to form the *rectouterine pouch* (see Fig. 40-1). Because of the proximity of the perimetrium to the urinary bladder, a bladder infection often causes uterine symptoms, particularly during pregnancy.

The middle muscle layer, the *myometrium,* forms the major portion of the uterine wall. It is continuous with the muscle layer of the uterine tubes and the vagina. The smooth muscle also extends into the ligaments connected to the uterus. The inner fibers of the myometrium run in various directions, giving it an interwoven appearance. Contractions of these muscle fibers help to expel menstrual flow and the products of conception during miscarriage or childbirth.

The *endometrium,* or inner layer of the uterus, is continuous with the epithelial lining of the uterine tubes and vagina. It is actively involved in the menstrual cycle, differing in structure with each stage of the cycle (to be discussed). If conception occurs, the products of conception are implanted in this layer; if conception does not occur, the inner surface of this layer is shed through menstruation.

The round cervix forms the neck of the uterus. The opening, or os, of the cervix forms a pathway between the uterus and the vagina. The vaginal opening is called the *external os,* and the uterine opening, the *internal os*. The space between these two openings is called the *endocervical (cervical) canal.* Secretions from the columnar epithelium of the endocervix protect the uterus from infection, alter receptivity to sperm, and form a mucoid "plug" during pregnancy. The endocervical canal provides a route for menstrual discharge and entry of sperm.

Fallopian (Uterine) Tubes

The *fallopian*, or *uterine*, tubes are slender cylindrical structures attached bilaterally to the uterus and supported by the upper folds of the broad ligament.[1,2] The end of the fallopian tube nearest the ovary forms a funnel-like opening with fringed, fingerlike projections, called *fimbriae,* that pick up the ovum after its release into the peritoneal cavity after ovulation (see Fig. 40-4). The fallopian tubes are formed of smooth muscle and lined with a ciliated, mucus-producing epithelial layer. The beating of the cilia, along with contractile movements of the smooth muscle, propels the nonmobile ovum toward the uterus. Besides providing a passageway for ova and sperm, the fallopian tubes permit drainage of tubal secretions into the uterus.

Ovaries

The ovaries are paired organs located on either side of the uterus below the ends of the two fallopian tubes. In the

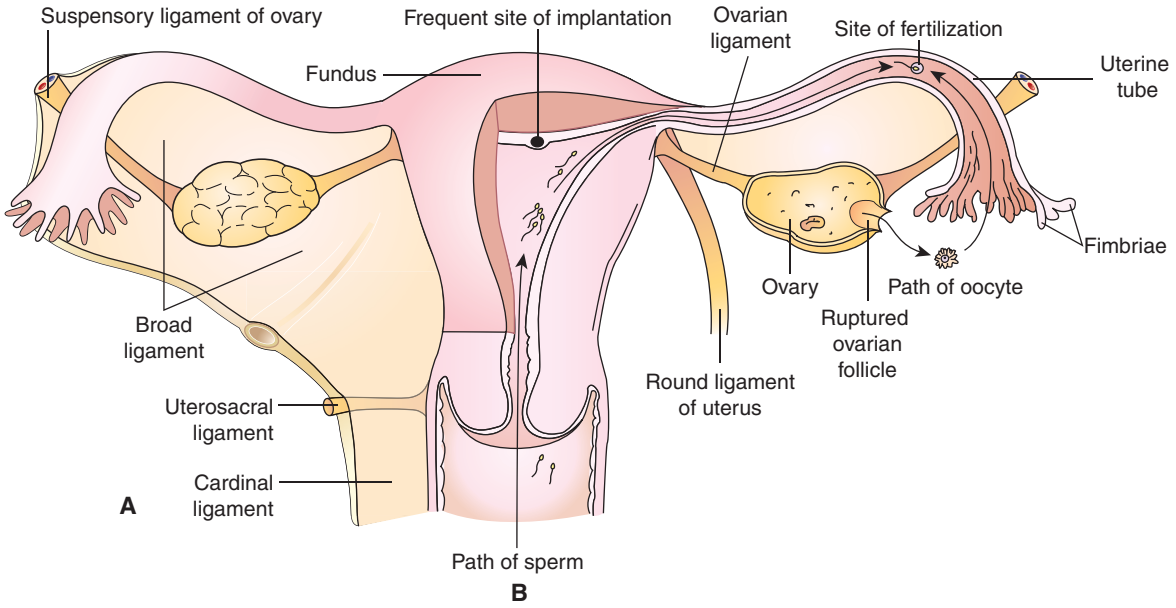


FIGURE 40-4. Schematic drawing of female reproductive organs, showing **(A)** suspensory ligament of the ovary and the broad, uterosacral, and cardinal ligaments on the left, and **(B)** the path of the oocyte as it moves from the ovary into the fallopian (uterine) tube; the path of sperm is also shown, as is the usual site of fertilization.

adult, the ovaries are flat, almond-shaped structures that measure 3 cm in length.[2] The ovaries are attached to the posterior surface of the broad ligament and to the uterus by the ovarian ligament (see Fig. 40-4). Structurally, the mature ovary is divided into a highly vascular inner medulla and an outer cortex. The medulla or medullary region is located in the central part of the ovary. It contains loose connective tissue, blood vessels, lymphatic vessels, and nerves. The ovarian cortex is composed of a connective tissue framework, the stroma (also known as the interstitial compartment), as well as ovarian follicles in various stages of development. The surface of the ovary is covered with a thin layer of surface epithelium that is continuous with the lining of the peritoneum. The integrity of this covering is periodically broken at the time of ovulation.

The Menstrual Cycle

Between menarche (i.e., first menstrual bleeding) and menopause (i.e., last menstrual bleeding), the female reproductive system undergoes cyclic changes called the *menstrual cycle*. This includes the maturation and release of oocytes from the ovary during ovulation and periodic vaginal bleeding resulting from the shedding of the endometrial lining. It is not necessary for a woman to ovulate to menstruate; anovulatory cycles do occur. The menstrual cycle produces changes in the breasts, uterus, skin, ovaries, and perhaps other, unidentified tissues.

The menstrual cycle is regulated by a complex interaction between the hypothalamic-pituitary axis, the ovaries, and the uterus[3,4] (Fig. 40-5). Although each part of the system is essential to normal function, the ovaries are primarily responsible for controlling the cyclic changes and the length of the menstrual cycle. In most women in the middle reproductive years, menstrual bleeding occurs every 25 to 35 days, with a median of 28 days.

The Hypothalamic-Pituitary Axis

The ovaries perform two interrelated functions—steroidogenesis, or production of the female sex hormones, and gametogenesis, or production of ova. Both of these functions are regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland[3,4] (Fig. 40-6). Because these hormones promote the growth of cells in the ovaries and testes as a means of stimulating the production of sex hormones, they are called the *gonadotropic hormones*. The secretion of LH and FSH is stimulated by gonadotropin-releasing hormone (GnRH) from the hypothalamus. These gonadotropins then trigger the ovary to release an oocyte that is capable of being fertilized. Concurrently, the ovary secretes hormones that act on the endometrial lining of the uterus to prepare for implantation. In addition, the ovarian hormones feed back to the hypothalamus and pituitary regarding the secretion of gonadotropins during the menstrual cycle.

In addition to LH and FSH, the anterior pituitary secretes a third hormone called *prolactin*. The primary function of prolactin is the stimulation of lactation in the postpartum period. During pregnancy, prolactin, along with other hormones such as estrogen, progesterone, insulin, and cortisol, contributes to breast development in preparation for lactation. Although prolactin does not appear to play a physiologic role in ovarian function, hyperprolactinemia can lead to hypogonadism. This may include an initial shortening of the luteal phase with subsequent anovulation, oligomenorrhea or amenorrhea, and infertility. The hypothalamic control of prolactin

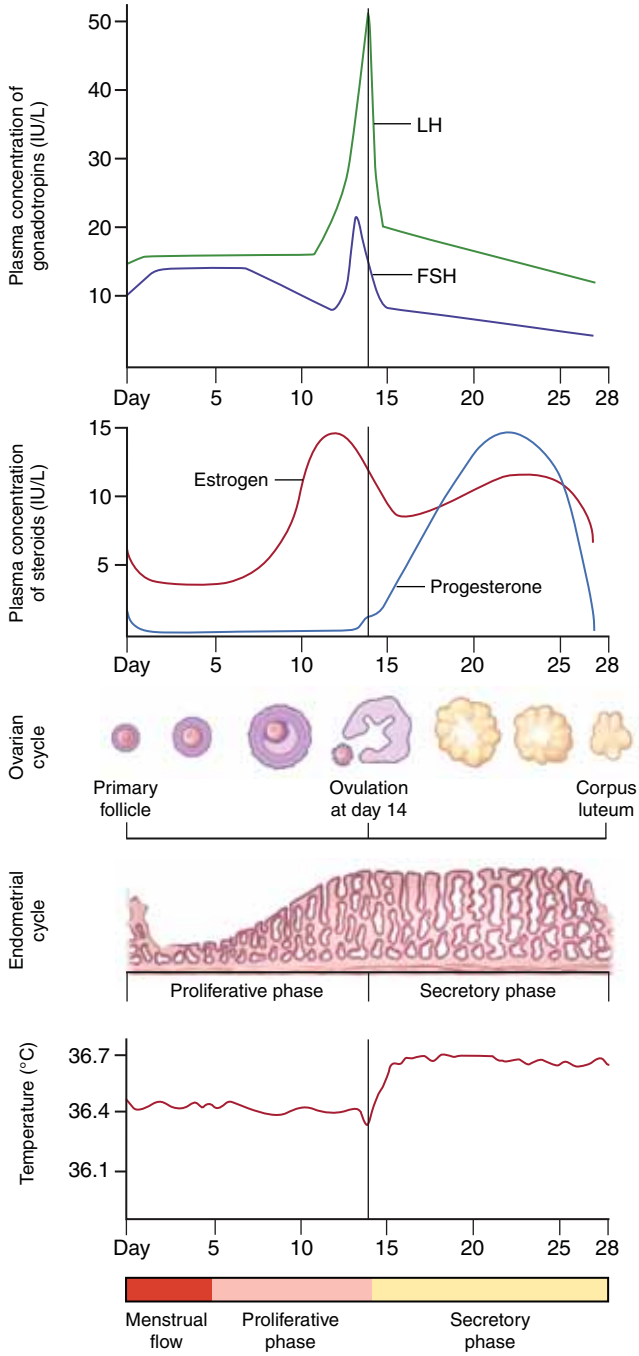


FIGURE 40-5. Hormonal and morphologic changes during the normal menstrual cycle.

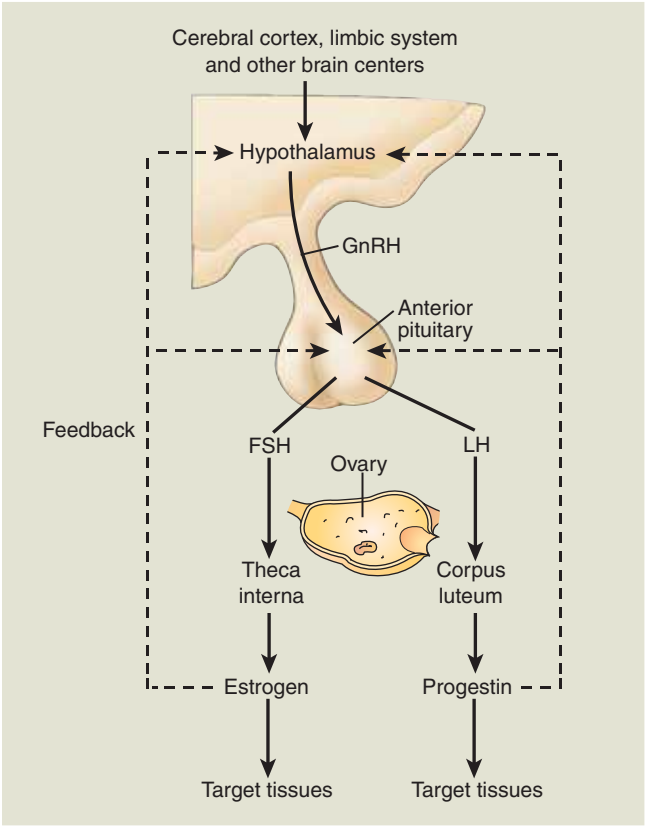


FIGURE 40-6. Hypothalamic-pituitary feedback control of estrogen and progesterone levels in the female. The *dashed line* represents negative feedback. GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

secretion is primarily inhibitory, and dopamine is the most important inhibitory factor. Hyperprolactinemia may occur as an adverse effect of drug treatment using phenothiazine derivatives (i.e., antipsychotic drugs that block dopamine receptors).

Ovarian Hormones

The ovaries produce estrogens, progesterone, and androgens. In the ovary, the main source of hormone production is the maturing follicle, including the theca cells, granulosa cells, and corpus luteum (to be discussed). The theca cells produce androgens, the granulosa cells produce estrogen, and the corpus luteum produces progesterone. The other stromal cells that contribute to the production of androgens can be divided into two populations: the secondary interstitial cells (derived from the theca) and the hilum cells. These cells are the major ones involved in androgen production during menopause.[3,4]

Estrogens. Estrogens are a family of structurally related female sex hormones synthesized and secreted by cells in the ovaries and, in small amounts, by cells in the adrenal cortex.[3–5] Androgens can be converted to estrogens peripherally, especially in adipose tissue. Three estrogens occur naturally in humans: estrone, estradiol, and estriol. Of these, estradiol is the most biologically potent and the most abundantly secreted product of the ovary. Estrogens are transported in the blood bound to specific plasma globulins, inactivated and conjugated in the liver, and then excreted in the bile.

Estrogens are necessary for normal female development.[3–5] They stimulate the development of the vagina, uterus, and uterine tubes in the embryo. They also stimulate the stromal development and ductal growth of the breasts at puberty, are responsible for the accelerated pubertal skeletal growth phase and for closure of the epiphyses of the long bones, contribute to the growth of

axillary and pubic hair, and alter the distribution of body fat to produce the typical female body contours. In concert with other hormones, estrogens provide for the reproductive processes of ovulation, implantation of the products of conception, pregnancy, parturition, and lactation by stimulating the development and maintaining the growth of the reproductive organs.

Estrogens also have a number of important other metabolic effects. They are responsible for maintaining the normal structure of skin and blood vessels in women. Estrogens decrease the rate of bone resorption by antagonizing the effects of calcitonin on bone; for this reason, osteoporosis is a common problem in estrogen-deficient postmenopausal women (see Chapter 44). In the liver, estrogens increase the synthesis of transport proteins for thyroxine, estrogen, testosterone, and other hormones. Estrogens also affect the composition of the plasma lipoproteins. They produce an increase in high-density lipoproteins (HDLs), a slight reduction in low-density lipoproteins (LDLs), and a reduction in cholesterol levels (see Chapter 18). Estrogens also increase plasma triglyceride levels, and they enhance the coagulability of blood by increasing the circulating levels of plasminogen and factors II, VII, IX, and X. Estrogens, which have a chemical structure similar to adrenal cortical hormones, can also cause sodium and water retention by the kidney. Most women retain sodium and water and gain weight just before menstruation. The actions of estrogens are summarized in Table 40-1.

Although the ovaries are the major source of estrogen, the biosynthesis of estrogens that occurs in adipose tissue may be a significant source of the hormone. There is evidence that a certain minimum body weight and fat content are necessary for menarche to occur and for the menstrual cycle to be maintained.[4] This is supported by the observation of amenorrhea in women with anorexia nervosa, chronic disease, and malnutrition and in those who are long-distance runners. In women with anorexia nervosa, gonadotropin and estradiol secretion, including LH release and responsiveness to the hypothalamic GnRH, can revert to prepubertal levels. With resumption of weight gain and attainment of sufficient body mass, the normal hormonal pattern usually is reinstated. Obesity or significant weight gain also is associated with oligomenorrhea or amenorrhea and infertility, although the mechanism is not well understood.

Progesterone. Although the word *progesterone* refers to a substance that maintains pregnancy, progesterone is secreted as part of the normal menstrual cycle.[3,4] The corpus luteum of the ovary secretes large amounts of progesterone after ovulation, and the adrenal cortex secretes small amounts. The hormone circulates in the blood attached to a specific plasma protein. It is metabolized in the liver and conjugated for excretion in the bile.

The local effects of progesterone on reproductive organs include the glandular development of the lobular and alveolar tissue of the breasts and the cyclic glandular development of the endometrium. Progesterone also can compete with aldosterone at the level of the renal tubule, causing a decrease in sodium reabsorption, with a resultant increase in secretion of aldosterone by the adrenal cortex (as occurs in pregnancy). Although the mechanism is uncertain, progesterone increases basal

TABLE 40-1 Actions of Estrogens

General Function	Specific Actions
Growth and development	
Reproductive organs	Stimulate development of vagina, uterus, and fallopian tubes in utero and of secondary sex characteristics during puberty
Skeleton	Accelerate growth of long bones and closure of epiphyses at puberty
Reproductive processes	
Ovulation	Promote growth of ovarian follicles
Fertilization	Alter the cervical secretions to favor survival and transport of sperm
	Promote motility of sperm within the fallopian tubes by decreasing mucus viscosity
Implantation	Promote development of endometrial lining in the event of pregnancy
Vagina	Proliferate and cornify vaginal mucosa
Cervix	Increase mucus consistency
Breasts	Stimulate stromal development and ductal growth
General metabolic effects	
Bone resorption	Decrease rate of bone resorption
Plasma proteins	Increase production of thyroid and other binding globulins
Lipoproteins	Increase high-density and slightly decrease low-density lipoproteins

body temperature and is responsible for the increase in body temperature that occurs with ovulation. Smooth muscle relaxation under the influence of progesterone plays an important role in maintaining pregnancy by decreasing uterine contractions and is responsible for many of the common discomforts of pregnancy, such as edema, nausea, constipation, flatulence, and headaches. The increased progesterone present during pregnancy and the luteal phase of the menstrual cycle enhances the ventilatory response to carbon dioxide, leading to a measurable change in arterial and alveolar carbon dioxide (PCO_2) levels.

Androgens. Ovarian cells also secrete androgens. In the female, androgens contribute to normal hair growth at puberty and may have other important metabolic effects. Androgen production takes place in the connective tissue (stroma) that surrounds the follicles.[4] During the reproductive years, the ovaries are directly responsible for one third of testosterone production. The remaining two thirds comes from the periphery and ovarian and adrenal precursors—mainly androstenedione, which is produced in equal proportions by the adrenal and ovary. The adrenal gland may directly secrete testosterone, but its main contribution is derived from its production of precursors.

Ovarian Follicle Development and Ovulation

Unlike the male gonads, which produce sperm throughout a man's reproductive life, the female gonads contain a fixed number of ova at birth that diminishes throughout a woman's life. The process of oogenesis (generation of ova by mitotic division) begins during the sixth week of fetal life and proceeds to the development of the primary oocytes, which become surrounded by a single layer of granulosa cells.[2–4] The primary oocytes with their surrounding granulosa cells are referred to as *primordial follicles*. These primitive germ cells provide the 1 to 2 million oocytes that are present in the ovaries at birth. Throughout childhood, the granulosa cells provide nourishment for the ovum and secrete an inhibiting factor that keeps the ovum suspended in a primordial state.

Beginning at puberty, a cyclic rise in the anterior pituitary hormones FSH and LH stimulates the development of several graafian, or mature, follicles. Follicles at all stages of development can be found in both ovaries, except in menopausal women (Fig. 40-7). Most follicles exist as primary follicles, each of which consists of a round oocyte surrounded by a single layer of flattened epithelial cells called *granulosa cells*. The primary follicles constitute an inactive pool of follicles from which all the ovulating follicles develop. Under the influence of endocrine stimulation, 6 to 12 primary follicles develop into secondary follicles once every ovulatory cycle. During the development of the secondary follicle, the primary oocyte increases in size, and the granulosa cells proliferate to form a multilayered wall around it. During this time, a membrane called the *zona pellucida* develops and surrounds the oocyte and small pockets of fluid begin to appear between the granulosa cells.

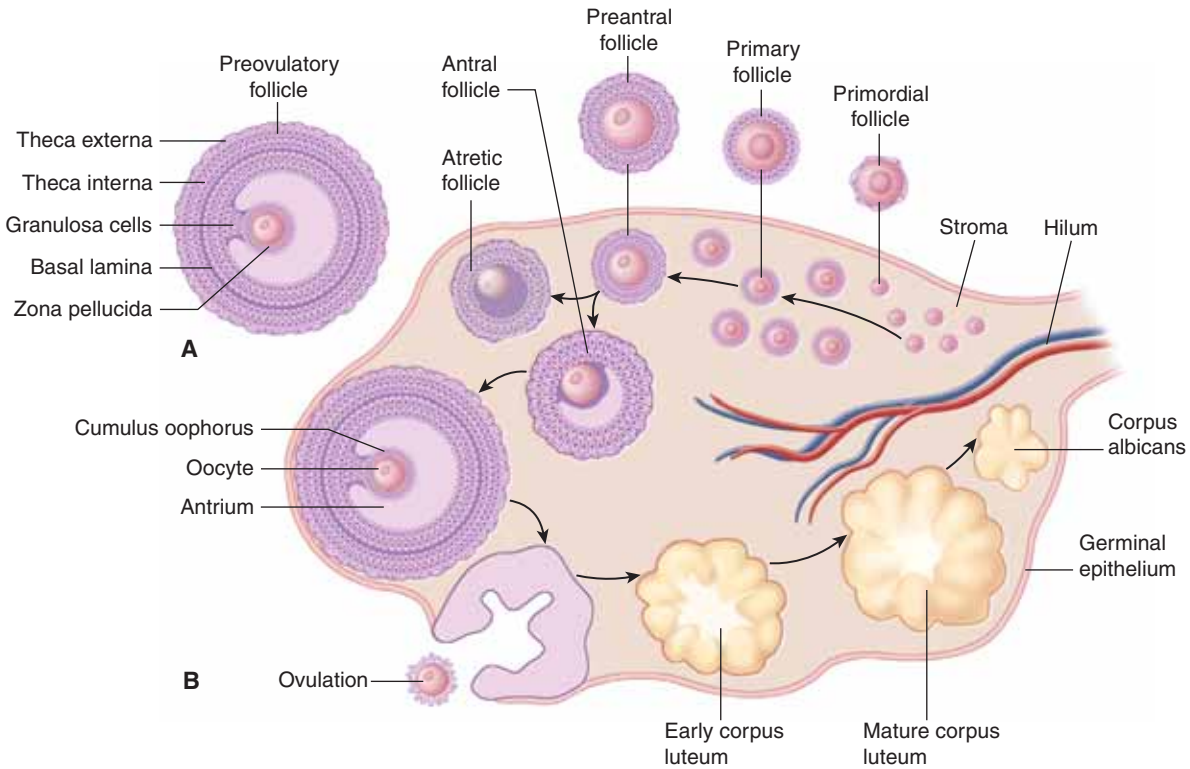


FIGURE 40-7. **(A)** Cross-section of preovulatory follicle. **(B)** Schematic diagram of an ovary, showing the sequence of events in the origin, growth, and rupture of an ovarian follicle and the formation and retrogression of a corpus luteum. The atretic follicles are those that show signs of degeneration and death.

As the follicles mature, FSH stimulates the development of the cell layers. Cells from the surrounding stromal tissue align themselves to form a sheath of connective tissue cells, known as the *theca folliculi*. The cells of the theca folliculi become differentiated into two layers: an inner layer of highly vascularized androgen-producing cells, called the *theca interna,* and an outer layer of connective tissue, called the *theca extern.* As the follicle enlarges, a single large cavity, or *antrum,* is formed, and a portion of the granulosa cells and the oocyte are displaced to one side of the follicle by the fluid that accumulates. The secondary oocyte remains surrounded by a crown of granulosa cells, the *corona radiata*. As the follicle matures, ovarian estrogen is produced by the granulosa cells. Selection of a dominant follicle occurs with the conversion to an estrogen microenvironment. The lesser follicles, although continuing to produce some estrogen, degenerate or become atretic. The dominant preovulatory follicle accumulates a greater mass of granulosa cells, and the theca becomes richly vascular, giving the follicle a hyperemic appearance. High levels of estrogen exert a negative feedback effect on FSH, inhibiting the development of multiple follicles and causing an increase in LH levels. This represents the follicular stage of the menstrual cycle. As estrogen suppresses FSH, the actions of LH predominate, and the mature follicle (measuring approximately 20 mm) bursts; the oocyte, along with the corona radiata, is ejected from the follicle. The ovum normally is then picked up and transported through the fallopian tube toward the uterus.

After ovulation, the follicle collapses, and the luteal stage of the menstrual cycle begins. The granulosa cells are invaded by blood vessels and yellow lipochrome-bearing cells from the theca layer. A rapid accumulation of blood and fluid forms a mass called the *corpus luteum.* Leakage of this blood onto the peritoneal surface that surrounds the ovary is thought to contribute to the *mittelschmerz* ("middle [or intermenstrual] pain") of ovulation. During the luteal stage, progesterone is secreted from the corpus luteum. If fertilization does not take place, the corpus luteum atrophies and is replaced by white scar tissue called the *corpus albicans;* the hormonal support of the endometrium is withdrawn and menstruation occurs. In the event of fertilization, a hormone called *human chorionic gonadotropin* is produced by the trophoblastic cells in the blastocyst. This hormone prevents luteal regression. The corpus luteum remains functional for 3 months and provides hormonal support for pregnancy until the placenta is fully functional.

Endometrial Changes

The endometrium consists of two distinct layers, or zones, that are responsive to hormonal stimulation: a basal layer and a functional layer. The *basal layer* lies adjacent to the myometrium and is not sloughed during menstruation.[2–4] The *functional layer* arises from the basal layer and undergoes proliferative changes and menstrual sloughing. It can be subdivided into two components: a thin, superficial, compact layer and a deeper spongiosa layer that makes up most of the secretory and fully developed endometrium. The endometrial cycle can be divided into three phases: proliferative, secretory, and menstrual (see Fig. 40-5). The proliferative, or preovulatory, phase is the period during which the glands and stroma of the superficial layer grow rapidly under the influence of estrogen. The secretory, or postovulatory, phase is the period during which progesterone produces glandular dilatation and active mucus secretion and the endometrium becomes highly vascular and edematous. The menstrual phase is the period during which the superficial layer degenerates and sloughs off.

In summary, the female reproductive system consists of external and internal genitalia. The external genitalia are situated in the anterior part of the perineum, and the internal structures (uterus, fallopian tubes, and ovaries) are located in the pelvic cavity. The uterus is a thick-walled, muscular organ. The wall of the uterus is composed of three layers: the outer perimetrium; the myometrium or muscle layer, which is continuous with the myometrium of the fallopian tubes and the vagina; and the inner lining or endometrium, which is continuous with the lining of the fallopian tubes and vagina. The paired gonads, or ovaries, have the dual function of steroidogenesis, or production of the female sex hormones, and gametogenesis, or production of female germ cells (ova). Unlike the male gonads, which produce sperm throughout a man's reproductive life, the female gonads contain a fixed number of ova at birth that diminishes throughout a woman's life.

Between menarche and menopause, the female reproductive system undergoes cyclic changes called the *menstrual cycle.* The normal menstrual cycle results from complex interactions among the hypothalamus, which produces GnRH; the anterior pituitary gland, which synthesizes and releases FSH, luteinizing hormone (LH), and prolactin; the ovaries, which synthesize and release estrogens, progesterone, and androgens; and the endometrium. Although each component of the system is essential for normal functioning, the ovarian hormones are largely responsible for controlling the cyclic changes and length of the menstrual cycle. Estrogens are necessary for normal female physical maturation, for growth of ovarian follicles, for generation of a climate that is favorable to fertilization and implantation of the ovum, and for promoting the development of the endometrium in the event of pregnancy. The functions of progesterone include the glandular development of the lobular and alveolar tissue of the breasts, the cyclic development of the glandular endometrium, and maintenance of pregnancy. Androgens, produced in the ovary, are derived from precursors produced by the ovary or adrenal gland, contribute to hair distribution in the female, and may have important metabolic effects.

Disorders of the Female Reproductive Organs

Disorders of the female reproductive system have widespread effects on physical, psychological, sexual, and reproductive function. The reproductive organs are located close to other pelvic structures, particularly those of the urinary system, and disorders of the reproductive system may affect urinary function. This section of the chapter focuses on infections and benign and malignant disorders of the external and internal genitalia.

Disorders of the External Genitalia

The external genitalia, which are covered with stratified squamous epithelium, are subject to dermatologic conditions that affect skin elsewhere in the body. The discussion in this section of the chapter focuses on Bartholin gland cysts and benign and malignant disorders of the vulva.

Bartholin Gland Cyst and Abscess

A Bartholin gland cyst is a fluid-filled sac located near the vaginal introitus that results from obstruction of the main duct of the gland.[6–8] It may become large, up to 3 to 5 cm in diameter, and produce pain and local discomfort. Infection of a Bartholin cyst produces acute inflammation within the gland and may result in an abscess. Acute symptoms are usually the result of infection and include pain, tenderness, and dyspareunia.

The treatment of symptomatic Bartholin gland cysts consists of the administration of appropriate antibiotics, local application of moist heat, and incision and drainage. Cysts that frequently are abscessed or are large enough to cause blockage of the introitus may require surgical intervention (i.e., marsupialization, a procedure that involves removal of a wedge of vulvar skin and the cyst wall).[8] Because the Bartholin glands usually shrink during menopause, a vulvar growth in postmenopausal women should be evaluated for malignancy.

Benign and Malignant Disorders of the Vulva

Disorders of the vulva often present as white lesions of the vulvar skin and mucosa that may produce pruritus (itching) and scaling. Although commonly referred to as *leukoplakia* because of their plaquelike appearance, these lesions can represent a number of disorders including inflammatory dermatoses (e.g., psoriasis or chronic dermatitis, discussed in Chapter 46), nonneoplastic epithelial disorders, and premalignant and malignant lesions of the vulva.[6]

Nonneoplastic Epithelial Disorders. The term *nonneoplastic epithelial disorders* refers to nonmalignant atrophic and hyperplastic changes of the vulvar skin and mucosa.[6,7,9] Depending on clinical and histologic characteristics, the lesions can be further categorized as lichen sclerosus and squamous cell hyperplasia (formerly known as *lichen simplex chronicus*).

Lichen sclerosus is an inflammatory disease of the vulva characterized by plaquelike areas that may progress to parchment-thin epithelium with focal areas of ecchymosis and superficial ulcerations secondary to scratching. Atrophy and contracture of the vulvar tissues with eventual stenosis of the introitus are common when this condition becomes chronic. Itching is common and dyspareunia (painful intercourse) is frequent. The condition develops insidiously and is progressive.

Squamous cell hyperplasia, which usually presents as thickened, gray-white plaques with an irregular surface, is a nonspecific condition resulting from rubbing or scratching on the skin to relieve pruritus. Presumed to be a response of the genital skin to some type of irritant, this diagnosis is used only when human papillomavirus (HPV) infection (see Chapter 41), fungal infections, or other known causative conditions have been excluded. Pruritus is the most common presenting complaint. Scaling is generally present, and excoriations due to recent scratching can often be seen. There is generally no increased predisposition to cancer, but similar lesions are often present at the margins of established cancer of the vulva.

Current treatment for lichen sclerosus includes the use of topical corticosteroids. Lichen sclerosus frequently recurs, and lifetime maintenance therapy may be required. Hyperplastic areas that occur in the field of lichen sclerosus may be sites of malignant change and warrant close follow-up and possible biopsy.

Premalignant and Malignant Neoplasms. Carcinoma of the vulva is a relatively rare cancer that accounts for approximately 3% to 5% of all cancers of the female reproductive system in the United States, occurring most often in women 60 years of age or older.[6] Approximately 90% of vulvar malignancies are squamous cell carcinomas.[10] Less common forms of vulvar cancer include malignant melanomas, adenocarcinoma, basal cell carcinoma, and metastatic cancers from various other sites.

In terms of etiology, pathogenesis, and clinical presentation, vulvar carcinoma can be divided into two general groups: (1) basaloid and warty carcinomas, related to infection with oncogenic strains of HPV (about 30% of cases), and (2) keratinizing squamous cell carcinoma, not related to HPV infection (about 70% of cases).[6,7]

Invasive basaloid and warty-type carcinomas develop from a precancerous in situ lesion called vulvar intraepithelial neoplasia (VIN). This type of lesion occurs in reproductive-age women, and risk factors are similar to those for cancer in situ of the cervix.[6] Spontaneous resolution of VIN lesions has occurred. The risk of progression to invasive cancer increases in older women and in women with suppressed immune function. The second form of vulvar cancer, which is seen more often in older women, is generally preceded by vulvar nonneoplastic disorders such as chronic vulvar irritation or lichen sclerosus. The etiology of this group of vulvar cancers is unclear, but they are not typically associated with HPV. Neoplastic changes may arise from lichen sclerosus lesions or hyperplasia, leading directly to invasion, or through an intermediate step involving cellular atypia.[6]

The initial lesion of squamous cell vulvar carcinoma may appear as an inconspicuous thickening of the skin, a small raised area or lump, or an ulceration that fails to heal. It may be single or multiple and vary in color from white to velvety red or black. The lesions may resemble eczema or dermatitis and may produce few symptoms other than pruritus, local discomfort, and exudation. The symptoms frequently are treated with various home remedies before medical treatment is sought. The lesion may become secondarily infected, causing pain and discomfort. The malignant lesion gradually spreads superficially or as a deep furrow involving all of one labial side. Because there are many lymph channels around the vulva, the cancer metastasizes freely to the regional lymph nodes, including those of the inguinal and femoral chains.[11]

Early diagnosis is important in the treatment of vulvar carcinoma. Because malignant lesions can vary in appearance and commonly are mistaken for other conditions, biopsy and treatment often are delayed. Any vulvar lesion that is increasing in size or has an unusual wartlike appearance should be biopsied.[11] Treatment is primarily wide surgical excision of the lesion for noninvasive cancer and radical excision or vulvectomy with node resection for invasive cancer.

Vulvodynia

Vulvodynia is a syndrome of unexplained vulvar pain, previously referred to as *vulvar pain syndrome* or *burning vulva syndrome*.[12,13] The terminology and diagnostic criteria used for this chronic disorder remain in flux, but the most recent classification system of the International Society for the Study of Vulvovaginal Disorders (ISSVD) defines it as a condition characterized by "burning, stinging, irritation, soreness or rawness in the absence of relevant visible findings or a specific, clinically identifiable, neurological disorder."[12] Vulvodynia is further classified as localized or generalized, and as to whether it is provoked, unprovoked, or of mixed origin.

Localized vulvodynia or *vestibulodynia,* formerly referred to as *vulvar vestibulitis syndrome,* is characterized by pain at onset of intercourse, localized point tenderness near the vaginal opening, and sensitivity to tampon placement, tight-fitting pants, bicycling, or prolonged sitting. It is the leading cause of dyspareunia in women younger than 50 years of age. The pain can be primary (present from first contact) or secondary (developing after a period of comfortable sexual relations). The etiology is unknown, but the problem may evolve from chronic vulvar inflammation or trauma. Nerve fibers that supply the vestibular epithelium may become highly sensitized, causing neurons in the dorsal horn of the spinal cord to respond abnormally, thus transforming the sensation of touch in the vestibule into pain.

Generalized vulvodynia, formerly called *vulvar dysesthesia* or *essential vulvodynia,* involves severe, constant, widespread burning that interferes with daily activities. No abnormalities are found on examination, but there is diffuse and variable hypersensitivity and altered sensation to light touch. The quality of this unprovoked pain shares many of the features of other neuropathic pain disorders, particularly complex regional pain syndrome (see Chapter 35) or pudendal neuralgia. Although the cause of the neuropathic pain is unknown, it has been suggested that it may result from myofascial restrictions affecting the sacral and pelvic floor nerves.[12,13]

There are many proposed triggers for vulvodynia, including chronic recurrent vaginal infections; chemical irritation or drug effects, especially prolonged use of topical steroid creams; the irritating effects of elevated urinary levels of calcium oxalate; and immunoglobulin A deficiency or other disorders of immune regulation. Often it is multifactorial in origin.

Careful history taking and physical assessment are essential for differential diagnosis and treatment. *Vulvodynia* is a diagnosis of exclusion after ruling out infections, such as candidiasis and genital herpes; inflammatory conditions, such as squamous cell hyperplasia and lichen sclerosus; vulvar cancer; or neurologic disorders, such as herpes neuralgia or spinal nerve compression, as causes for the pain.

Treatment of vulvodynia is aimed at symptom relief, is frequently long term, and often needs to be managed from a multidimensional, chronic pain perspective.[12,13] Local measures include avoidance of harsh soaps and perfumed products, use of sitz baths, and application of topical anesthetic agents (i.e., lidocaine ointment). Because dermatologic conditions such as atopic dermatitis and candidiasis are responsible for many of the symptoms of vulvodynia, some health care providers recommend treatment with antihistamines and antifungal medications, as well as avoidance of irritating contactants.[14] Biofeedback and physical therapy may be used to reverse the changes in pelvic floor musculature and help women control the muscles, regaining strength and improving relaxation. Oral medications, including tricyclic antidepressants and other antidepressants, are often used to treat the neuropathic pain associated with vulvodynia.

Disorders of the Vagina

The normal vaginal ecology depends on the delicate balance of hormones and bacterial flora. Normal estrogen levels maintain a thick, protective squamous epithelium that contains glycogen. Döderlein bacilli, part of the normal vaginal flora, metabolize glycogen, and in the process produce the lactic acid that normally maintains the vaginal pH of 3.8 to 4.5.[15] Disruptions in these normal environmental conditions predispose to infection.

Vaginitis

Vaginitis represents an inflammation of the vagina that is characterized by vaginal discharge and burning, itching, redness, and swelling of vaginal tissues. Pain often occurs with urination and sexual intercourse. Vaginitis may be caused by chemical irritants, foreign bodies, or infectious agents. The causes of vaginitis differ in various age groups. In premenarchal girls, most vaginal infections have nonspecific causes, such as poor hygiene, intestinal parasites, or the presence of foreign bodies. *Candida albicans, Trichomonas vaginalis,* and bacterial vaginosis are

the most common causes of vaginitis in the childbearing years, and some of these organisms can be transmitted sexually[15] (see Chapter 41).

The decrease in estrogen levels that occurs during perimenopause and after menopause can lead to an atrophic form of vaginitis.[16] Estrogen deficiency results in a lack of regenerative growth of the vaginal epithelium and changes in the vaginal pH and flora, rendering these tissues more susceptible to infection and irritation. Döderlein bacilli disappear, and the vaginal secretions become less acidic. The symptoms of atrophic vaginitis include itching, burning, and dyspareunia. These symptoms usually can be reversed by local application of estrogen.

Every woman normally experiences vaginal discharge during the menstrual cycle, but it should not cause burning or itching or have an unpleasant odor. These symptoms suggest inflammation or infection. Because these symptoms are common to the different types of vaginitis, precise identification of the organism is essential for proper treatment. A careful history should include information about systemic disease conditions, the use of drugs such as antibiotics that foster the growth of yeast, dietary habits, stress, and other factors that alter the resistance of vaginal tissue to infections. A physical examination usually is done to evaluate the nature of the discharge and its effects on the genital structures. Microscopic examination of a saline wet-mount smear is the primary means of identifying the organism responsible for the infection.[15,16] Culture methods and deoxyribonucleic acid (DNA) probe tests may be needed when the organism is not apparent on a wet-mount preparation.

Cancer of the Vagina

Primary cancers of the vagina are extremely rare, accounting for approximately 1% to 2% of all cancers of the female reproductive system.[6,7,10] Like vulvar carcinoma, cancer of the vagina is largely a disease of older women, with a peak incidence between 60 and 70 years of age.[7] The exception to that is the clear cell adenocarcinoma associated with diethylstilbestrol (DES) exposure in utero. DES is a hormonal drug that was given to some women to prevent miscarriage during the years between 1940 and 1971.[17] Vaginal cancers may also result from local extension of cervical cancer, from exposure to sexually transmitted HPV, or rarely from local irritation such as occurs with prolonged use of a pessary. Smoking and human immunodeficiency virus (HIV) infection also increase the risk of vaginal cancer.

Approximately 70% of vaginal cancers are squamous cell carcinomas, with other less common types being adenocarcinomas (15%), malignant melanomas (9%), and sarcomas (up to 4%).[17] Squamous cell carcinomas begin in the epithelium and progress over many years from precancerous lesions called *vaginal intraepithelial neoplasia* (VAIN). Not infrequently, squamous cell carcinoma develops some years after cervical or vulvar carcinoma, a sequence that supports the carcinogenic effect in the lower genital tract related to HPV infection.

The most common symptom of vaginal carcinoma is abnormal bleeding. Other signs or symptoms include an abnormal vaginal discharge, a palpable mass, or dyspareunia. Most women with preinvasive vaginal carcinoma are asymptomatic, with the cancer being discovered during a routine pelvic examination. The anatomic proximity of the vagina to other pelvic structures (urethra, bladder, and rectum) permits early spread to these areas. Pelvic pain, dysuria, and constipation can be associated symptoms.

Since most preinvasive and early invasive cancers are silent, the routine use of vaginal cytology (Papanicolaou [Pap] smear) is the most effective way to detect vaginal cancer. Diagnosis requires biopsy of suspect lesions or areas. Both radiation and surgical methods are used in treatment of vaginal cancer, with the treatment plan being determined by the cancer type, stage of the disease (i.e., size, location, and spread), and the woman's age. Radiation therapy is the mainstay for treatment of squamous cell carcinomas. Radical hysterectomy combined with upper vaginectomy and pelvic lymph node dissection may be used for selected cases.[11]

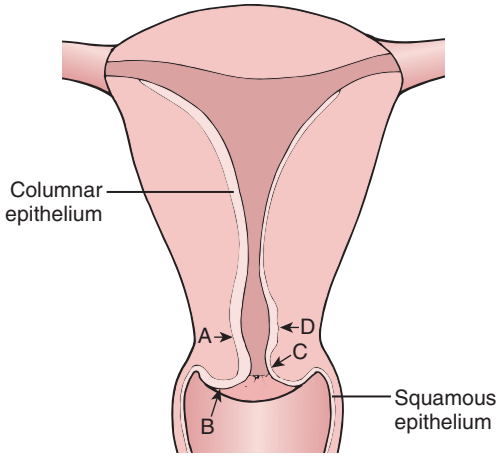
Disorders of the Uterine Cervix

The cervix is composed of two types of epithelial tissue: stratified squamous and columnar epithelium. The exocervix, or visible portion, is covered with stratified squamous epithelium, which also lines the vagina. The endocervix, which is the canal that leads to the endometrial cavity, is lined with columnar epithelium that contains large, branched mucus-secreting glands. The amount and properties of the mucus secreted by the gland cells vary during the menstrual cycle. Blockage of the mucosal glands results in trapping of mucus in the deeper glands, leading to the formation of dilated cysts in the cervix called *nabothian cysts*. These are benign cysts that require no treatment unless they become so numerous that they cause cervical enlargement.

The junction of the squamous epithelium of the exocervix and mucus-secreting columnar epithelium of the endocervix (i.e., squamocolumnar junction) appears at various locations on the cervix at different points in a woman's life (Fig. 40-8). During childhood, the squamocolumnar junction is located just inside the external os. The combination of hormones and the acidification of the vaginal environment that occurs during puberty lead to a gradual transformation from columnar to squamous epithelium—a process called *metaplasia* (see Chapter 2). The metaplasia in these cells causes the squamocolumnar junction to "roll out" or evert from its original position inside the external os to a position of enlarged cervical surface, where it is exposed to vaginal secretions, irritants, and a changing hormonal environment. The area of dynamic change where metaplasia takes place is called the *transformation zone*.[6,7] The transformation zone is a critical area for the development of cervical cancer.

Cervicitis

Cervicitis is an acute or chronic inflammation of the cervix. Acute cervicitis may result from the direct infection of the cervix or may be secondary to a vaginal or uterine infection. It may be caused by a variety of



A. Menarchial
B. Menstruating
C. Menopausal
D. Postmenopausal

FIGURE 40-8. Location of the squamocolumnar junction (transformation zone) in menarchial, menstruating, menopausal, and postmenopausal women.

infective agents, including *C. albicans, T. vaginalis, Neisseria gonorrhoeae, Gardnerella vaginalis, Chlamydia trachomatis, Ureaplasma urealyticum,* and herpes simplex virus. *C. trachomatis* is the organism most commonly associated with mucopurulent cervicitis. With acute cervicitis, the cervix becomes reddened and edematous. Irritation from the infection results in copious mucopurulent drainage. Depending on the causative agent, acute cervicitis is treated with appropriate antibiotic therapy.

Chronic cervicitis represents a low-grade inflammatory process. It is seen most commonly in parous women and may be sequelae to minute lacerations that occur during childbirth, instrumentation, or other trauma. The organisms usually are nonspecific—often staphylococcal, streptococcal, or coliform bacilli. The symptoms of chronic cervicitis are less well defined than those of acute cervicitis. The cervix may be ulcerated or normal in appearance; it may contain nabothian cysts; the cervical os may be distorted by old lacerations or everted to expose areas of columnar epithelium; and a mucopurulent drainage may be present.

Untreated cervicitis may extend to include the development of pelvic cellulitis, low back pain, dyspareunia, cervical stenosis, dysmenorrhea, and ascending infection of the uterus or fallopian tubes. Diagnosis of chronic cervicitis is based on vaginal examination, colposcopy, Pap smears, and occasionally biopsy to exclude malignant changes. Treatment usually involves cryosurgery or cauterization, which causes the tissues to slough and leads to eradication of the infection.

Premalignant Lesions and Cancer of the Cervix

Cervical cancer is one of the best-understood cancers and potentially one of the most preventable. In the 1950s cervical cancer was the leading cause of cancer deaths in women in the United States, but the death rate has declined steadily over the past several decades due to prevention and early detection by cancer screening.[6] Worldwide, however, cervical cancer continues to remain a commonly diagnosed cancer in women. More than 80% of these cases occur in developing countries, where cervical cancer kills more women than any other cancer.[18]

Pathogenesis and Risk Factors. The pathogenesis of cervical cancer has been linked to HPV infection by a series of epidemiologic, pathologic, and molecular genetic studies. Of the approximate 100 types of HPV, about 40 affect the anogenital tract. About 15 of these types are associated with cancer and are known as high-risk groups, with subtypes 16 and 18 being the most important in terms of cervical cancer pathology (see Chapter 41).[6] HPV 16 accounts for almost 60% of cervical cancer cases, and HPV 18 for another 10%.[7] By contrast, low-risk types 6 and 11 are associated with genital warts (condylomata acuminata).

Most cervical cancers begin their development in the transformation zone. The metaplastic cells within this zone represent the newest and least mature cells in the cervix, and it is thought that they are most vulnerable to oncogenic change. Even though HPV has been firmly established as a causative factor in cervical cancer, the evidence does not implicate HPV as the only risk factor. Most HPV infections are transient, indicating the host's defense system is able to eradicate the virus before it can cause neoplastic changes in cervical cells. Other factors such as cigarette smoking, dietary and nutritional factors, early age of first sexual intercourse, family history of cervical cancer, immunodeficiency (e.g., HIV infection), multiparity, use of oral contraceptive agents, and a history of

Gynecologic Cancers

- Cancers of the vulva, cervix, endometrium, and ovaries represent a spectrum of malignancies.
- Cancers of the vulva and cervix are mainly squamous cell carcinomas. Certain types of sexually transmitted human papillomaviruses are risk factors for cervical intraepithelial neoplasia, which can be a precursor lesion of invasive carcinoma.
- Endometrial cancers, which are seen most frequently in women 55 to 65 years of age, are strongly associated with conditions that produce excessive estrogen stimulation and endometrial hyperplasia.
- Ovarian cancer is the second most common female cancer and the most lethal. The most significant risk factors for ovarian cancer are the length of time that a woman's ovarian cycles are not suppressed by pregnancy, lactation, or oral contraceptive use, and family history.

chlamydial, *Trichomonas*, or herpes virus infection may play a contributing role in determining whether a woman with HPV infection develops cervical cancer.[6,19]

A quadrivalent vaccine (Gardasil) to prevent infection with the HPV subtypes 16, 18, 6, and 11 is now available.[20,21] The target population for the vaccine is females between the ages of 9 and 26 years, optimally before initiation of sexual activity. Clinical studies have confirmed that the vaccine appears safe and effective in inducing long-term immunity to HPV.[21] Although its use in males and older women or those who have already become sexually active has not been studied, it may offer some protection.

Premalignant and Malignant Lesions. One of the most important advances in the early diagnosis and treatment of cancer of the cervix was made possible by the observation that this cancer arises from precancerous lesions that begin with the development of atypical cervical cells. There are variations in cell size and shape and changes in the nuclear and cytoplasmic parts of the cell, commonly referred to as *dysplasia* (see Chapter 7). These precancerous changes represent a continuum of morphologic changes with indistinct boundaries that may gradually progress to cancer in situ and then to invasive cancer, or they may spontaneously regress.

The classification of cervical precancerous lesions has changed over time, and terms from different classification systems are currently used interchangeably. An initial system of grading described the dysplastic changes of cervical cancer precursors using the term *cervical intraepithelial neoplasia* (CIN).[6,7,11] This system, based on histology, divided the precursors into three categories of dysplasia severity: CIN I (mild dysplasia), CIN II (moderate dysplasia), and CIN III (severe dysplasia). This system has been largely replaced by the Bethesda system, which divides epithelial lesions into squamous and glandular lesions.[11,22] In both categories, lesions are either precancerous or cancerous. Precancerous cell precursor lesions are described as either atypical squamous cells (ASCs), low-grade intraepithelial lesions (LSILs), or high-grade intraepithelial lesions (HSILs), and cancerous lesions are termed invasive squamous carcinoma. ASC can be further divided into ASC of underdetermined significance (ASC-US) or ASC-cannot exclude HSIL. Precancerous glandular lesions are classified in a similar manner as atypical glandular carcinoma (AGC). Cancerous glandular lesions are classified as adenocarcinoma.[6,11,22]

Squamous cell carcinoma is the most common histologic subtype of cervical cancer, accounting for 80% of cases. Most LSILs regress spontaneously, with only a small percentage of lesions progressing to HSIL. In HSIL, there is progressive disruption of the cell cycle by HPV, resulting in increased cell proliferation and degree of dysplasia. Cancers of the cervix have a long latent period; untreated dysplasia gradually progresses to carcinoma in situ, which may remain static for 7 to 10 years before it becomes invasive. After the preinvasive period, growth may be rapid, and survival rates decline significantly depending on the extent of disease at the time of diagnosis.

The atypical cellular changes that precede frank neoplastic changes consistent with cancer of the cervix can be recognized by a number of direct and microscopic techniques, including the Pap smear, colposcopy, and cervicography. Currently, Pap smears are used for cervical cancer screening. The appropriate use of Pap smears in cervical screening programs has been controversial. The American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG), and the U.S. Preventative Services Task Force (USPSTF) have developed evidence-based guidelines for cancer screening.[23–25] The ACOG guidelines recommend that screening begin at age 21 years regardless of sexual history and be done at every 2 years between the ages of 21 years and 29 years.[24] After age 30 women who have a normal Pap test results may be tested less often—every 2 to 3 years.[23] After age 65 or 70, screening may be discontinued if there have been no abnormalities on at least three cytologic examinations.[23,25]

Testing for the presence of high-risk HPV DNA is now being used as an adjunct to the Pap smear in women over age 30 and in women with abnormal Pap results. It is also being used as a triage tool for women with Pap test results reported as ASC-US and in the management of nonadolescent women with LSIL. HPV DNA can also identify women who have abnormal Pap results caused by other, non–HPV-associated phenomena, such as infection, thus eliminating the need for unnecessary colposcopic evaluations.[11]

Diagnosis and Treatment. In its early stages, cervical cancer often manifests as a poorly defined lesion of the endocervix. Frequently, women with cervical cancer present with abnormal vaginal bleeding, spotting, and discharge. Although bleeding may assume any course, it is reported most frequently after intercourse. Women with more advanced disease may present with pelvic or back pain that may radiate down the leg, hematuria, fistulas (rectovaginal or vesicovaginal), or evidence of metastatic disease to supraclavicular or inguinal lymph node areas.

Diagnosis of cervical cancer requires pathologic confirmation. Pap smear results demonstrating squamous intraepithelial lesions often require further evaluation by colposcopy, during which a biopsy sample may be obtained from suspect areas and examined microscopically.[26] An alternative diagnostic tool in areas where colposcopy is not readily available is a noninvasive photographic technique in which a cervicography camera is used to take photographs of the cervix. The projected cervicogram (a slide made from the film) is then sent for expert evaluation.[26,27]

Early treatment of cervical cancer involves removal of the lesion by one of various techniques. Biopsy or local destruction of the affected cervical tissue may be therapeutic in and of itself. Electrocautery, cryosurgery, or carbon dioxide laser therapy may be used to treat moderate to severe dysplasia that is limited to the exocervix (i.e., squamocolumnar junction clearly visible). Therapeutic conization becomes necessary if the lesion extends into the endocervical canal and can be done surgically or with a large loop electrocautery procedure (LEEP) in the physician's office.[26]

Depending on the stage of involvement of the cervix, invasive cancer is treated with surgery, radiation therapy, chemoradiation, or chemotherapy.[27] External-beam irradiation and intracavitary irradiation or *brachytherapy* (i.e., insertion of radioactive materials into the body) can be used in the treatment of cervical cancer (see Chapter 7). Intracavitary radiation provides direct access to the central lesion and increases the tolerance of the cervix and surrounding tissues, permitting curative levels of radiation to be used. External-beam radiation eliminates metastatic disease in pelvic lymph nodes and other structures, as well as shrinking the cervical lesion to optimize the effects of intracavitary radiation. Surgery can include extended hysterectomy (i.e., removal of the uterus, fallopian tubes, ovaries, and upper portion of the vagina) without pelvic lymph node dissection, and radical hysterectomy with pelvic lymph node dissection. The choice of treatment is influenced by the stage of the disease as well as the woman's age and health.

Disorders of the Uterus

Infectious Disorders of the Uterus and Pelvic Structures

The uterus and pelvic structures are subject to infections by a number of agents, including the sexually transmitted organisms *N. gonorrhoeae* and *C. trachomatis,* as well as endogenous microorganisms such as anaerobes, *Haemophilus influenzae,* enteric gram-negative rods, and streptococci. Tuberculosis salpingitis is rare in the United States but more common in developing countries.

Endometritis. The endometrium and myometrium are relatively resistant to infections, primarily because the endocervix normally forms a barrier to ascending infections. Acute endometritis is uncommon and usually occurs after the cervical barrier is compromised by abortion, delivery, or instrumentation.[6,7] Curettage is diagnostic and often curative because it removes the necrotic tissue that has served as a site for microbial growth.

Chronic inflammation of the endometrium is associated with intrauterine devices (IUDs), pelvic inflammatory disease, and retained products of conception after delivery or abortion. The presence of plasma cells (which are not present in the normal endometrium) is required for diagnosis. The clinical picture is variable, but often includes abnormal vaginal bleeding, mild to severe uterine tenderness, fever, malaise, and foul-smelling discharge. Treatment involves oral or intravenous antibiotic therapy, depending on the severity of the condition.

Pelvic Inflammatory Disease. Pelvic inflammatory disease (PID) is a polymicrobial infection of the upper reproductive tract (uterus, fallopian tubes, or ovaries) associated with the sexually transmitted organisms and with endogenous organisms.[28–30] The organisms ascend through the endocervical canal to the endometrial cavity, and then to the fallopian tubes and ovaries (Fig. 40-9). The endocervical canal is slightly dilated during menstruation, allowing bacteria to gain entrance to the uterus and other pelvic structures. After entering the upper reproductive tract, the organisms multiply rapidly in the favorable environment of the sloughing endometrium and ascend to the fallopian tube.

Factors that predispose women to the development of PID include an age of 16 to 24 years, nulliparity, history of multiple sexual partners, and previous history of PID. Although the use of an IUD has been associated with a three- to fivefold increased risk for development of pelvic

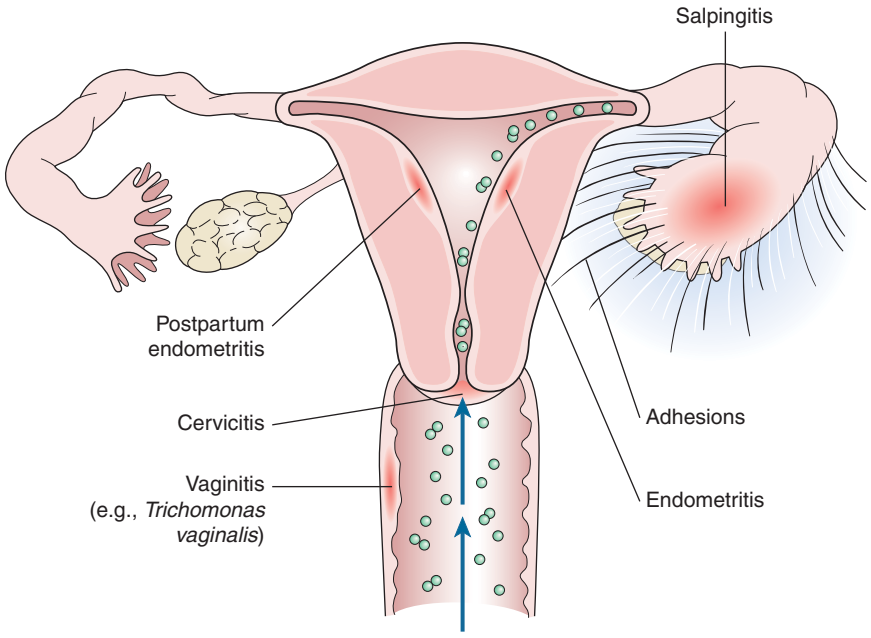


FIGURE 40-9. Pelvic inflammatory disease. Microbial agents enter through the vagina and ascend to involve the uterus, fallopian tubes, and pelvic structures.

inflammatory disease, studies have shown that women with only one sexual partner who are at low risk of acquiring sexually transmitted infections have no significant risk for development of PID from using an IUD.

Clinical Features. The symptoms of PID include lower abdominal pain, which may start just after a menstrual period; dyspareunia; back pain; purulent cervical discharge; and the presence of lower abdominal tenderness and exquisitely painful cervix on bimanual pelvic examination. New-onset breakthrough bleeding in women who are on oral contraceptives or medroxyprogesterone contraceptive injection (Depo-Provera) has been associated with PID. Fever (>101°F), increased erythrocyte sedimentation rate, and an elevated white blood cell count (>10,000 cells/mL) commonly are seen, even though the woman may not appear acutely ill. Elevated C-reactive protein (CRP) levels equate with inflammation and can be used as another diagnostic tool. Laparoscopy, which allows for direct visualization of the ovaries, fallopian tubes, and uterus, is one of the most specific procedures for diagnosing PID, but is costly and carries the inherent risks of surgery and anesthesia.[30] Minimal criteria for a presumptive diagnosis of PID require only the presence of lower abdominal pain, adnexal tenderness, and cervical motion tenderness on bimanual examination with no other apparent cause.

Treatment may involve hospitalization with intravenous administration of antibiotics. If the condition is diagnosed early, outpatient antibiotic therapy may be sufficient. Treatment is aimed at preventing complications, which can include pelvic adhesions, infertility, ectopic pregnancy, chronic abdominal pain, and tuboovarian abscesses. Accurate diagnosis and appropriate antibiotic therapy may decrease the severity and frequency of PID sequelae.

Endometriosis

Endometriosis is the condition in which functional endometrial tissue is found in ectopic sites outside the uterus.[11,31–33] The site may be the ovaries, posterior broad ligaments, uterosacral ligaments, pouch of Douglas (cul-de-sac), pelvis, vagina, vulva, perineum, or intestines (Fig. 40-10). Rarely, endometrial implants have been found in the nostrils, umbilicus, lungs, and limbs.

The cause of endometriosis is largely unknown. There appears to have been an increase in its incidence in the developed Western countries during the past four to five decades. Approximately 10% to 15% of premenopausal women have some degree of endometriosis. The incidence may be higher in women with infertility (15% to 70%) or women younger than 20 years of age with chronic pelvic pain (47% to 73%).[31] It is also more common in women who have postponed childbearing. Risk factors for endometriosis may include early menarche; regular periods with shorter cycles (<27 days), longer duration (>7 days), or heavier flow; increased menstrual pain; and other first-degree relatives with the condition.

Several theories attempt to explain the origin of the dispersed endometrial lesions that occur in women with endometriosis.[7,11,31] One theory, the *regurgitation/implantation theory,* suggests that menstrual blood containing fragments of endometrium is forced upward through the fallopian tubes into the peritoneal cavity. Retrograde menstruation is not an uncommon phenomenon, and it is unknown why endometrial cells implant and grow in some women but not in others. A second theory, the *vascular* or *lymphatic theory,* suggests that the endometrial tissue may metastasize through the lymphatics or vascular system. Another theory, the *metaplastic theory,* proposes that dormant, immature cellular elements, spread over a wide area during embryonic development, persist into adult life and then differentiate into endometrial tissue.

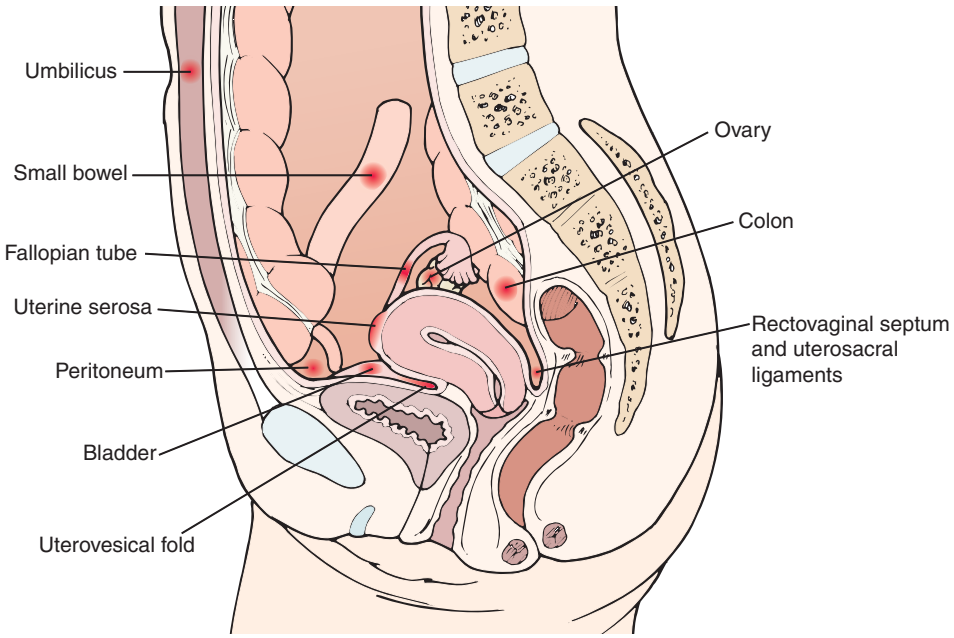


FIGURE 40-10. Common locations of endometriosis in the pelvis and abdomen.

Genetic and immune factors also have been studied as contributing factors to the development of endometriosis.

Endometriosis usually becomes apparent in the reproductive years when the lesions are stimulated by ovarian hormones in the same way as normal endometrium, becoming proliferative, then secretory, and finally undergoing menstrual breakdown. Bleeding into the surrounding structures can cause pain and the development of significant pelvic adhesions. Symptoms tend to be more severe premenstrually, subsiding after cessation of menstruation. Pelvic pain is the most common presenting symptom; other symptoms include back pain, dyspareunia, and pain on defecation and micturition. Endometriosis is associated with infertility because of adhesions that distort the pelvic anatomy and cause impaired ovum release and transport.

The gross pathologic changes that occur in endometriosis differ with location and duration. In the ovary, the endometrial tissue may form cysts (i.e., endometriomas filled with old blood that resembles chocolate syrup [chocolate cysts]). Rupture of these cysts can cause peritonitis and adhesions. Elsewhere in the pelvis, the tissue may take the form of small hemorrhagic lesions that may be black, bluish, red, clear, or opaque (Fig. 40-11). Some may be surrounded by scar tissue.

Endometriosis may be difficult to diagnose because its symptoms mimic those of other pelvic disorders and the severity of the symptoms does not always reflect the extent of the disease. Definitive diagnosis can be accomplished only through laparoscopy. This minimally invasive surgery allows direct visualization of pelvic organs to determine the presence and extent of endometrial lesions. Imaging techniques, including ultrasonography and magnetic resonance imaging (MRI), can be useful tools in evaluating endometriomas and deep endometriosis.[31,32] Serum cancer antigen 125 (CA-125), which is known for its use in diagnosis and monitoring of ovarian cancer, may be elevated in the presence of endometriosis. It has limitations as a screening tool, but can be useful in monitoring response to therapy and recurrence.

FIGURE 40-11. Endometriosis. Implants of endometrium on the ovary appear as red-blue nodules. (From Robboy S.J., Merino M.J., Mutter G.L. [2008]. The female reproductive system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 829]. Philadelphia: Lippincott Williams & Wilkins.)

Treatment modalities fall into three categories: pain relief, endometrial suppression, and surgery.[11,29,31,32] In young women, simple observation and analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs]) may be sufficient treatment. The use of hormones to induce physiologic amenorrhea is based on the observation that pregnancy and menopause afford pain relief by inducing atrophy of the endometrial tissue. This can be accomplished through administration of oral contraceptives, continuous progestogen therapy, androgenic agents (danazol), or long-acting GnRH analogs that inhibit the pituitary gonadotropins and suppress ovulation.

Surgery may offer more definitive therapy for women with large or symptomatic endometriomas, or those who have failed medical therapy for endometriosis.[31,34,35] Laparoscopic surgical options include the use of cautery, laser ablation, and excision techniques. Definitive treatment involves total hysterectomy and bilateral salpingo-oophorectomy when the symptoms are unbearable or the woman's childbearing is completed. Continuous combined estrogen–progestogen therapy is recommended to manage menopausal symptoms and minimize the risk of endometriosis recurrence.[33]

Adenomyosis

Adenomyosis is the condition in which endometrial glands and stroma are found within the myometrium, interspersed between the smooth muscle fibers.[6,7] In contrast to endometriosis, which usually is a problem of young, infertile women, adenomyosis typically is found in multiparous women in their late fourth or fifth decade. It is thought that events associated with repeated pregnancies, deliveries, and uterine involution may cause the endometrium to be displaced throughout the myometrium. Adenomyosis frequently coexists with uterine myomas or endometrial hyperplasia. Heavy, painful periods with clots and dyspareunia are common complaints of women with adenomyosis. Adenomyosis resolves with menopause. Conservative therapy using oral contraceptives or GnRH agonists is usually the first choice of treatment. Hysterectomy (with preservation of the ovaries in premenopausal women) is considered when this approach fails.

Endometrial Cancer

Endometrial cancer is the most frequent invasive cancer of the female reproductive tract in the United States and Western countries of the world. Endometrial cancer is typically a disease of postmenopausal women. Between 15% and 25% of postmenopausal women with bleeding have endometrial cancer.[11]

Most primary endometrial cancers are adenocarcinomas that arise from the glandular elements of the endometrium. Endometrial hyperplasia, which is the most common precursor of endometrial cancer, can be divided into four types: simple hyperplasia, complex hyperplasia,

and hyperplasia (simple or complex) with cytologic atypia.[11] Simple hyperplasia is characterized by proliferation of both the glandular and stromal elements of the endometrium. It is not commonly associated with progression to endometrial carcinoma. Complex hyperplasia represents abnormal proliferation primarily of the glandular elements of the endometrium with concomitant proliferation of the stromal elements. It is thought to represent a true intraepithelial neoplastic process, and is occasionally found coexisting in areas of endometrial adenocarcinoma. Hyperplasia characterized by significant numbers of glandular cells that exhibit cytologic atypia and disordered maturation is considered a precursor lesion to endometrial carcinoma.

Epidemiology and Pathogenesis. Endometrial cancer occurs most frequently in postmenopausal women (peak age of 55 to 65 years) and is uncommon in women younger than 40 years of age.[6] Two groups in which endometrial cancers arise are perimenopausal women with estrogen excess and older women with endometrial atrophy. Endometrial cancers that arise in women with estrogen excess are described as type I or endometrioid carcinoma, and those that arise in women with endometrial atrophy as type II or serous carcinoma.[6,36–38]

Type I is the most common type of endometrial cancer, accounting for 80% of cases. Most of these tumors are well differentiated and mimic proliferative endometrial glands, and as such are referred to as *endometrioid carcinoma*. Endometrioid carcinoma is associated with prolonged estrogen stimulation and mutations in PTEN, a tumor-suppressor gene. In addition to unopposed estrogen therapy, other risks for endometrioid carcinoma are obesity, diabetes, nulliparity, early menarche, and late menopause. Many of these risk factors are the same as those for endometrial hyperplasia.[36] Obesity predisposes to insulin resistance, ovarian androgen excess, anovulation, and chronic progesterone deficiency. These hormonal changes stimulate endometrial cell proliferation, inhibit apoptosis, and promote angiogenesis. The degree of risk correlates with body weight: the risk increases 10-fold in women who are 25 kg (50 lb) overweight.[7] Progesterone counteracts the effects of estrogen. Pregnancy, with intense placental production of progestins, protects against endometrial cancer. Thus, multiparity protects against endometrial cancer, whereas nulliparity increases risk, especially when infertility is also present. Diabetes mellitus, hypertension, and polycystic ovary syndrome are conditions that alter estrogen metabolism and elevate estrogen levels.

Type II endometrial cancers occur in a small subset of women who do not exhibit increased estrogen levels. These women usually acquire the disease at an older age and in a setting of endometrial atrophy rather than hyperplasia. This type of endometrial cancer usually is associated with a poorer prognosis than type I carcinomas.[7,36]

Clinical Features. The major symptom of endometrial hyperplasia or overt endometrial cancer is abnormal, painless bleeding. Abnormal bleeding is an early warning sign of endometrial cancer in up to 90% of women, and because endometrial cancer tends to be slow growing in its early stages, the chances of cure are good if prompt medical care is sought.[36] In menstruating women, this takes the form of bleeding between periods or excessive, prolonged menstrual flow. In postmenopausal women, any bleeding is abnormal and warrants investigation. Later signs of uterine cancer may include cramping, pelvic discomfort, postcoital bleeding, lower abdominal discomfort, and enlarged lymph nodes.

Although the Pap smear can identify a small percentage of endometrial cancers, it is not a good screening tool for the tumor. Endometrial biopsy is far more accurate. Dilatation and curettage (D&C), which consists of dilating the cervix and scraping the uterine cavity, is the definitive procedure for diagnosis because it provides a more thorough evaluation. Transvaginal ultrasonography may be used to determine the endometrial thickness as an indicator of hypertrophy and possible neoplastic change.

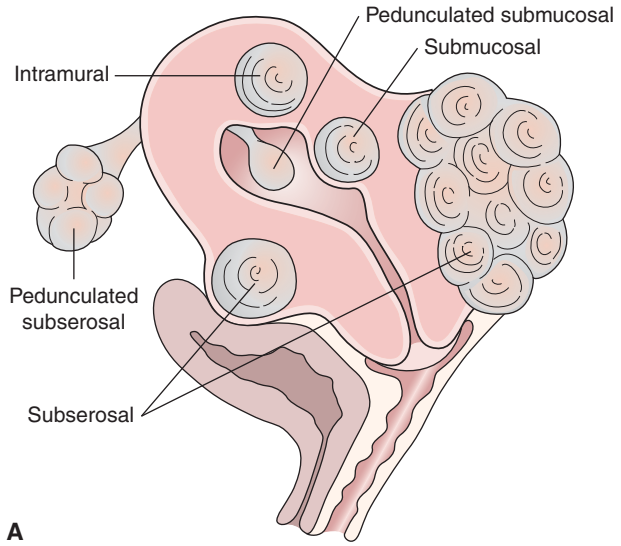
The prognosis for endometrial cancer depends on the clinical stage of the disease when it is diagnosed and its histologic grade and type. Surgery and radiation therapy are the most successful methods of treatment for endometrial cancer. With early diagnosis and treatment, the 5-year survival rate is approximately 80% to 85%.[6,37]

Uterine Leiomyomas

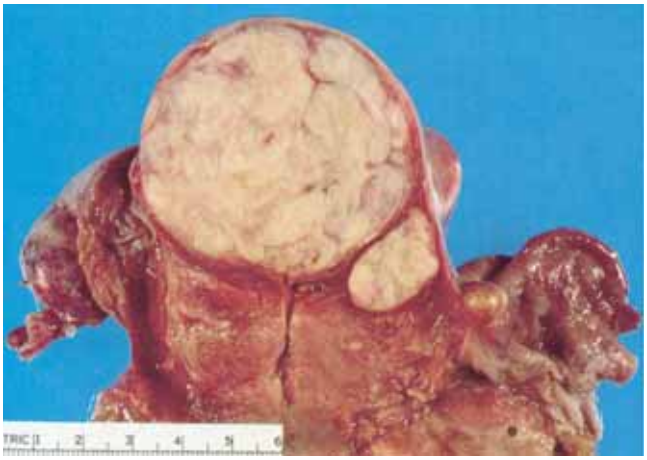
Uterine leiomyomas (commonly called *fibroids*) are benign neoplasms of smooth muscle origin.[6,7,39] They are the most common female reproductive tumor. Leiomyomas usually develop in the corpus of the uterus as intramural, subserosal, or submucosal growths (Fig. 40-12). Intramural fibroids are embedded in the myometrium. They are the most common type of fibroid and present as a symmetric enlargement of the nonpregnant uterus. Subserosal tumors are located beneath the perimetrium of the uterus. These tumors are recognized as irregular projections on the uterine surface; they may become pedunculated, displacing or impinging on other genitourinary structures and causing hydroureter or bladder problems. Submucosal fibroids displace endometrial tissue and are more likely to cause bleeding, necrosis, and infection than either of the other types.

Leiomyomas are asymptomatic approximately half of the time and may be discovered during routine pelvic examination, or they may cause menorrhagia (excessive menstrual bleeding), anemia, urinary frequency, rectal pressure/constipation, abdominal distention, and infrequently pain. Their rate of growth is variable, but they may increase in size during pregnancy or with exogenous estrogen stimulation (i.e., oral contraceptives or menopausal estrogen replacement therapy). Interference with pregnancy is rare unless the tumor is submucosal and interferes with implantation or obstructs the cervical outlet. These tumors may outgrow their blood supply, become infarcted, and undergo degenerative changes.

Most leiomyomas regress with menopause, but if bleeding, pressure on the bladder, pain, or other problems persist, hysterectomy may be indicated. Myomectomy (removal of just the tumors) can be done to preserve the uterus for future childbearing. Cesarean section may be



A



B

FIGURE 40-12. **(A)** Submucosal, intramural, and subserosal leiomyomas. **(B)** A bisected uterus displays a prominent, sharply circumscribed, fleshy tumor. (From Robboy S.J., Merino M.J., Mutter G.L. [2008]. The female reproductive system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 813]. Philadelphia: Lippincott Williams & Wilkins.)

recommended if the uterine cavity is entered during myomectomy. Hypothalamic GnRH agonists may be used to suppress leiomyoma growth before surgery. Uterine artery embolization is a nonsurgical therapy for management of heavy bleeding.[39]

Disorders of Uterine Support

The uterus and the pelvic structures are maintained in proper position by the uterosacral ligaments, round ligaments, broad ligament, and cardinal ligaments. The two cardinal ligaments maintain the cervix in its normal position (see Fig. 40-4A). The uterosacral ligaments hold the uterus in a forward position, and the broad ligaments suspend the uterus, fallopian tubes, and ovaries in the pelvis. The vagina is encased in the semirigid structure of the strong supporting fascia (Fig. 40-13A). The muscular floor of the pelvis is a strong, slinglike structure that supports the uterus, vagina, urinary bladder, and rectum (Fig. 40-14). In the female anatomy, nature is faced with the problems of supporting the pelvic viscera against the force of gravity and increases in intra-abdominal pressure associated with coughing, sneezing, defecation, and laughing while at the same time allowing for urination, defecation, and normal reproductive tract function, especially the delivery of an infant.

Relaxation of the pelvic outlet usually comes about because of overstretching of the perineal supporting tissues during pregnancy and childbirth. Although the tissues are stretched only during these times, there may be no difficulty until later in life, such as in the fifth or sixth decade, when further loss of elasticity and muscle tone occurs.[11] Even in a woman who has not borne children, the combination of aging and postmenopausal changes may give rise to problems related to relaxation of the pelvic support structures. The three most common conditions associated with this relaxation are cystocele, rectocele, and uterine prolapse.[11] These may occur separately or together.

Cystocele is a herniation of the bladder into the vagina. It occurs when the normal muscle support for the bladder is weakened, and the bladder sags below the uterus. This causes the anterior vaginal wall to stretch and bulge downward, allowing the bladder to herniate into the vagina due to the force of gravity and pressures from coughing, lifting, or straining at stool (see Fig. 40-13B). The symptoms of cystocele include an annoying bearing-down sensation, difficulty in emptying the bladder, frequency and urgency of urination, and cystitis. Stress incontinence may occur at times of increased abdominal pressure, such as during squatting, straining, coughing, sneezing, laughing, or lifting (see Chapter 27).

Rectocele is the herniation of the rectum into the vagina. It occurs when the posterior vaginal wall and underlying rectum bulge forward, ultimately protruding through the introitus as the pelvic floor and perineal muscles are weakened. The symptoms include discomfort because of the protrusion of the rectum and difficulty in defecation (see Fig. 40-13C). Digital pressure (i.e., splinting) on the bulging posterior wall of the vagina may become necessary for defecation. The area between the uterosacral ligaments just posterior to the cervix may weaken and form a hernial sac into which the small bowel protrudes when the woman is standing. This defect, called an *enterocele,* may extend into the rectovaginal septum. It may be congenital or acquired through birth trauma. Enterocele can be asymptomatic or cause a dull, dragging sensation and occasionally low backache.

Uterine prolapse is the bulging of the uterus into the vagina that occurs when the primary supportive ligaments (i.e., cardinal ligaments) are stretched (see Fig. 40-13D). Prolapse is ranked as first, second, or third degree, depending on how far the uterus protrudes through the introitus. First-degree prolapse shows some descent, but the cervix has not reached the introitus. In second-degree prolapse, the cervix or part of the uterus has passed through the introitus. The entire uterus protrudes through the vaginal opening in third-degree prolapse (i.e., procidentia). The symptoms associated with uterine prolapse result from

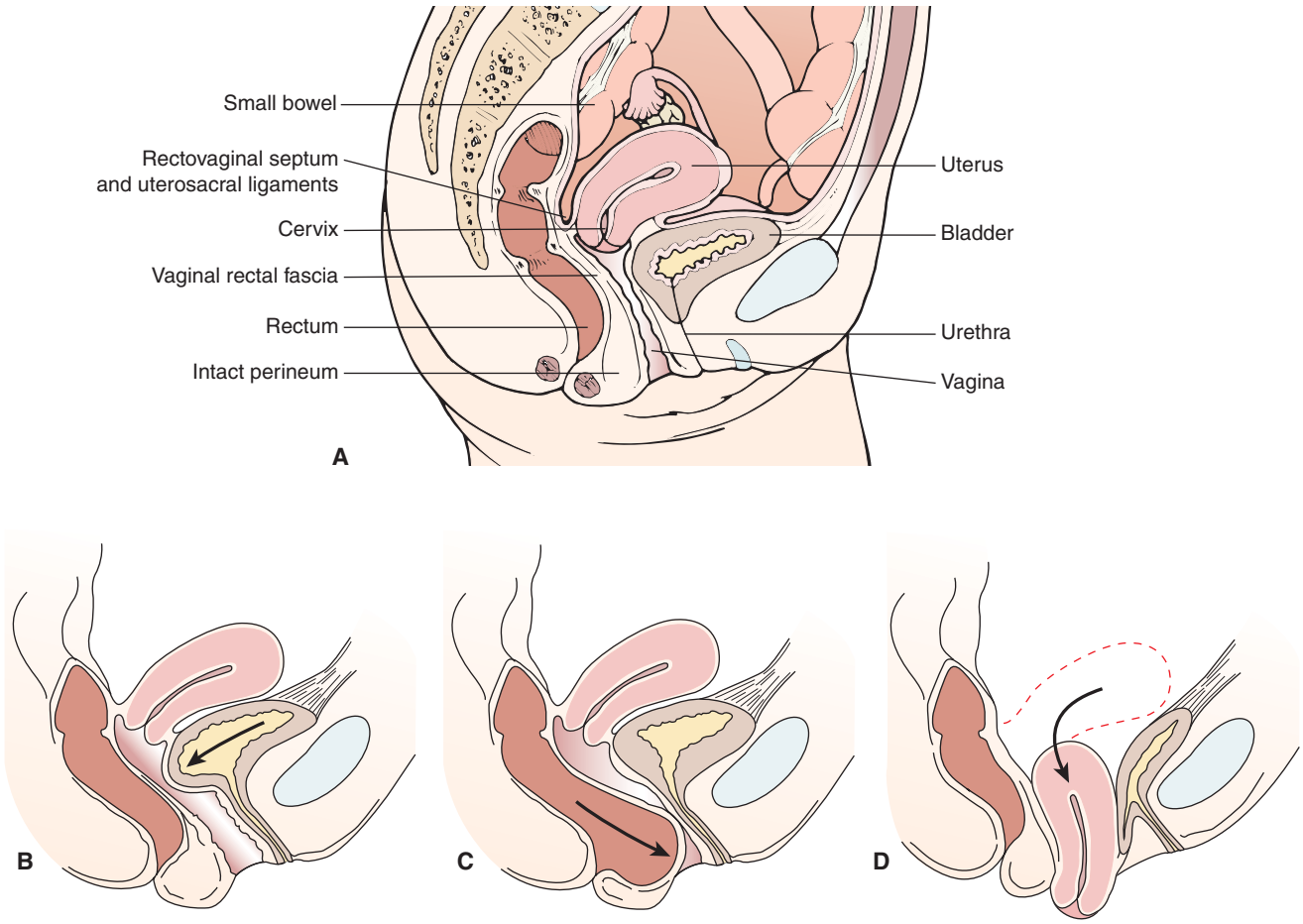


FIGURE 40-13. **(A)** Normal support of the uterus and vagina, **(B)** cystocele, **(C)** rectocele, and **(D)** uterine prolapse.

irritation of the exposed mucous membranes of the cervix and vagina and the discomfort of the protruding mass.

Most of the disorders of pelvic relaxation require surgical correction. These are elective surgeries and usually are deferred until after the childbearing years. The symptoms associated with the disorders often are not severe enough to warrant surgical correction. In other cases, the stress of surgery is contraindicated because of other physical disorders; this is particularly true of older women, in whom many of these disorders occur. Kegel exercises, which strengthen the pubococcygeus muscle, may be helpful in cases of mild cystocele or rectocele or after surgical repair to help maintain the improved function. In women with uterine prolapse, a pessary may be inserted to hold the uterus in place and may stave off surgical intervention in women who want to have children or in older women for whom the surgery may pose a significant health risk.

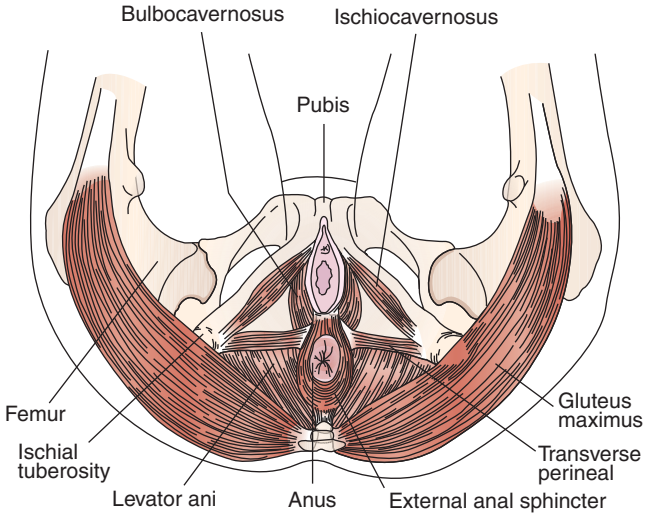


FIGURE 40-14. Muscles of the pelvic floor (female perineum).

Disorders of the Ovaries

Disorders of the ovaries frequently cause menstrual and fertility problems. Benign conditions can present as primary lesions of the ovarian structures or as secondary disorders related to hypothalamic, pituitary, or adrenal dysfunction.

Cystic Lesions of the Ovaries

Cysts are the most common cause of enlarged ovaries.[7] Many are benign. A follicular cyst is one that results from occlusion of the duct of the follicle. Each month,

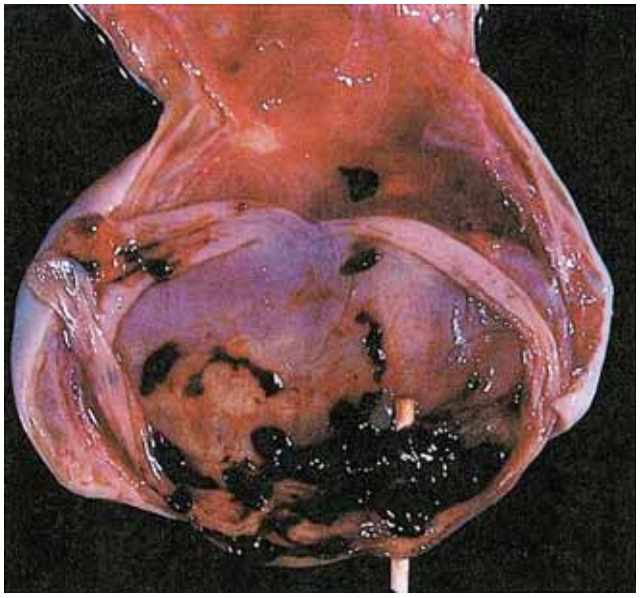


FIGURE 40-15. Follicular cyst of the ovary. The rupture of this thin-walled follicular cyst (dowel stick) led to intra-abdominal hemorrhage. (From Robboy S.J., Merino M.J., Mutter G.L. [2008]. The female reproductive system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 815]. Philadelphia: Lippincott Williams & Wilkins.)

several follicles begin to develop and are blighted at various stages of development. These follicles form cavities that fill with fluid, producing a cyst. The dominant follicle normally ruptures to release the egg (i.e., ovulation) but occasionally persists and continues growing. Likewise, a luteal cyst is a persistent cystic enlargement of the corpus luteum that is formed after ovulation and does not regress in the absence of pregnancy. Functional cysts are asymptomatic unless there is substantial enlargement or bleeding into the cyst. This can cause considerable discomfort or a dull, aching sensation on the affected side. However, these cysts usually regress spontaneously. Occasionally, a cyst may become twisted or may rupture into the intra-abdominal cavity (Fig. 40-15).

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 5% to 10% of women of reproductive age, and is a frequent source of chronic anovulation. The disorder is characterized by varying degrees of menstrual irregularity, signs of hyperandrogenism (acne, excess body hair [hirsutism], male-pattern hair loss), and infertility, and is often associated with hyperinsulinemia or insulin resistance.[4,40–43] A substantial number of women who are diagnosed with PCOS are obese, and most have polycystic ovaries.

Chronic anovulation, causing amenorrhea or irregular menses, is now thought to be the underlying cause of the bilaterally enlarged "polycystic" ovaries. Hence, the appearance of the ovary is a sign, not the disease itself. There is increasing evidence that the disorder may begin before adolescence and that many of the manifestations of PCOS begin to make their appearance at that time. Because many of the symptoms common to PCOS, such as excess hair, acne, and obesity, can be detrimental to a teenage girl's health and self-esteem, early detection and treatment of PCOS in adolescents are essential.[44]

The underlying etiology of the disorder is unknown, although most women have altered gonadotropin levels.[4,43] This is manifested by increased release of LH in relation to FSH release, with a resultant increase in production of androstenedione and testosterone by the theca cells of the ovary. Androstenedione, in turn, is converted to estrone within adipocytes. Although estrone is a weak estrogen, it causes suppression of pituitary FSH release and stimulation of LH release. Although the presence of some FSH allows for new follicular development, full maturation is not attained, and ovulation does not occur. The elevated LH level results in increased androgen production, which in turn prevents normal follicular development and contributes to a vicious cycle of anovulation and multiple cyst formation. Increased androgen levels also lead to the development of acne and hirsutism.

The typical woman with PCOS has hyperinsulinemia and many of the signs of the metabolic syndrome (see Chapter 33).[4,11] It has been shown that the cause of hyperinsulinemia is insulin resistance. The frequency and degree of hyperinsulinemia in women with PCOS is often amplified by the presence of obesity. In addition to its clinical manifestations, long-term health problems including cardiovascular disease and type 2 diabetes have been linked to PCOS. Classic lipid abnormalities include elevated triglyceride levels, low HDL levels, and elevated LDL levels. Hypertension is also common in women with PCOS. There is also concern that women with PCOS who are anovulatory do not produce progesterone. This, in turn, may subject the endometrium to an unopposed estrogen environment, which is a significant risk factor for the development of endometrial cancer.[4,43]

The diagnosis of PCOS can be suspected from the clinical presentation. Although there is no consensus as to which tests should be used, laboratory evaluation to exclude hyperprolactinemia, late-onset adrenal hyperplasia, and androgen-secreting tumors of the ovary and adrenal gland is commonly done. Because of the high risk of insulin resistance, a fasting blood glucose, 2-hour oral glucose tolerance test, and insulin levels are done to evaluate for hyperinsulinemia. Confirmation with ultrasonography or laparoscopic visualization of the ovaries is often done, but not required.[41]

The overall goal of treatment should be directed toward symptom relief, prevention of potential malignant endometrial sequelae, and reduction in risk for development of diabetes and cardiovascular disease. The preferred and most effective treatment for PCOS is lifestyle modification. Weight loss may be beneficial in restoring normal ovulation when obesity is present. Combined oral contraceptive agents ameliorate menstrual irregularities and improve hirsutism and acne. The addition of spironolactone, a mineralocorticoid antagonist that inhibits the production of androgens by the adrenal gland, may be beneficial to women with severe hirsutism.[4]

Insulin-sensitizing agents (metformin or thiazolidinedione [rosiglitazone or pioglitazone]) alone or with ovulation-inducing medications are emerging as an important component of PCOS treatment.[43] In addition to expected improvements in insulin sensitivity and glucose metabolism, they have been associated with reductions in androgen and LH levels and are highly effective in restoring normal menstrual regularity and ovulatory cycles.

Benign Ovarian Tumors

Ovarian tumors can be benign, borderline, or malignant. About 80% are benign and occur mainly in young women between the ages of 20 and 45 years. Borderline tumors occur at a slightly older age. Malignant tumors are more common in older women, between the ages of 45 and 65 years.[6]

Ovarian neoplasms can arise from any of the ovarian tissue types—serosal surface epithelium (65% to 75%), germ cells layers (10% to 20%), or gonadal stroma tissue (5% to 10%)[6,7] (Fig. 40-16). Benign epithelial cell neoplasms are almost always serous (serous cystadenoma) or mucinous (mucinous cystadenoma) adenomas. These neoplasms are large, often 15 to 30 cm in diameter. Benign cystic teratomas, or dermoid cysts, are derived from primordial germ cells and are composed of various combinations of well-differentiated ectodermal, mesodermal, and endodermal elements. Not uncommonly, they contain sebaceous material, hair, or teeth. Approximately 80% of these tumors occur during the reproductive years, with a median age of 30 years.

Although most benign tumors are nonfunctional and tend to produce relatively few symptoms until they reach a large size, some are hormonally active.[6] One such tumor, the granulosa cell tumor, is associated with excess estrogen production.[11] When it develops during the reproductive period, the persistent and uncontrolled production of estrogen interferes with the normal menstrual cycle, causing irregular and excessive bleeding, endometrial hyperplasia, or amenorrhea and fertility problems. When it develops after menopause, it causes postmenopausal bleeding, stimulation of the glandular tissues of the breast, and other signs of renewed estrogen production. Androgen-secreting tumors (i.e., Sertoli-Leydig cell tumor or androblastoma) inhibit ovulation and estrogen production.[11] They tend to cause hirsutism and development of masculine characteristics, such as baldness, acne, oily skin, breast atrophy, and deepening of the voice.

Treatment for benign ovarian tumors is surgical excision. Ovarian tissue that is not affected by the tumor can be left intact if frozen-section analysis does not reveal malignancy. When ovarian tumors are very large, as is frequently the case with serous or mucinous cystadenomas, the entire ovary must be removed.

Approximately 10% of seemingly benign epithelial cell tumors may contain histologic evidence of intraepithelial

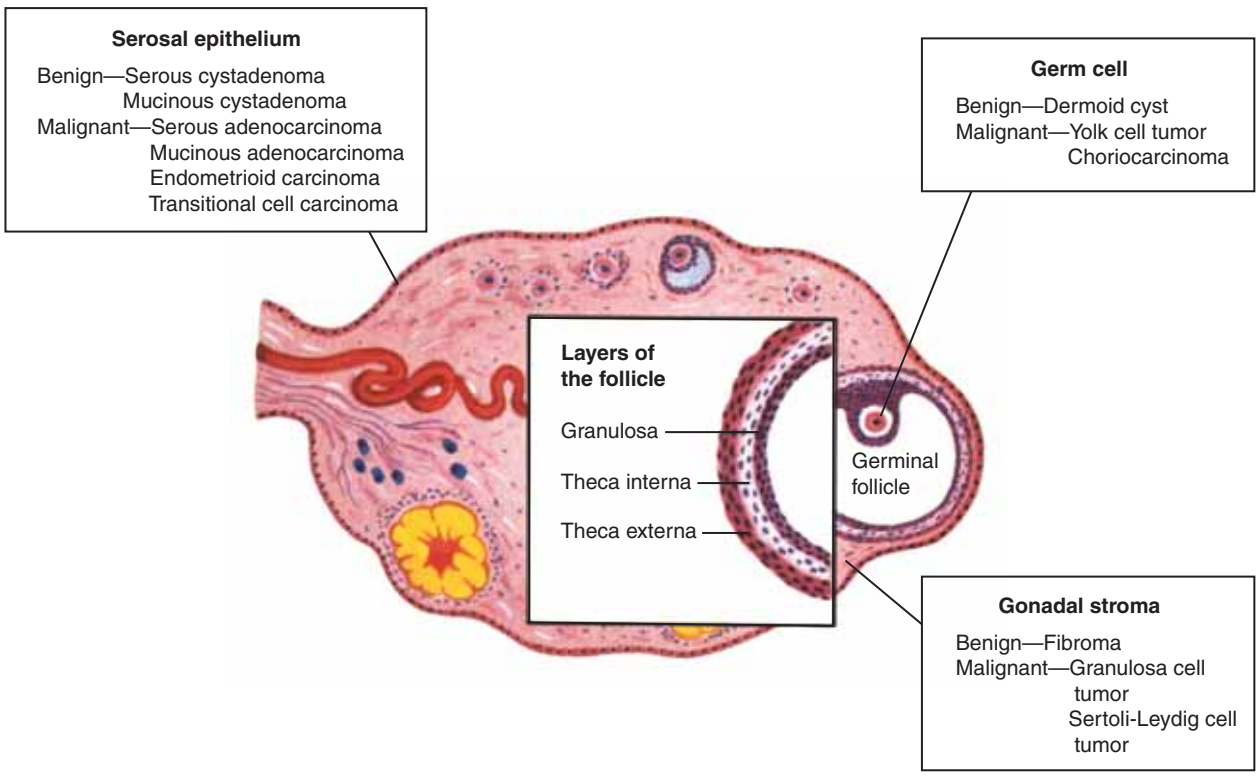


FIGURE 40-16. Classification of ovarian neoplasms based on cell type. (From Robboy S.J., Merino M.J., Mutter G.L. [2008]. The female reproductive system. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 818]. Philadelphia: Lippincott Williams & Wilkins.)

neoplasia, commonly referred to as borderline malignancies.[11] These tumors generally remain confined to the ovary, are more common in premenopausal women (30 to 50 years of age), and have a good prognosis. They require careful frozen-section analysis and individualized therapy following the initial surgical removal of the tumor.

Ovarian Cancer

Ovarian cancer is the second most frequent gynecologic malignancy after endometrial cancer in the United States, and it carries the highest mortality rate of all genital cancers combined.[6,7,44,45] The incidence of ovarian cancer increases with age, being greatest between 45 and 60 years of age. Ovarian cancer is difficult to diagnose, and up to 75% of women are diagnosed at an advanced state when the 5-year survival rate is 20% to 30%.[11]

As with benign ovarian tumors, malignant ovarian tumors are categorized according to cell type of origin—epithelial cell tumors, germ cell tumors, and gonadal stromal cell tumors (see Fig. 46-16). Approximately 90% of ovarian cancers are of epithelial cell origin. These tumors tend to occur in older women, are usually discovered late in the disease, and have a high mortality rate. The nonepithelial ovarian cancers, which include germ cell tumors and stromal cell tumors, tend to occur in a younger population of women. They typically present with earlier signs of disease and excellent survival potential when detected early.

The most significant risk factor for ovarian cancer appears to be ovulatory age—the length of time during a woman's life when her ovarian cycle is not suppressed by pregnancy, lactation, or oral contraceptive use. The incidence of ovarian cancer is much lower in countries where women bear numerous children. Epithelial cancer of the ovaries derives from malignant transformation of the epithelium of the ovarian surface. When these epithelial cells are situated over developing follicles, they undergo metaplastic transformation whenever ovulation occurs.[11,44,46] It follows that repeated stimulation of the epithelium of the ovarian surface, which occurs with uninterrupted ovulation, may predispose the epithelium to malignant transformation. Family history also is a significant risk factor for ovarian cancer. The breast cancer susceptibility genes, *BRCA1* and *BRCA2* mutations, which are tumor-suppressor genes, increase the susceptibility to ovarian cancer (see Chapter 7). The estimated risk of ovarian cancer in women bearing the BRCA1 and BRCA2 mutations is 20% to 60% by the age of 70 years. A high-fat Western diet and use of powders containing talc in the genital area are other factors that have been linked to the development of ovarian cancer.

Clinical Features. Until recently it was believed that most cancers of the ovary produce no symptoms. Several studies have now established that symptoms are often present and reported by women before diagnosis, but are nonspecific and therefore difficult to interpret. Symptoms that are believed to have a strong correlation to ovarian cancer include increased abdominal size, dyspepsia, early satiety, or bloating as the result of increased pressure from ascites (i.e., fluid in the peritoneal cavity) or involvement of the omentum. Occasionally, women with early-onset disease present with abdominal or pelvic pain, due to ovarian torsion, although most women with early-stage disease are asymptomatic. Because the gastrointestinal manifestations can occur for a variety of reasons, many women self-treat with antacids and other remedies for a time before seeking treatment, and health care providers may dismiss the woman's complaints as being caused by other conditions, further delaying diagnosis and treatment. Recent onset (<12 months) and frequent occurrence (>12 times per month) of these symptoms should increase the index of suspicion for ovarian cancer and suggest the need for further evaluation.[47] It is not fully understood why the initial symptoms of ovarian cancer are manifested as gastrointestinal disturbances. It is thought that biochemical changes in peritoneal fluids may irritate the bowel or that pain originating in the ovary may be referred to the abdomen and be interpreted as a gastrointestinal disturbance. Clinically evident ascites is seen in approximately one fourth of women with malignant ovarian tumors and is associated with a worse prognosis.

At present, no good screening tests or other early methods of detection exist for ovarian cancer.[48,49] The serum tumor marker CA-125 is a cell surface antigen that can be used in monitoring therapy and recurrences when preoperative levels have been elevated. Despite its role in diagnostic evaluation and follow-up, CA-125 is not cancer or tissue specific for ovarian cancer. Levels also are elevated in the presence of endometriosis, uterine fibroids, pregnancy, liver disease, and other benign conditions and with cancers of the endometrium, cervix, fallopian tube, and pancreas. Transvaginal ultrasonography (TVS) has been used to evaluate ovarian masses for malignant potential. Although TVS has demonstrated high sensitivity and specificity as a screening tool, cost precludes its use as a universal screening method.

When ovarian cancer is suspected, surgical evaluation is required for diagnosis, complete and accurate staging, and cytoreduction and debulking procedures to reduce the size of the tumor. The most common surgery involves removal of the uterus, fallopian tubes, ovaries, and omentum. Recommendations regarding treatment beyond surgery and prognosis depend on the stage of the disease. Women with early-stage disease usually do not require adjuvant treatment; women with intermediate disease or advanced disease can often benefit from chemotherapy using a combination of a platinum compound (cisplatin or carboplatin) and a taxane (paclitaxel or docetaxel). When this combination therapy fails, salvage chemotherapy with newer drugs may prolong survival.

In summary, the external genitalia are affected by disorders that affect skin on other parts of the body. Bartholin cysts are the result of occluded ducts in Bartholin glands. They often are painful and can become infected. Vulvar dystrophies are characterized by thinning and hyperplastic thickening of vulvar tissues. Vulvodynia

is a chronic vulvar pain syndrome with several classifications and variable treatment results. Cancer of the vulva, which accounts for 3% of all female genitourinary cancers, is associated with HPV infections.

The normal vaginal ecology depends on the delicate balance of hormones and bacterial flora. Vaginitis or inflammation of the vagina is characterized by vaginal discharge and burning, itching, redness, and swelling of vaginal tissues. It may be caused by chemical irritants, foreign bodies, and infectious agents. Primary cancers of the vagina are uncommon, accounting for 1% of all cancers of the female reproductive system.

Disorders of the cervix and uterus include inflammatory conditions (i.e., cervicitis and endometritis), cancer (i.e., cervical and endometrial cancer), endometriosis, leiomyomas, and disorders of uterine support. Cervicitis, which may be caused by a number of agents, may result from the direct infection of the cervix or may be secondary to a vaginal or uterine infection. Cervical cancer is caused by HPV and arises from precursor lesions that can be detected on a Pap smear, and if detected early, is the most easily cured of all the cancers of the female reproductive system.

Pelvic inflammatory disease is an inflammation of the upper reproductive tract that involves the uterus (endometritis), fallopian tubes (salpingitis), or ovaries (oophoritis). It is most commonly caused by *N. gonorrhoeae* or *C. trachomatis*. Endometriosis is the condition in which functional endometrial tissue is found in ectopic sites outside the uterus. It causes dysmenorrhea, dyspareunia, and infertility.

Adenomyosis is the condition in which endometrial glands and stroma are found in the myometrium interspersed between the smooth muscle fibers. Leiomyomas are benign uterine wall neoplasms of smooth muscle origin. They can develop in the corpus of the uterus and can be submucosal, subserosal, or intramural. Submucosal fibroids displace endometrial tissue and are more likely to cause bleeding, necrosis, and infection than either of the other types. Endometrial cancer is the most common cancer found in the female pelvis; it occurs twice as frequently as cervical cancer. Prolonged estrogen stimulation with hyperplasia of the endometrium has been identified as a major risk factor for endometrial cancer.

Disorders of uterine support result from weakness and relaxation of the pelvic floor muscles. Cystocele and rectocele involve herniation of the bladder or rectum into the vagina. Uterine prolapse occurs when the uterus bulges into the vagina. Pelvic relaxation disorders typically result from overstretching of the supporting muscles during pregnancy and childbirth. The loss of elasticity in these structures that is a normal accompaniment of aging contributes to these problems.

Disorders of the ovaries include cystic disorders, PCOS, and benign and malignant tumors. Functional cysts usually are asymptomatic unless there is substantial enlargement or bleeding into the cyst or the cyst becomes twisted or ruptures. PCOS is a disorder characterized by various degrees of hirsutism, obesity, and infertility, and often is associated with hyperinsulinemia and insulin resistance. Ovarian tumors, benign, borderline, and malignant, can arise from any of the ovarian tissue types—serosal surface epithelium, germ cells, or gonadal stromal tissue. Cancer of the ovary is the second most common female genitourinary cancer and the most deadly. A family history of cancer, particularly breast and ovarian cancer, and nulliparity increase the risk of developing ovarian cancer, whereas oral contraceptive use, pregnancy, and lactation decrease the risk. Because there are no effective screening methods and the symptoms of early-stage ovarian cancer are often nonspecific, the disease is often far advanced at the time of diagnosis.

Menstrual Disorders

Between menarche (i.e., first menstrual bleeding) and menopause (i.e., last menstrual bleeding), the female reproductive system undergoes cyclic changes called the *menstrual cycle*. This includes the maturation and release of oocytes from the ovary during ovulation and periodic vaginal bleeding resulting from the shedding of the endometrial lining (Fig. 40-5). It is not necessary for a woman to ovulate to menstruate; anovulatory cycles do occur. The menstrual cycle produces changes in the breasts, uterus, skin, ovaries, and perhaps other unidentified tissues.

Dysfunctional Menstrual Cycles

Although unexplained uterine bleeding can occur for many reasons, such as pregnancy, abortion, bleeding disorders, and neoplasms, the most frequent cause in the nonpregnant woman is what is commonly called *dysfunctional menstrual cycles* or *bleeding*. Dysfunctional cycles may take the form of *amenorrhea* (absence of menstruation), *hypomenorrhea* (scanty menstruation), *oligomenorrhea* (infrequent menstruation, periods more than 35 days apart), *polymenorrhea* (frequent menstruation, periods less than 21 days apart), *menorrhagia* (excessive menstruation), or *metrorrhagia* (bleeding between periods). *Menometrorrhagia* is heavy bleeding during and between menstrual periods.

Dysfunctional Bleeding

Dysfunctional bleeding is related to alterations in the hormones that support normal cyclic endometrial changes. Estrogen deprivation causes retrogression of a previously built-up endometrium and bleeding. Such bleeding often is irregular in amount and duration, with the flow varying with the time and degree of estrogen stimulation and with the degree of estrogen withdrawal. A lack of progesterone can cause abnormal menstrual bleeding; in its absence, estrogen induces development of a much thicker endometrial layer with a richer blood supply. The absence of progesterone results from the

Dysfunctional Menstrual Cycles

- The pattern of menstrual bleeding tends to be fairly consistent in most healthy women with regard to frequency, duration, and amount of flow.
- Dysfunctional bleeding in postpubertal women can take the form of absent or scanty periods, infrequent periods, excessive and irregular periods, excessive bleeding during periods, and bleeding between periods.
- When the basic pattern of bleeding is changed, it is most often due to a lack of ovulation and disturbances in the pattern of hormone secretion.
- When the basic pattern is undisturbed and there are superimposed episodes of bleeding or spotting, the etiology is more likely to be related to organic lesions or hematologic disorders.

failure of any of the developing ovarian follicles to mature to the point of ovulation, with the subsequent formation of the corpus luteum and production and secretion of progesterone.

Periodic bleeding episodes alternating with amenorrhea are caused by variations in the number of functioning ovarian follicles present. If sufficient follicles are present and active and if new follicles assume functional capacity, high levels of estrogen develop, causing the endometrium to proliferate for weeks or even months. In time, estrogen withdrawal and bleeding develop. This can occur for two reasons: an absolute estrogen deficiency may develop when several follicles simultaneously degenerate, or a relative deficiency may develop as the needs of the enlarged endometrial tissue mass exceed the capabilities of the existing follicles, even though estrogen levels remain constant. Estrogen and progesterone deficiencies are associated with the absence of ovulation, hence the term *anovulatory bleeding*. Because the vasoconstriction and myometrial contractions that normally accompany menstruation are caused by progesterone, anovulatory bleeding seldom is accompanied by cramps, and the flow frequently is heavy. Anovulatory cycles are common among adolescents during the first several years after menarche, when ovarian function is becoming established, and among perimenopausal women, whose ovarian function is beginning to decline.

Dysfunctional bleeding can originate as a primary disorder of the ovaries or uterus or as a secondary defect in ovarian function related to hypothalamic-pituitary stimulation. The latter can be initiated by emotional stress, marked variation in weight (i.e., sudden gain or loss), or nonspecific endocrine or metabolic disturbances. Nonhormonal causes of irregular menstrual bleeding include endometrial polyps, submucosal myoma (i.e., fibroid), bleeding disorder (e.g., von Willebrand disease, platelet dysfunction), endometrial dysplasia, and cancer.

The treatment of dysfunctional bleeding depends on what is identified as the probable cause. The minimum evaluation should include a detailed history with emphasis on bleeding pattern and a physical examination. Endocrine studies (e.g., FSH/LH ratio, prolactin, androgen levels), β-hCG pregnancy test, ultrasonography of the endometrium, endometrial biopsy, D&C with or without hysteroscopy, and progesterone withdrawal tests may be needed for diagnosis. Nonhormonal causes generally require surgical intervention. D&C can be therapeutic as well as diagnostic. Endometrial ablation (destruction of the basal layer of the endometrium from which the monthly buildup generates) has become a primary treatment method for abnormal uterine bleeding.[11] Various ablation devices are available; some use heat, and others use cryotherapy. If nonhormonal problems have been excluded and alterations in hormone levels are the primary cause, treatment may include the use of oral contraceptives, cyclic progesterone therapy, or long-acting progesterone injections.

Amenorrhea

There are two types of amenorrhea: primary and secondary. Primary amenorrhea is the failure to menstruate by 15 years of age, or by 13 years of age if failure to menstruate is accompanied by absence of secondary sex characteristics.[50] Secondary amenorrhea is the cessation of menses for at least 6 months in a woman who has established normal menstrual cycles. Primary amenorrhea usually is caused by gonadal dysgenesis, congenital müllerian agenesis, testicular feminization, or a hypothalamic-pituitary-ovarian axis disorder. Causes of secondary amenorrhea include ovarian, pituitary, or hypothalamic dysfunction; intrauterine adhesions; infections (e.g., tuberculosis, syphilis); pituitary tumor; anorexia nervosa; or strenuous physical exercise, which can alter the critical body fat–to–muscle ratio needed for menses to occur.[50]

Diagnostic evaluation resembles that for dysfunctional uterine bleeding, with the possible addition of a computed tomographic scan or MRI to exclude a pituitary tumor. Treatment is based on correcting the underlying cause and inducing menstruation with cyclic progesterone or combined estrogen–progesterone regimens.

Dysmenorrhea

Dysmenorrhea is pain or discomfort with menstruation.[11] Although not usually a serious medical problem, it causes some degree of monthly disability for a significant number of women. There are two forms of dysmenorrhea: primary and secondary. Primary dysmenorrhea is caused by the effects of excess prostaglandin (i.e., prostaglandin F_{2a}) production in the endometrium. Prostaglandins are potent smooth muscle stimulants that cause intense uterine contractions. Prostaglandin production in the uterus normally increases under the influence of progesterone, reaching a peak at or soon after the onset of menstruation. With onset of menstruation, formed prostaglandins are released from the shedding endometrium. Prostaglandins also cause contraction of

smooth muscle elsewhere in the body. Severe dysmenorrhea may be associated with systemic symptoms such as headache, nausea, vomiting, and diarrhea. The pain of primary dysmenorrhea is often diffusely located in the lower abdomen or suprapubic area, often radiating to the lower back. The pain is often described as cramping and spasmodic, or similar to labor pains. Secondary dysmenorrhea is menstrual pain caused by structural abnormalities or disease processes such as endometriosis, uterine fibroids, adenomyosis, pelvic adhesions, IUDs, or PID. In women with secondary dysmenorrhea, the pain often lasts longer than the menstrual period; it may begin before menstrual bleeding begins; and it may become worse during menstruation.

Treatment for primary dysmenorrhea is directed at symptom control. Women with primary dysmenorrhea generally experience dramatic pain relief with the nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen, mefenamic acid), which are prostaglandin synthetase inhibitors. Ovulation suppression and symptomatic relief of dysmenorrhea can be instituted simultaneously with the use of oral contraceptives. Relief of secondary dysmenorrhea depends on identifying the cause of the problem. Medical or surgical intervention may be needed to eliminate the problem.

Premenstrual Syndrome Disorders

Premenstrual syndrome disorders are a group of physical, emotional, and behavioral changes that occur in a regular, cyclic relationship to the luteal phase of the menstrual cycle and that interfere with some aspect of a woman's life.[11] The severity of this cyclic symptom complex can vary from *premenstrual molimina* on the mild end; through *premenstrual syndrome* (PMS), which is characterized by mild to moderate physical and psychological symptoms limited to 3 to 14 days preceding menstruation and relieved by onset of the menses; to *premenstrual dysphoric disorder* (PMDD), which is the most severe form of premenstrual distress and generally is associated with mood disorders.

According to recent surveys, 75% to 80% of women in the United States experience some emotional or physical premenstrual changes; in approximately 3% to 8% of these women, extreme or severe symptoms cause a negative impact on their life.[51,52] The incidence of PMS and PMDD seems to increase with age. It is less common in women in their teens and twenties, and most of the women seeking help for the problem are in their mid thirties. The disorder is not culturally distinct; it affects both Westerners and non-Westerners.

Physical symptoms of PMS include painful and swollen breasts, bloating, abdominal pain, headache, and backache. Psychologically, there may be depression, anxiety, irritability, and behavioral changes. In some cases, there are puzzling alterations in motor function, such as clumsiness and altered handwriting. Women with PMS may report one or several symptoms, with symptoms varying from woman to woman and from month to month in the same patient. PMS can significantly affect a woman's ability to perform at normal levels. Family responsibilities and relationships may suffer and she may lose time from or function ineffectively at work. Students have had lower grades during the premenstrual period. More crimes are committed by women during the premenstrual phase of the cycle, and more lives are lost to suicide during this period.

Although the causes of PMS are poorly documented, they probably are multifactorial. Like dysmenorrhea, it is only recently that PMS has been recognized as a bona fide disorder rather than merely a psychosomatic illness. Because there appear to be no measurable differences in hormone levels between women with and without PMS, it is presumed that normal cyclic variation in the hormones is the trigger for symptoms in vulnerable or predisposed women.[52] Currently, data suggest a relationship between normal gonadal fluctuations and central neurotransmitter activity, particularly serotonin. It is unclear whether decreased levels of serotonin are present during the luteal phase and only susceptible women respond with varying degrees of premenstrual symptoms, or if women with PMDD have a neurotransmitter abnormality.[51–54]

Diagnosis of PMS and PMDD focuses on documentation of the relationship of a woman's symptoms to the luteal phase of the menstrual cycle (Chart 40-1). Diagnosis focuses on identification of symptoms by means of a daily calendar on which the woman records her symptoms for 2 to 3 consecutive months.[51] A complete history and physical examination are necessary to exclude other physical causes of the symptoms. Depending on the symptom pattern, blood studies, including thyroid hormones, glucose, and prolactin assays, may be done. Psychosocial evaluation is helpful to exclude emotional illness that is merely exacerbated premenstrually.

PMDD is a psychiatric diagnosis that has been developed to distinguish those women whose symptoms are severe enough to interfere significantly with activities of daily living.[51–54] It requires prospective symptom charting, and a minimum of 5 of the 11 symptom groups as described in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) to establish a diagnosis of PMDD (Chart 40-1).

Management of PMS/PMDD has been largely symptomatic and includes education and support directed toward lifestyle changes for women with mild symptoms. An integrated program of personal assessment by diary, regular exercise, avoidance of caffeine, and a diet low in simple sugars and high in lean proteins is often beneficial. In addition to lifestyle changes, pharmacologic treatment includes the use of diuretics to reduce fluid retention, nonsteroidal anti-inflammatory agents for pain, and anxiolytic drugs to treat mood changes. Because symptoms are associated with ovulatory cycles, suppressing ovulation may be beneficial for some women with PMS and can be accomplished by using oral contraceptives, danazol (a synthetic androgen), or GnRH agonists.[51,52] Oral contraceptives can be used for women who also require contraception. However, some women find their symptoms worsen when taking contraceptives. The pharmacologic treatment of PMDD differs from that of PMS.

CHART 46-1 DSM-IV-TR Criteria for Premenstrual Dysphoric Disorder (PMDD)

Core Symptoms

Depressed mood
Moodiness
Anxiety, edginess, nervousness
Anger, irritability

Other Symptoms

Fatigue, lethargy
Insomnia, hypersomnia
Difficulty concentrating
Appetite changes or cravings
Diminished interest in usual activities
Feeling overwhelmed or out of control
Physical symptoms (headache, breast tenderness or swelling, bloating, joint and muscle pain)

PMDD = patient must exhibit five or more symptoms, including at least one core symptom during the premenstrual period, confirmed by prospective charting during at least two consecutive menstrual cycles. Symptoms must cause marked impairment in the woman's ability to carry out her usual activities, must abate within a few days of the onset of menses, and not recur during the week after menses.

From American Psychiatric Association. (2000). Premenstrual dysphoric disorder. In *Diagnostic and statistical manual of mental disorders, fourth edition, text revision* (pp. 771–774). Washington, DC: Author.

Ovulation suppression does not seem to help women with PMDD. Although many medications have been studied, only three antidepressants (fluoxetine, sertraline, and paroxetine controlled release) and an oral contraceptive that contains drospirenone (a spironolactone derivative) have been approved for treatment of the emotional and physical symptoms of PMDD.[51,52]

Menopause and Aging Changes

Menopause is the cessation of menstrual cycles. Like menarche, it is more of a process than a single event.[55,56] Most women stop menstruating between 48 and 55 years of age. *Perimenopause* (the years immediately surrounding menopause) precedes menopause by approximately 4 years and is characterized by menstrual irregularity and other menopausal symptoms. *Climacteric* is a more encompassing term that refers to the entire transition to the nonreproductive period of life. Premature ovarian failure describes the approximately 1% of women who experience menopause before the age of 40 years. A woman who has not menstruated for a full year or has an FSH level greater than 30 mIU/mL is considered menopausal.[11]

Menopause results from the gradual cessation of ovarian function and the resultant diminished levels of estrogen. Although estrogens derived from the adrenal cortex continue to circulate in a woman's body, they are insufficient to maintain the secondary sexual characteristics in the same manner as ovarian estrogens. As a result, breast tissue, body hair, skin elasticity, and subcutaneous fat decrease; the ovaries and uterus diminish in size; and the cervix and vagina become pale and friable. Problems that can arise as a result of this urogenital atrophy include vaginal dryness, urinary stress incontinence, urgency, nocturia, vaginitis, and urinary tract infection.[55,56] The woman may find intercourse painful and traumatic, although some type of vaginal lubrication may be helpful.

Systemically, a woman may experience significant vasomotor instability secondary to the decrease in estrogens and the relative increase in other hormones, including FSH, LH, GnRH, dehydroepiandrosterone, and androstenedione. This instability may give rise to "hot flashes," palpitations, dizziness, and headaches as the blood vessels dilate. Despite the association with these biochemical changes, the underlying cause of hot flashes is unknown. Tremendous variation exists in the onset, frequency, severity, and length of time that women experience hot flashes. When they occur at night and are accompanied by significant perspiration, they are referred to as *night sweats*. Insomnia as well as frequent awakening because of vasomotor symptoms can lead to sleep deprivation. A woman may experience irritability, anxiety, and depression as a result of these uncontrollable and unpredictable events.

Consequences of long-term estrogen deprivation include osteoporosis due to an imbalance in bone remodeling (see Chapter 44), and an increased risk for cardiovascular disease, which is the leading cause of death for women after menopause. With perimenopause, changes occur in the cardiovascular lipid profile: total cholesterol increases, HDL cholesterol decreases, and LDL cholesterol increases.

Menopausal hormonal therapy has come under scrutiny with the publication of the Women's Health Care Initiative.[57] Since the publication of these trials, there has been great interest in developing alternative doses, delivery systems, and medications for hormone therapy. Many products are now available, including transdermal delivery systems and lower-dose traditional hormone therapy. Vaginal estrogen preparations are available to treat symptoms related to vaginal atrophy. Selective estrogen receptor modulators (SERMs) may be used in place of estrogen to prevent osteoporosis.

In summary, menstrual disorders include dysfunctional menstrual cycles, dysmenorrhea, and premenstrual syndromes. Dysfunctional menstrual cycles produce amenorrhea, oligomenorrhea, metrorrhagia, or menorrhagia. Dysmenorrhea is characterized by pain or discomfort during menses. It can occur as a primary or secondary disorder. Primary dysmenorrhea is caused by excess prostaglandin F_{2a}, a potent smooth muscle stimulant that causes intense uterine contractions. Secondary dysmenorrhea is caused by structural abnormalities; disease processes such as endometriosis, uterine fibroids, pelvic adhesions, or PID; or IUDs. The terms

premenstrual syndrome and *premenstrual dysphoric disorder* represent an array of predictable physical, cognitive, affective, and behavioral symptoms that occur during the luteal phase of the menstrual cycle and that are resolved by menstruation or within a few days of the onset. Although the etiology of these disorders is currently unknown, it is probably the result of an interaction between the sex hormones and central neurotransmitters, particularly serotonin.

Menopause is the cessation of ovarian function and menstrual cycles. It is accompanied by a decline in secondary sexual characteristics, vasomotor instability, and long-term consequences, including osteoporosis and increased risk of heart disease.

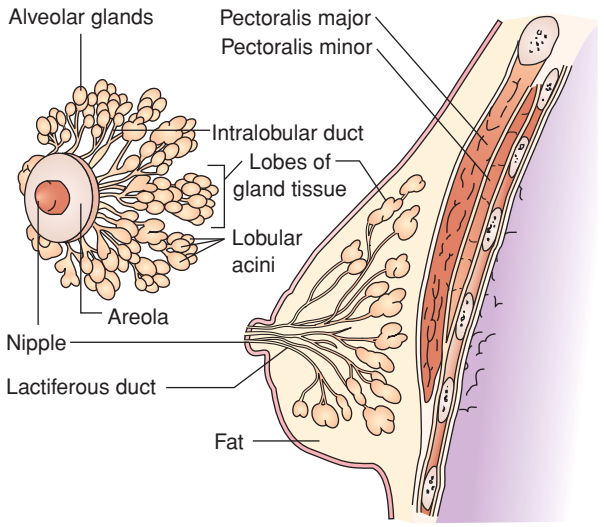


FIGURE 40-18. The breast, showing the glandular tissue and ducts of the mammary glands.

Disorders of the Breast

Although anatomically separate, the breasts are functionally related to the female reproductive system in that they respond to the cyclic changes in sex hormones and produce milk for infant nourishment. The breasts are composed of specialized epithelium and stroma that may give rise to both benign and malignant lesions.

Breast Structures

The breasts, or mammary glands, are located between the third and seventh ribs of the anterior chest wall and are supported by the pectoral muscles and superficial fascia. They are specialized glandular structures that have an abundant shared nervous, vascular, and lymphatic supply[1,2] (Fig. 40-17). Structurally the breast consists of fat, fibrous connective tissue, and glandular tissue. The superficial fibrous connective tissue is attached to the skin, a fact that is important in the visual observation of skin movement over the breast during breast self-examination. A nipple is located near the tip of the breast at about the level of the fourth intercostal space and is surrounded by an area of pigmented skin called the *areola* (Fig. 40-18). The areola contains sebaceous glands and modified sweat glands (glands of Montgomery). These glands have a structure intermediate between sweat glands and true mammary glands, and produce small elevations at the surface of the areola.

The breast mass is supported by the fascia of the pectoralis major and minor muscles and by the fibrous connective tissue of the breast. Fibrous tissue ligaments, called *Cooper ligaments*, extend from the outer boundaries of the breast to the nipple area in a radial manner, like the spokes on a wheel. These ligaments further support the breast and form septa that divide the breast into 15 to 20 lobes. Each lobe consists of grapelike clusters of glands (alveolar glands) and a duct (lactiferous duct) that lead to the nipple and opens to the outside (see Fig. 40-18). Two epithelial cell types line the ducts and alveolar glands of

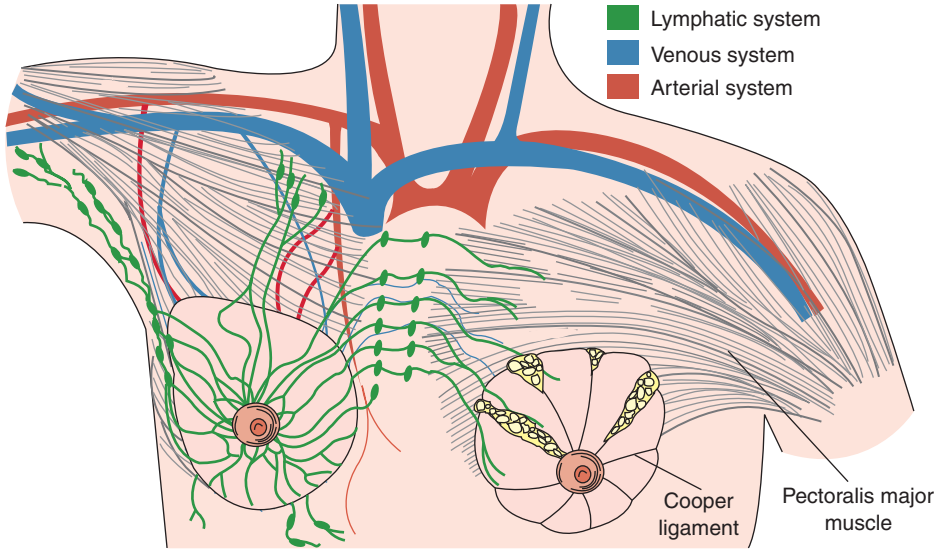


FIGURE 40-17. The breasts, showing the shared vascular and lymphatic supply as well as the pectoral muscles.

the lobules—myoepithelial and luminal epithelial cells. Contractile epithelial cells, which lie between the surface epithelium and the basement membrane, provide structural support for the lobules and assist in milk ejection during lactation. The luminal epithelial cells, which are the only cells capable of producing milk, overlie the myoepithelial cells.

The structure of the breast changes with the menstrual cycle and pregnancy. Estrogen stimulates the growth of the ductal system, whereas progesterone stimulates the growth and development of the ductile and glandular secretory epithelium. Early in the menstrual cycle, the ducts appear as cords with little or no lumen. Under estrogen stimulation, at the time of ovulation, the secretory cells increase in size, lumina appear in the ducts as small amounts of secretions accumulate, and fluid collects in the connective tissue. This causes a feeling of breast fullness and discomfort. During pregnancy, placental estrogen and progesterone produce further changes in the mammary glands. Beginning at about the fifth week of pregnancy, the anterior pituitary releases increasing amounts of the hormone *prolactin*. The alveolar glands are lined with secretory cells capable of producing milk under the influence of prolactin. However, milk production does not occur until after birth. This is because placental hormones inhibit milk production. Following childbirth and expulsion of the placenta, the maternal concentration of placental hormones declines rapidly and the action of prolactin is no longer inhibited.

Benign Disorders

Breast disease may be described as benign or cancerous.[7,11,58] Benign breast conditions are nonmalignant conditions of the breast. They include inflammatory disorders and benign epithelial disorders. Some benign disorders may increase the risk of malignant disease and others may present with signs that resemble malignant disease.

Inflammatory Disorders

Inflammatory diseases of the breast are uncommon, accounting for less than 1% of breast disorders.[11] They include mastitis, mammary duct ectasia, and fat necrosis.

Mastitis. Mastitis is inflammation of the breast.[11,59,60] It most frequently occurs during lactation but may also result from other conditions. In the lactating woman, inflammation results from an ascending infection that travels from the nipple to the ductal structures. The most common organisms isolated are *Staphylococcus aureus* and *Streptococcus*.[59] The offending organisms often originate from the suckling infant's nasopharynx or the mother's hands. During the early weeks of nursing, the breast is particularly vulnerable to bacterial invasion because of minor cracks and fissures that occur with vigorous suckling. Infection and inflammation cause obstruction of the ductal system. The breast area becomes hard, inflamed, and tender if not treated early. Without treatment, the area becomes walled off and may abscess, requiring incision and drainage. It is advisable for the mother to continue breast-feeding during antibiotic therapy to prevent this.

Mastitis is not confined to the postpartum period; it can occur as a result of hormonal fluctuations, tumors, trauma, or skin infection. Cyclic inflammation of the breast occurs most frequently in adolescents, who commonly have fluctuating hormone levels. Tumors may cause mastitis secondary to skin involvement or lymphatic obstruction. Local trauma or infection may develop into mastitis because of ductal blockage of trapped blood, cellular debris, or the extension of superficial inflammation. The treatment for mastitis symptoms may include application of heat or cold, excision, aspiration, mild analgesics, antibiotics, and a supportive brassiere or breast binder.

Mammary Duct Ectasia. Mammary duct ectasia refers to the presence of dilated breast ducts containing a thick pasty material, with accompanying periductal inflammation and fibrosis.[11,59] The dilated ducts may rupture, resulting in grayish-green nipple discharge. Palpation of the breast increases the discharge. The disorder is usually unilateral, occurring after menopause, most often in elderly multiparous women. Women typically present with a poorly defined perialveolar mass that is often associated with thick, white nipple secretions and sometimes with nipple retraction. Pain and erythema are uncommon. Duct ectasia may be difficult to distinguish clinically from carcinoma and may require biopsy.

Fat Necrosis. Fat necrosis is a distinct clinical and histologic entity, resulting in either a localized or diffuse mass lesion of the breast. The majority of women have a history of trauma, surgery, or radiation therapy.[11,58,59] Initially the lesion consists of necrotic adipocytes and hemorrhage, after which the inflammatory cells phagocytize the lipid debris. Macrophages may produce a granulomatous inflammatory response. Fibroblast proliferation and collagen deposition during healing may lead to scar tissue (fibrosis). As a result, an irregular fixed hard mass may form that clinically resembles breast cancer. Unlike a malignant mass, however, fat necrosis is typically very tender and has a specific mammographic appearance.

Benign Epithelial Disorders

A wide variety of benign alterations in ducts and lobules are observed in the breast. Most are detected by mammography or as incidental findings on surgical specimens. These lesions have been divided into three groups according to the subsequent risk of developing carcinoma: nonproliferative (fibrocystic) changes, proliferative breast disease without atypia, and proliferative breast disease with atypia.[11,59]

Nonproliferative (Fibrocystic) Breast Changes. Formerly called *fibrocystic disease*, fibrocystic changes are the most frequent lesion of the breast. They encompass a wide variety of lesions and breast changes. Microscopically, fibrocystic changes refer to a constellation of

morphologic changes manifested by (1) cystic dilation of terminal ducts, (2) relative increase in fibrous tissue, and (3) variable proliferation of terminal duct epithelial elements.[59] They are most common in women 30 to 50 years of age and are rare in postmenopausal women not receiving hormone replacement.[59,60]

Fibrocystic changes usually present as nodular (i.e., "shotty"), granular breast masses that are more prominent and painful during the luteal or progesterone-dominant portion of the menstrual cycle. Discomfort ranges from heaviness to exquisite tenderness, depending on the degree of vascular engorgement and cystic distention.

Although fibrocystic changes have been thought to increase the risk of breast cancer, only certain variants in which proliferation of the epithelial components is demonstrated represent a true risk. Fibrocystic changes with giant cysts and proliferative epithelial lesions with atypia are more common in women who are at increased risk for development of breast cancer. The nonproliferative form of fibrocystic changes that does not carry an increased risk for development of cancer is more common.

Diagnosis of fibrocystic changes is made by physical examination, mammography, ultrasonography, and biopsy (i.e., aspiration or tissue sample). Mammography may be helpful in establishing the diagnosis, but increased breast tissue density in women with fibrocystic changes may make an abnormal or cancerous mass difficult to discern among the other structures. Ultrasonography is useful in differentiating a cystic from a solid mass. Because a mass caused by fibrocystic changes may be indistinguishable from carcinoma on the basis of clinical findings, suspect lesions should undergo biopsy. Any discrete mass or lump on the breast should be viewed as possible carcinoma, and cancer should be excluded before instituting the conservative measures used to treat fibrocystic changes.

Treatment for fibrocystic changes is usually symptomatic. Mild analgesics (e.g., aspirin, acetaminophen, or NSAIDs), vitamin E, and local application of heat or cold may be used for pain relief. Prominent or persistent cysts may be aspirated and any fluid obtained sent to the laboratory for cytologic analysis. Women should be encouraged to wear a good supporting brassiere, and are advised to avoid foods that contain xanthines (e.g., coffee, cola, chocolate, and tea) in their daily diets, particularly premenstrually. Danazol, a synthetic androgen, may be used for women with severe pain.[11] While it suppresses pituitary gonadotropins, the androgenic effects (acne, edema, hirsutism) of danazol often make this treatment intolerable. Similarly, tamoxifen reduces some of the symptoms of the fibrocystic condition, but because of its side effects, it is not useful in young women unless it is given to reduce the risk of cancer.

Proliferative Lesions without Atypia. Proliferative lesions without atypia, which are commonly detected as mammographic densities or calcifications, include epithelial hyperplasia, sclerosing adenosis, and intraductal papillomas.[11,59] They are characterized by proliferation of ductile or lobular epithelial cells.

In a normal breast, only myoepithelial cells and a single layer of luminal cells rest on the basement membrane. If there are more than two cell layers, the abnormality is known as *epithelial hyperplasia*. If there is increased fibrosis within the expanded lobule, with distortion and compression of the epithelium, the lesion is termed *sclerosing adenosis*. Papillomas are intraductal growths composed of supporting tissue and lined with both myoepithelial and luminal cells. Solitary *intraductal papillomas* are found in the major lactiferous ducts of women, typically between the ages of 30 and 50. The papillomas, which can range in size from 2 mm to 5 cm, often present with serous or serosanguineous drainage.

Proliferative Lesions with Atypia. Proliferative disease with atypia includes atypical ductile hyperplasia and atypical lobular hyperplasia.[11,59] The hyperplasia is accompanied by replacement of the normal epithelial cells lining the ducts or lobules with atypical cells resembling those of carcinoma in situ. The basement membrane remains intact and, therefore, the cells cannot metastasize.[11]

There are two types of atypical hyperplasia: lobular and ductile.[59] Atypical ductile hyperplasia is recognized by its histologic resemblance to ductile carcinoma in situ (DCIS). It is distinguished from DCIS by its limited extent and partial filling of the ducts. Atypical lobar hyperplasia is defined by proliferation of cells identical to those of lobar carcinoma in situ (LCIS), but the cells do not fill or distend more than 50% of the acini within the lobule. Management of LCIS consists of excisional biopsy.[11] Women with DCIS are at increased risk for developing invasive cancer or recurrence of the DCIS lesion.[11] For this reason, DCIS is evaluated with core-needle biopsy (to be discussed) followed by surgical biopsy or excision. Women with both types of lesions require careful follow-up to prevent and detect the presence of invasive cancer.

Breast Cancer

Cancer of the breast is the most common female cancer. Currently, one in nine American women will have breast cancer in her lifetime.[60] Although the breast cancer mortality rate has shown a slight decline, it is second only to lung cancer as a cause of cancer-related deaths in women. Incidence rates for carcinoma in situ have increased dramatically since the mid-1970s because of recommendations regarding mammography screening. A 3.9% decrease in breast cancer incidence has been observed between 2001 and 2004, along with a 2.2% decrease in breast cancer mortality. The decline in the breast cancer mortality rate undoubtedly is due to earlier diagnosis through screening programs and increased awareness, as well as improvements in cancer treatments.

Risk factors for breast cancer include increasing age, personal or family history of breast cancer (i.e., at highest risk are those with multiple affected first-order relatives), history of benign breast disease (i.e., primary "atypical" hyperplasia), and hormonal influences that promote breast maturation and may increase the chance

of cell mutation (i.e., early menarche, late menopause, and no term pregnancies or first child after 30 years of age). Modifiable risk factors include obesity (particularly after menopause), physical inactivity, alcohol intake greater than one drink per day, and long-term use of postmenopausal hormone therapy (especially combined estrogen and progestin). Most women with breast cancer have no identifiable risk factors.

Approximately 5% to 10% of all breast cancers are hereditary, with genetic mutations causing up to 80% of breast cancers in women younger than 50 years of age.[61] Mutations in two breast cancer susceptibility genes—*BRCA1* on chromosome 17 and *BRCA2* on chromosome 13—may account for most inherited forms of breast cancer (see Chapter 7). *BRCA1* is known to be involved in tumor suppression. A woman with known mutations in *BRCA1* has a lifetime risk of 60% to 85% for breast cancer and an increased risk of ovarian cancer. *BRCA2* is another susceptibility gene that carries an elevated cancer risk similar to that with *BRCA1*.[61] Breast cancer risk reduction options available to known carriers of *BRCA1* and *BRCA2* mutations include surveillance and surgery. Breast evaluation using MRI is generally preferred over standard mammography for these women because of its enhanced sensitivity and lack of radiation exposure, which may be safer for them. Prophylactic surgery, in the form of bilateral mastectomy, bilateral oophorectomy, or both, has been shown to decrease the risk of developing cancer. These controversial surgeries can have physical and psychological side effects that warrant careful consideration before proceeding.

Detection

Cancer of the breast may manifest clinically as a mass, a puckering, nipple retraction, or unusual discharge. Many cancers are found by women themselves—sometimes when only a thickening or subtle change in breast contour is noticed. The variety of symptoms and potential for self-discovery underscore the need for all women to have an awareness of what their normal breast appearance and texture are like. In 2003, the American Cancer Society dropped its recommendation that all women perform regular, systematic self-examination.[62] Research has indicated that most women who discover their own cancer do so at times other than scheduled breast self-examination (BSE). American Cancer Society screening guidelines now place primary emphasis for breast cancer diagnosis on clinical breast examination and mammography, while encouraging women in the area of self-awarenenss.[62] Women should have a clinical examination by a trained health professional and mammography at least every 3 years between 20 and 40 years of age, and annually after 40 years of age.

Mammography is the only effective screening technique for the early detection of clinically inapparent breast lesions. A generally slow-growing form of cancer, breast cancer may have been present for 2 to 9 years before it reaches 1 cm, the smallest mass normally detected by palpation. Mammography can disclose lesions as small as 1 mm and the clustering of calcifications that may warrant biopsy to exclude cancer. Mammography has a sensitivity of 80% to 90% for the detection of breast cancer even when performed by the most capable institutions. Therefore, palpable masses need further evaluation and potentially biopsy even if the mammogram is negative. Approximately 40% of breast cancers can be detected only by palpation and another 40% only by mammography. The most comprehensive approach to screening is a combination of individual self-awareness, clinical breast evaluation by a health professional, and mammogram.

Diagnosis and Classification

Procedures used in the diagnosis of breast cancer include physical examination, mammography, ultrasonography, percutaneous needle aspiration, stereotactic needle biopsy (i.e., core biopsy), and excisional biopsy. Figure 46-19 illustrates the appearance of breast cancer on mammography. Breast cancer often manifests as a solitary, painless firm fixed lesion with poorly defined borders. It can be found anywhere in the breast but is most common in the upper outer quadrant. Because of the variability in presentation, any suspect change in breast tissue warrants further investigation. The diagnostic use of mammography enables additional definition of the clinically suspect area (e.g., appearance, character, calcification). Placement of a wire marker under radiographic guidance can ensure accurate surgical biopsy of nonpalpable suspect areas. Ultrasonography is useful as a diagnostic adjunct to differentiate cystic from solid tissue in women with nonspecific thickening.

Fine needle aspiration is a simple in-office procedure that can be performed repeatedly in multiple sites and with minimal discomfort. It can be accomplished by stabilizing a palpable mass between two fingers or in conjunction with handheld sonography to define cystic masses or fibrocystic changes and to provide specimens for cytologic examination. Fine needle aspiration can identify the presence of malignant cells, but it cannot differentiate in situ from infiltrating cancers. Stereotactic needle biopsy is an outpatient procedure done with the guidance of a mammography machine. After the lesion is localized radiologically, a large-bore needle is mechanically thrust quickly into the area, removing a core of tissue. Discomfort is similar to that with ear piercing, and even when multiple cores are obtained, healing occurs quite rapidly. Cells are available for histologic evaluation with 96% accuracy in detecting cancer. This procedure is less costly than excisional biopsy. Excisional biopsy to remove the entire lump provides the only definitive diagnosis of breast cancer, and often is therapeutic without additional surgery. MRI, positron emission tomography (PET), and computer-based or digital mammography are available as additional diagnostic modalities for breast cancer, and may be recommended to supplement conventional mammography in women with radiographically dense breasts or a strong family history of cancer, or who are known carriers of *BRCA1* or *BRCA2*.[63]

Tumors are classified histologically according to tissue characteristics and staged clinically according to tumor size, nodal involvement, and presence of metastasis.

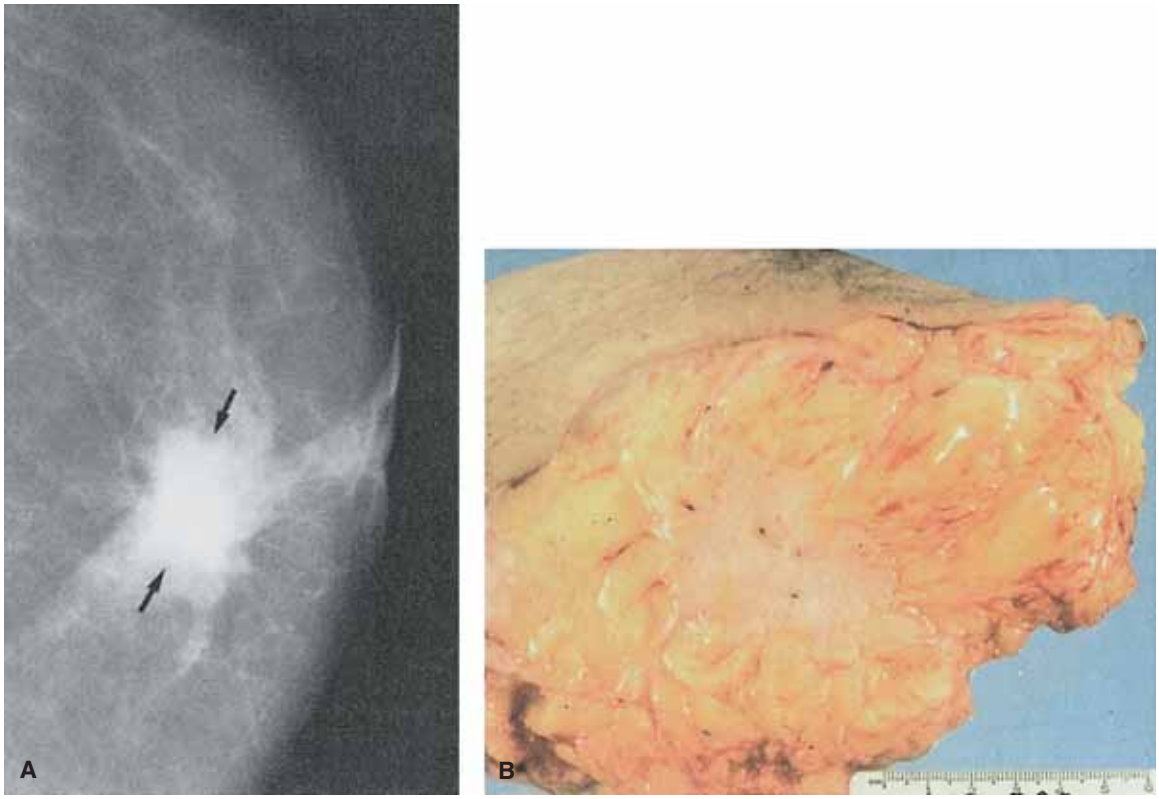


FIGURE 40-19. Carcinoma of the breast. **(A)** Mammogram. An irregularly shaped, dense mass (*arrows*) is seen in this otherwise fatty breast. **(B)** Mastectomy specimen. The irregular white, firm mass in the center is surrounded by fatty tissue. (From Thor A.D., Osunkoya A.O. [2008]. The breast. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 851]. Philadelphia: Lippincott Williams & Wilkins.)

It is recommended that estrogen and progesterone receptor analysis be performed on surgical specimens. Information about the presence or absence of estrogen and progesterone receptors can be used in predicting tumor responsiveness to hormonal manipulation. High levels of both receptors improve the prognosis and increase the likelihood of remission.

Treatment

The treatment methods for breast cancer include surgery, chemotherapy, radiation therapy, and hormonal manipulation. Radical mastectomy (i.e., removal of the entire breast, underlying muscles, and all axillary nodes) rarely is used today as a primary surgical therapy unless breast cancer is advanced at the time of diagnosis. Modified surgical techniques (i.e., mastectomy plus axillary dissection or lumpectomy for breast conservation) accompanied by chemotherapy or radiation therapy have achieved outcomes comparable with those obtained with radical surgical methods and constitute the preferred treatment methods.

The prognosis for women with breast cancer is related more to the extent of nodal involvement than to the extent of breast involvement. Greater nodal involvement requires more aggressive postsurgical treatment, and many cancer specialists believe that a diagnosis of breast cancer is not complete until dissection and testing of the axillary lymph nodes have been accomplished. A newer technique for evaluating lymph node involvement is a sentinel lymph node (SLN) biopsy. A radioactive substance or dye is injected into the region of the tumor. In theory, the dye is carried to the first (sentinel) node to receive lymph from the tumor.[64] This would therefore be the node most likely to contain cancer cells if the cancer has spread. If the sentinel node biopsy is positive, more nodes are removed. If it is negative, further lymph node evaluation may not be needed.

Systemic therapy refers to the administration of chemotherapy, biologic therapy, or hormonal therapy. Neoadjuvant therapy is given before surgery to shrink the tumor and make surgical removal more effective. Adjuvant therapy is given after surgery to women with and without detectable metastatic disease. The goal of this therapy depends on nodal involvement, menopausal status, and hormone receptor status. Systemic adjuvant therapy has been widely studied and has demonstrated benefits in reducing rates of recurrence and death from breast cancer.[64] Biologic therapy, using the drug trastuzumab (Herceptin), is used to stop the growth of breast tumors that express the HER2/neu receptor on their cell surface. The HER2/neu receptor binds an epidermal growth factor that contributes to cancer cell growth. Trastuzumab is a recombinant DNA-derived

monoclonal antibody that binds to the HER2/neu receptor, thereby inhibiting proliferation of tumor cells that overexpress the receptor gene.[65]

Hormone therapy is used to block the effects of estrogen on the growth of breast cancer cells. Tamoxifen is a nonsteroidal antiestrogen that binds to estrogen receptors and blocks the effects of estrogens on the growth of malignant cells in the breast. Studies have shown decreased cancer recurrence, decreased mortality rates, and increased 5-year survival rates in women with estrogen receptor–positive tissue samples who have been treated with the drug. Aromatase inhibitors block the enzyme that converts androstenedione and testosterone to estrogen in the peripheral tissues. This reduces the circulating estrogen levels in postmenopausal women and is becoming the most effective adjuvant therapy for women with early-stage breast cancer.[66] Autologous bone marrow transplantation and peripheral stem cell transplantation are experimental therapies that may be used for treatment of advanced disease or in women at increased risk for recurrence.

Paget Disease

Paget disease accounts for 1% of all breast cancers.[59,60] The disease presents as an eczematoid lesion of the nipple and areola. Paget disease usually is associated with an infiltrating, intraductal carcinoma. When the lesion is limited to the nipple only, the rate of axillary metastasis is approximately 5%. Complete examination is required and includes a mammogram and biopsy. Treatment depends on the extent of spread.

In summary, the breast contains alveolar glands and ducts that are lined with epithelial tissue that may give rise to benign and malignant lesions. The benign conditions include inflammatory disorders (mastitis, mammary duct dysplasia, and fat necrosis) and benign epithelial lesions (nonproliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia). Some benign conditions, such as proliferative lesions, may predispose to malignant disease, and others, such as fibrocystic changes and fat necrosis, may present with a mass and signs that resemble malignant disease. By far the most important disease of the breast is breast cancer, which is a significant cause of death for women. Risk factors for breast cancer include increasing age, personal or family history of breast cancer, history of benign breast disease (i.e., proliferative lesions with atypia), and hormonal influences (e.g., early menarche and late menopause) that promote breast maturation and may increase the chance of cell mutation. Some inherited breast cancers are associated with mutations in breast cancer genes *BRCA1* and *BRCA2*. Both physical examination and mammography afford a woman the best protection against breast cancer. They provide the means for early detection of breast cancer and, in many cases, allow early treatment and cure. The choice of treatment, which includes surgical resection, radiation, and chemotherapy, depends on the stage of the disease.

REVIEW EXERCISES

1. Most oral contraceptive agents use low doses of estrogen and progestin to prevent conception.

- **A.** Use Figure 40-4 to explain how these oral agents prevent ovulation and pregnancy.

2. A 32-year-old woman has been told that the report of her annual Pap test revealed the presence of mild cervical dysplasia.

- **A.** What questions should this woman ask to become informed about the significance of these findings?
- **B.** In obtaining additional information about the results of her Pap test, the woman is informed that the dysplastic changes are consistent with a CIN1 classification.
  - **a.** Does this mean that the woman has cervical cancer?
  - **b.** Cervical cancer is often referred to as a sexually transmitted disease. Explain.
  - **c.** What type of follow-up care would be indicated?

3. A 30-year-old woman consults her gynecologist because of amenorrhea and inability to become pregnant. Physical examination reveals an obese woman with hirsutism. The physician tells her that she might have a condition known as *polycystic ovary syndrome* and that further laboratory tests are indicated.

- **A.** Among tests ordered were a fasting blood glucose and serum LH, FSH, and dehydroepiandrosterone levels. What information can these tests provide that would help in establishing a diagnosis of polycystic ovary syndrome?
- **B.** What is the probable cause of this woman's amenorrhea, hirsutism, and failure to become pregnant?
- **C.** What type of treatment might be used to help this woman become pregnant?

4. A 45-year-old woman makes an appointment to see her physician because of a painless lump in her breast that she has discovered.

- **A.** What tests should be done to confirm the presence or absence of breast cancer?
- **B.** During the removal of breast cancer, a sentinel node biopsy is often done to determine whether the cancer has spread to the lymph nodes. Explain how this procedure is done and its value in determining lymph node spread.
- **C.** After surgical removal of breast cancer, tamoxifen may be used as an adjuvant systemic therapy for women without detectable metastatic disease. The presence or absence of estrogen receptors in the cytoplasm of tumor cells is important in determining the selection of an agent for use in adjuvant therapy. Explain.

REFERENCES

1. Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 105–112, 410–442). Philadelphia: Lippincott Williams & Wilkins.
2. Ross M.H., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 772–809). Philadelphia: Lippincott Williams & Wilkins.
3. Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 1011–1024). Philadelphia: Elsevier Saunders.
4. Rosen M.P., Cedars M.I. (2007). Female reproductive endocrinology and infertility. In Gardner D.G., Shoback D. (Eds.), *Greenspan's basic & clinical endocrinology* (5th ed., pp. 502–561). New York: McGraw-Hill Medical.
5. Gruber C.J., Tschugguel W., Huber J. (2002). Production and actions of estrogens. *New England Journal of Medicine* 346, 340–350.
6. Ellenson L.H., Pirog E.C. (2010). The female genital tract. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1005–1063). Philadelphia: Saunders Elsevier.
7. Robboy S.J., Merino M.J., Mutter G.L. (2008). The female reproductive system. In Rubin R., Strayer D.A. (Eds.), *Rubin's pathology: Clinicopathologic foundation of medicine* (5th ed., pp. 781–839). Philadelphia: Lippincott Williams & Wilkins.
8. Omole F., Simmons B.J., Hacker Y. (2003). Management of Bartholin duct cyst and gland abscess. *American Family Physician* 68, 135–140.
9. O'Connell T.X., Leena S.N., Satmary W.A., et al. (2008). Non-neoplastic epithelial disorders of the vulva. *American Family Physician* 77(3), 321–330.
10. Duong T.H., Flowers L.C. (2007). Vulvo-vaginal cancers: Risks, evaluation, prevention, and early detection. *Obstetrics and Gynecology Clinics of North America* 34, 783–802.
11. American College of Obstetrics and Gynecology (ACOG) with Beckmann C.R.B., Ling F.W., Barzansky B.M., et al. (2010). *Obstetrics and gynecology* (6th ed., pp. 259–267, 269–294, 323–327, 365–387, 393–401). Philadelphia: Wolters Kluwer/ Lippincott Williams & Wilkins.
12. Jerzak L.A., Smith S.K. (2006). Vulvodynia: Diagnosis and treatment of a chronic pain syndrome. *Women's Health Care* 5(4), 29–50.
13. Cooper A.S., Boardman L.A. (2005). Diagnosing and treating vulvar pain syndromes. *Women's Health Gynecology Edition* 5(3), 153–162.
14. Reed D.D. (2006). Vulvodynia: Diagnosis and management. *American Family Physician* 73, 1231–1339.
15. Eckert L.O. (2006). Acute vulvovaginitis. *New England Journal of Medicine* 355, 1244–1252.
16. Owen M.K., Clenney T.L. (2004) Management of vaginitis. *American Family Physician* 70(11), 2125–2140.
17. American Cancer Society. (2009). *Detailed guide: Vaginal cancer.* [Online] Available: http://www.cancer.org. Accessed July 3, 2010.
18. American Cancer Society. *Global cancer facts and figures 2007.* [Online] Available: http://www.cancer.org. Accessed July 3, 2010.
19. Warren J.B., Gullett H., King V.J. (2009). Cervical cancer: Screening and updated Pap guidelines. *Primary Care Clinics in Office Practice* 26, 131–149.
20. Waxman A.G., Zsemlye M.M. (2008). Preventing cervical cancer: The Pap test and the HPV vaccine. *Medical Clinics of North America* 92, 1059–1082.
21. Saslow D., Castle P.E., Cox T., et al. (2007). American Cancer Society guideline for human papillomavirus (HPV) vaccine to prevent cervical cancer and its precursors. *CA: A Cancer Journal for Clinicians* 57, 7–28.
22. Solomon D., Davey D., Kurman R., et al., for the Forum Group Members and the Bethesda 2001 Workshop. (2002). The 2001 Bethesda System. *Journal of the American Medical Association* 287(16), 2114–2119.
23. American Cancer Society. (2009). *Cervical cancer: Prevention and early detection.* [Online]. Available: http: //www. cancer.org. Accessed July 3, 2010.
24. American College of Obstetricians and Gynecologists (2009). *Cervical cystology screening.* ACOG practice Bulletin No. 109. [Online]. Available: http://www.acog.org. Accessed July 3, 2010.
25. U.S. Preventative Services Task Force. (2003). *Screening for cervical cancer.* [Online] Available: http://www.ahrq.gov/clinic/ 3rduspstf/cervcan/cervcanrr.htm. Accessed July 3, 2010.
26. Spitzer M., Apgar B.S., Brotzman G.L. (2006). Management of histologic abnormalities of the cervix. *American Family Physician* 73, 105–112.
27. Long H.J., Laack N.N.I., Gostout B.S. (2007). Prevention, diagnosis, and treatment of cervical cancer. *Mayo Clinic Proceedings* 82(12), 1566–1574.
28. Crossman S.H. (2006). The challenge of pelvic inflammatory disease. *American Family Physician* 73, 859–864.
29. Lareau S.M., Beigi R.H. (2008). Pelvic inflammatory disease and tubo-ovarian abscess. *Infectious Disease Clinics of North America* 22, 693–708.
30. Centers for Disease Control and Prevention. (2006). Sexually transmitted diseases treatment guidelines, 2006. *Morbidity and Mortality Weekly Report* 55(30), 1–94.
31. Grow D.R., Hsu A.L. (2006). Endometriosis, part 1: Clinical diagnosis and analgesia. *Female Patient* 31(11), 62–29.
32. Bulun S.E. (2009). Endometriosis. *New England Journal of Medicine* 360(3), 268–279.
33. Mounsey A.L., Wilgu A., Slawson D.C. (2006). Diagnosis and management of endometriosis. *American Family Physician* 74, 594–602.
34. Practice Committee of the American Society for Reproductive Medicine. (2006). Treatment of pelvic pain associated with endometriosis. *Fertility and Sterility* 86(Suppl 4), S18–S27.
35. Grow D.R., Hsu A.L. (2006). Endometriosis, part 2: Surgery for symptom relief and infertility. *Female Patient* 31(12), 54–59.
36. Bakkum-Gamez J., Gonzalez-Bosquet J., Laack N.N., et al. (2008). Current issues in the management of endometrial cancer. *Mayo Clinic Proceedings* 83(1), 97–112.
37. Amant F., Moeman P., Neven P., et al. (2005). Endometrial cancer. *Lancet* 366, 491–505.
38. DiCristofano A., Ellenson L.H. (2007). Endometrial carcinoma. *Annual Review of Pathology: Mechanisms of Disease* 2, 57–85.
39. Evans P., Brunsell S. (2007). Uterine fibroid tumors: Diagnosis and treatment. *American Family Physician* 75, 1503–1508.
40. Azziz R. (2005). Diagnostic criteria for polycystic ovary syndrome: A reappraisal. *Fertility and Sterility* 83, 1343–1346.
41. Sheriff K. (2006). Polycystic ovary syndrome in primary care. *Female Patient* 31(2), 25–29.
42. Ehrmann D.A. (2005). Polycystic ovary syndrome. *New England Journal of Medicine* 352, 1223–1236.
43. Salmi D.J., Zisser H.C., Jovanovic L. (2004). Screening for and treatment of polycystic ovary syndrome in teenagers: A mini review. *Experimental Biology and Medicine* 229, 369–377.
44. Cannistra S.A. (2004). Cancer of the ovary. *New England Journal of Medicine* 351, 2519–2529.
45. Chobanian N., Dietrich C.S. (2008). Ovarian cancer. *Surgical Clinics of North America* 88, 285–299.
46. Vo C., Carney M.E. (2007). Ovarian cancer hormonal and environmental risk effect. *Obstetrics and Gynecology Clinics of North America* 34, 687–700.
47. Goff B.A., Mandel L.S., Drescher C.W., et al. (2006). Development of an ovarian cancer symptom index: Possibilities for earlier detection. *Cancer* 109, 221–227.

48. Goff B.A., Muntz H.G. (2005). Screening and early diagnosis of ovarian cancer. *Women's Health* 5(4), 194–206.
49. U.S. Preventive Services Task Force. (2005). Screening guidelines for ovarian cancer: Recommendation statement of the USPSTF. *American Family Physician* 71, 759–762.
50. Practice Committee of the American Society for Reproductive Medicine. (2006). Current evaluation of amenorrhea. *Fertility and Sterility* 86(Suppl 4), S148–S155.
51. Minkin M.J., Moore A.E. (2006). Identifying and managing premenstrual disorders: Putting strategies into practice. *Clinical Advisor* November (Suppl), 4–15.
52. Steiner M., Pearlstein T., Cohen L.S., et al. (2006). Expert guidelines for the treatment of severe PMS, PMDD and co-morbidities: The role of SSRIs. *Journal of Women's Health* 15(1), 57–69.
53. Dickerson V.M. (2007). Premenstrual syndrome and premenstrual dysphoric disorder: Individualizing therapy. *Female Patient* 32(1), 38–46.
54. ACOG Practice Bulletin. (2000). Clinical management guidelines for obstetricians-gynecologists: Premenstrual syndrome. *Obstetrics and Gynecology* 95(4), 1–9.
55. Grady D. (2006). Management of menopausal symptoms. *New England Journal of Medicine* 355(22), 2338–2347.
56. Martin K.A., Manson J.E. (2008). Approach to the patient with menopausal symptoms. *Journal Clinical Endocrinology and Metabolism* 93(12), 4567–4575.
57. Gass M. (2008). Highlights from the latest WHI publications and the latest North American Menopause Society position statement on use of menopausal hormone therapy. *Cleveland Clinic Journal of Medicine* 75(4), S13–S16.
58. Miltenburg D.M., Speights V.O. Jr. (2008). Benign breast disease. *Obstetrics and Gynecology Clinics of North America* 35, 285–300.
59. Lester S.C. (2010). The breast. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1065–1095). Philadelphia: Saunders Elsevier.
60. Thor A.D., Osunkoya A.O. (2008). The breast. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 841–855). Philadelphia: Lippincott Williams & Wilkins.
61. Kolesar J.M. (2004). Clinical implications of BRCA1 and BRCA2 genes in hereditary breast and ovarian cancer. *Female Patient* 29(6), 39–45.
62. Smith R.A., Saslow D., Sawyers K.A., et al. (2003). American Cancer Society guidelines for breast cancer screening updated 2003. *CA: A Cancer Journal for Clinicians* 53, 141–169.
63. Pisano E.D., Gatsonis C., Hendrick E., et al. (2005). Diagnostic performance of digital versus film mammography for breast-cancer screening. *New England Journal of Medicine* 353, 1773–1783.
64. American Cancer Society. (2010). *Breast cancer facts & figures 2009–2010*. [Online] Available: www.cancer.org. Accessed July 3, 2010.
65. Piccart-Gehart M.J., Procter M., Leylan-Jones B., et al. (2005). Trastuzumab after adjuvant chemotherapy in Her2-positive cancer. *New England Journal of Medicine* 353, 1659–1672.
66. Geller M.L., Chlebowski R.T. (2006). The role of aromatase inhibitors in breast cancer therapy. *Female Patient* 31(1), 23–32.

Infections of the External Genitalia
Human Papillomavirus Infection and Genital Warts
Genital Herpes
Chancroid
Lymphogranuloma Venereum
Vaginal Infections
Candidiasis
Trichomoniasis
Bacterial Vaginosis
Vaginal-Urogenital-Systemic Infections
Chlamydial Infections
Gonorrhea
Syphilis

Chapter 41

Sexually Transmitted Infections

Sexually transmitted infections (STIs), previously referred to as sexually transmitted diseases (STDs), encompass a broad range of infectious diseases that are spread by sexual contact. Although the incidence of syphilis and gonorrhea as reported in the professional literature and public health statistics has decreased slightly, the incidence of other STIs is increasing. The actual figures are probably much higher than those reported because many STIs are not reportable or not reported. The agents of infection include bacteria, *Chlamydia,* viruses, fungi, and unidentified microorganisms (see Chapter 14). The initial site of an STI may be the urethra, genitalia, rectum, or oral pharynx. The organisms that cause these infections tend to be short lived outside the host, so they usually depend on person-to-person spread. The rates of many STIs are highest among adolescents; all STIs are more common in persons who have more than one sexual partner; and it is not uncommon for a person to be concurrently infected with more than one type of STI.

There are many factors that contribute to the increased prevalence and the continued spread of STIs, including the fact that STIs are frequently asymptomatic, which promotes the spread of infection by persons who are unaware that they are carrying the infection. Furthermore, partners of infected persons are often difficult to notify and treat. Condoms could prevent the spread of many STIs, but they often are not used or are used improperly. In addition, there currently are no cures for viral STIs (e.g., human immunodeficiency virus [HIV], herpes simplex virus); although there are drugs available that may help to manage the infections, they do not entirely control the spread. Also, drug-resistant microorganisms are rapidly emerging, making treatment of many STIs more difficult.

This chapter discusses the manifestations of STIs in men and women in terms of infections of the external genitalia, vaginal infections, and infections that have genitourinary as well as systemic manifestations. HIV infection is presented in Chapter 16.

Sexually Transmitted Infections

- Sexually transmitted infections (STIs) are spread by sexual contact and involve both male and female partners. Portals of entry include the mouth, genitalia, urinary meatus, rectum, and skin. All STIs are more common in persons who have more than one sexual partner, and it is not uncommon for a person to be concurrently infected with more than one type of STI.
- In general, STIs due to bacterial pathogens can be successfully treated and the pathogen eliminated by antimicrobial therapy. However, many of these pathogens are developing antibiotic resistance.
- STIs due to viral pathogens such as genital herpes simplex virus infections (HSV-1 and HSV-2) are not eliminated by current treatment modalities and persist with risk of recurrence.
- Untreated, STIs such as chlamydial infection and gonorrhea can spread to involve the internal genital organs with risk of complications and infertility.
- Intrauterine or perinatally transmitted STIs can have potentially fatal or severely debilitating effects on a fetus or an infant.

Infections of the External Genitalia

Sexually transmitted infections can selectively infect the mucocutaneous tissues of the external genitalia, cause vaginitis in women, or produce both genitourinary and systemic effects. Some STIs may be transmitted by an infected mother to a fetus or newborn, causing congenital defects or death of the child. The discussion in this section of the chapter focuses on STIs that affect the mucocutaneous tissues of the oropharynx and external genitalia, and anorectal tissues. These infections include condylomata acuminata, genital herpes, chancroid, and lymphogranuloma venereum.

Human Papillomavirus Infection and Genital Warts

Genital warts (condylomata acuminata) are caused by the human papillomavirus (HPV) that infects epithelial cells and can cause a number of benign and malignant growths.[1–7] Although recognized for centuries, HPV-induced genital warts have become one of the fastest-growing STIs of the past decade. The Centers for Disease Control and Prevention (CDC) estimates that 20 million Americans 15 to 49 years of age (approximately 15% of the population) are currently infected with the HPV.[1] Transmission of HPV is usually through skin-to-skin contact, most often through penetration (oral–genital, manual–genital, and genital–genital contact).[1,2] HPV can also be transmitted though nonsexual routes including mother to newborn (vertical transmission) and fomites. Prevention of HPV transmission through condom use has not been adequately demonstrated. Most HPV infections are asymptomatic and transient, and resolve without treatment.[1–4] However, in some cases, HPV infection results in genital warts, Papanicolaou (Pap) test abnormalities, or, rarely, cervical cancer.

HPVs are nonenveloped double-stranded deoxyribonucleic acid (DNA) viruses that cause proliferative lesions of the squamous epithelium.[1,2] More than 100 distinct HPV subtypes have been identified, over 40 of which affect the anogenital area. These subtypes are routinely classified into low-risk and high-risk categories. Low-risk types such as 6 and 11 are typically associated with genital warts. Types 16, 18, 31, 33, and 45 are considered to be high risk because of their association with cervical dysplasia and cervical cancer. Of the high-risk types, HPV 16 and 18 account for approximately two thirds of cervical cancer.[1,4] Only a subset of women infected with HPV go on to develop cervical cancer, however, suggesting that even the most virulent HPV strains may vary in terms of their oncogenic potential. Cofactors that may increase the risk for cancer include smoking, immunosuppression, and exposure to hormonal alteration (e.g., pregnancy, oral contraceptives).[1] The recent release of a quadrivalent vaccine to protect against HPV types 6, 11, 16, and 18 may eventually reduce the risk of cervical cancer associated with HPV.[1,2,8] Currently, however, there is no treatment to eradicate the virus once a person has become infected.

HPV infection begins with viral inoculation into a stratified squamous epithelium, where infection stimulates replication of the squamous epithelium, producing the various HPV-proliferative lesions.[5] The incubation period for HPV-induced genital warts ranges from 6 weeks to 8 months, with a mean of 2 to 3 months. Genital warts typically present as soft, raised, fleshy lesions on the external genitalia, including the penis (Fig. 41-1), vulva, scrotum, perineum, and perianal skin. External warts may appear as small bumps, or they may be flat, rough surfaced, or pedunculated. Less commonly, they can appear as smooth reddish or brown raised papules or as dome-shaped lesions on keratinized skin. Internal warts are cauliflower-shaped lesions that affect the mucous membranes of the vagina, urethra, anus, or mouth. They may cause discomfort, bleeding, or painful intercourse.[6]

Although warts can be a disturbing clinical feature of HPV infection, subclinical infection is common. Approximately 70% of women with HPV become HPV DNA negative within 1 year, and as many as 91% of them become negative within 2 years.[1] Many women with transient HPV infections develop atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSILs) of the cervix as

FIGURE 41-1. Condylomata of the penis. Raised circumscribed lesions are seen on the shaft of the penis. (From Damjanov I. [2005]. The lower urinary tract and male reproductive system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 904]. Philadelphia: Lippincott Williams & Wilkins.)

detected on a Pap test, colposcopy, or biopsy (see Chapter 40). In men, transient HPV infection may be associated with intraepithelial neoplasia of the penis and anus.[1] Development of an effective immune response helps clear the infection, but the virus can remain dormant for years and reactivate at a later time.

Diagnosis of genital warts is usually made by visualization or palpation of nontender papillomatous genital lesions. A diagnosis of genital warts may be confirmed by biopsy. There are no approved serologic tests for HPV or routine methods for culturing the virus. The only test that is currently approved by the U.S. Food and Drug Administration (FDA) is a solution hybridization method to test for high-risk HPV DNA.[1] The HPV DNA test determines whether one or more of the high-risk types of HPV is present, but does not identify the individual HPV type. HPV DNA testing is warranted with equivocal (ASC-US) Pap test results, and is now recommended to determine which women older than 30 years of age need annual Pap smear screening (see Chapter 40). There is currently no FDA-approved HPV DNA test for men, nor is testing for men recommended.[1]

The choice of treatment for genital warts is based on the number, size, site, and morphology of the lesions, as well the person's preference. If left untreated, the warts may resolve spontaneously, so expectant management is acceptable if the person is comfortable with this approach. Evaluation and treatment of sexual partners may be suggested, although this may be difficult considering that warts often do not become clinically apparent for several years after exposure.

The CDC identifies several pharmacologic treatments for symptomatic removal of visible genital warts, including patient-applied (podofilox and imiquimod) and provider-administered (podophyllin and trichloroacetic acid) therapies.[9] Podofilox is a topical antimitotic agent that results in visible necrosis of wart tissue. The safety of podofilox during pregnancy has not been established. Imiquimod cream is a new type of therapeutic agent that stimulates the body's immune system (i.e., production of interferon-α and other cytokines). It is a category B drug and therefore potentially safe for use in pregnancy. Podophyllin, a topical cytotoxic agent, has long been used for treatment of visible external growths. Multiple applications may be required for resolution of lesions. The amount of drug used and the surface area treated should be limited with each treatment session to avoid systemic absorption and toxicity. This treatment is contraindicated in pregnancy for the same reason. An alternative therapy is the topical application of a solution of trichloroacetic acid. This weak destructive agent produces an initial burning in the affected area, followed in several days by a sloughing of the superficial tissue. Several applications at 1- to 2-week intervals may be necessary to eradicate the lesion. Sexual abstinence is suggested during any type of treatment to enhance healing.

Genital warts also may be removed using cryotherapy (i.e., freezing therapy), surgical excision, laser vaporization, or electrocautery. Because it can penetrate deeper than other forms of therapy, cryotherapy often is the treatment of choice for cervical HPV lesions. Laser surgery can be used to remove large or widespread lesions of the cervix, vagina, or vulva, or lesions that have failed to respond to other first-line methods of treatment. Electrosurgical treatment has become more widespread for these types of lesions because it is more readily available in outpatient settings and is much less expensive than laser.

Genital Herpes

Genital herpes is one of the most common causes of genital ulcers in the United States. Because herpesvirus infection is not reportable in all states, reliable data on its true incidence and prevalence are lacking. Recent estimates in the United States indicate 67 million people (1 in 4 adolescents or adults) are infected with genital herpes.[10] Women have a greater mucosal surface area exposed in the genital area and therefore are at greater risk of acquiring the infection.

Genital herpes is caused by the herpes simplex virus (HSV), a large double-stranded DNA virus.[11–15] Herpes simplex infections are highly contagious. There are eight types of HSV, including HSV-1 (usually associated with fever blisters and cold sores) and HSV-2 (usually associated with genital herpes).[11,12] HSV-1 and HSV-2 are genetically similar; both cause a similar set of primary and recurrent infections, and both can cause oropharyngeal and genital lesions. HSV-1 and HSV-2 are *neurotropic* viruses, meaning that they grow in neurons and share the biologic property of latency. Latency refers to the ability to

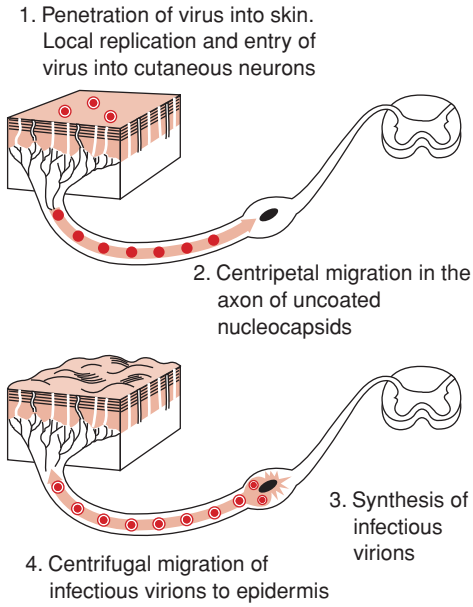


FIGURE 41-2. Pathogenesis of primary mucocutaneous herpes simplex virus infection. (From Corey L., Spear P.G. [1986]. Infections with herpes simplex viruses: Part 1. *New England Journal of Medicine* 314, 686.)

maintain disease potential in the absence of clinical signs and symptoms. In genital herpes, the virus ascends through the peripheral nerves to the sacral dorsal root ganglia (Fig. 41-2). The virus can remain dormant in the dorsal root ganglia, or it can reactivate, in which case the viral particles are transported back down the nerve root to the skin, where they multiply and cause a lesion to develop. During the dormant or latent period, the virus replicates in a different manner so that the immune system or available treatments have no effect on it. It is not known what reactivates the virus. It may be that the body's defense mechanisms are altered. Numerous studies have shown that host responses to infection influence initial development of the disease, severity of infection, development and maintenance of latency, and frequency of HSV recurrences.

HSV is transmitted by contact with infectious lesions or secretions. Most HSV genital infections are caused by HSV-2, but genital HSV-1 infections are becoming increasingly common, particularly among adolescents and young women. Women infected with HSV-1 remain at risk for acquiring HSV-2. Most cases of HSV-2 infection are subclinical, manifesting as truly asymptomatic or symptomatic but unrecognized infections. These subclinical infections can occur in people who have never had a symptomatic outbreak or they can occur between recognized clinical recurrences. Up to 70% of genital herpes is spread through asymptomatic shedding by people who do not realize they have the infection.[15] This "unknown" transmission of the virus to sex partners explains why this infection has reached epidemic proportions throughout the world.

The incubation period for HSV is 2 to 12 days.[14] Genital HSV infection may manifest as a first-episode or recurrent infection. The initial symptoms of primary genital herpes infections include tingling, itching, and pain in the genital area, followed by eruption of small pustules and vesicles. These lesions rupture on approximately the fifth day to form wet ulcers that are excruciatingly painful to touch and can be associated with dysuria, dyspareunia, and urine retention. This period is followed by a 10- to 12-day interval during which the lesions crust over and gradually heal. Involvement of the cervix, vagina, urethra, and inguinal lymph nodes is common in women with primary infections. In men, the infection can cause urethritis and lesions of the penis and scrotum. Rectal and perianal infections are possible with anal contact. Systemic symptoms associated with primary infections include fever, headache, malaise, muscle ache, and lymphadenopathy. Primary infections may be debilitating enough to require hospitalization, particularly in women. First episodes of nonprimary infections (acquisition of HSV-2 in persons with preexisting antibodies to HSV-1 or, more rarely, acquisition of HSV-1 in persons with preexisting HSV-2 antibodies) are associated with fewer lesions, a shorter duration of disease, and a lower rate of complications than primary infections.

Recurrent HSV episodes are usually milder than the initial episode—there typically are fewer lesions, and viral shedding occurs at a lower concentration and for a shorter duration (about 3 days). However, the prodromal symptoms of itching, burning, and tingling at the lesion site are similar. Except for the greater tendency of HSV-2 to recur, the clinical manifestations of genital HSV-2 and HSV-1 infections are similar. The frequency and severity of recurrence vary from person to person. Numerous factors, including emotional stress, lack of sleep, overexertion, other infections, vigorous or prolonged coitus, and premenstrual or menstrual distress, have been identified as triggering mechanisms.

Diagnosis of genital herpes is based on symptoms, appearance of the lesions, and identification of the virus taken from the lesions for cell culture. Viral culture can generally isolate the virus in 5 days, is relatively inexpensive, and is highly specific.[7] However, it is not very sensitive, with false-negative results of 25% with primary infections and as high as 50% with recurrent infections.[4] Polymerase chain reaction (PCR) testing for HSV DNA (see Chapter 14) may be used to confirm a diagnosis of genital HSV infection; however, it is more expensive than other methods and is not routinely used.[9,13,14] In addition to viral detection methods, the detection of type-specific antibodies to HSV-1 and HSV-2 also can help to establish the diagnosis. These tests yield false-negative results when used in the early stages of infection, since it takes approximately 22 days for the body to produce antibodies to the virus.[4] Approximately 20% of patients may remain seronegative for 3 months, particularly if they have received antiviral medications.[4] This type of testing may prove useful in confirming infection in persons with recurrent genital symptoms and negative HSV cultures, or in establishing a clinical diagnosis of genital herpes without laboratory confirmation or in a partner of a person with genital herpes.[9]

There is no known cure for genital herpes, and the methods of treatment are largely symptomatic. The oral

antiviral drugs acyclovir, valacyclovir, and famciclovir have become the cornerstone for management of genital herpes.[4,13–15] By interfering with viral DNA replication, these drugs decrease the frequency of recurrences, shorten the duration of active lesions, reduce the number of new lesions formed, and decrease viral shedding with primary infections. Valacyclovir, the active component of acyclovir, and famciclovir have greater bioavailability, which enables improved dosing schedules and increased compliance. Episodic intervention reduces the duration of viral shedding and the healing time for recurrent lesions. Continuous antiviral suppressive therapy may be advised when more than six outbreaks occur within 1 year.[9] These drugs are well tolerated, with few adverse effects. This long-term suppressive therapy does not limit latency, and reactivation of the disease frequently occurs after the drug is discontinued. In 2002, the FDA approved long-term suppressive therapy with valacyclovir for the prevention of HSV-2 transmission to an uninfected sexual partner.

Current information indicates that the risk of neonatal infection is very low when the mother has developed type-specific antibodies, which are then transmitted to the neonate. Newborns at highest risk are those born to women who shed the virus and have not developed antibodies from previous infections. Disseminated neonatal infection carries high mortality and morbidity rates. Active infection during labor may necessitate cesarean delivery, ideally before membranes rupture. Recommendations from the CDC direct health care providers to obtain cultures only when a woman has active lesions during the third trimester. Vaginal delivery is acceptable if visible lesions are not present at the onset of labor.[9]

Chancroid

Chancroid is a disease of the external genitalia and lymph nodes caused by the gram-negative bacterium *Haemophilus ducreyi*.[4] The disease is most common in tropical and subtropical regions. It is one of the most common causes of genital ulcers in less developed countries, especially in Africa and parts of Asia, where it probably serves as an important cofactor in the transmission of HIV infection.[11] This STI has become uncommon in the United States, with only 20 to 50 reported cases in the last several years.[11] However, recent evidence suggests that chancroid may be underdiagnosed because many STI clinics do not have the facilities to test for *H. ducreyi*.

Chancroid is highly infectious and is usually transmitted by sexual intercourse or through skin and mucous membrane abrasions. Autoinoculation may lead to multiple chancres. Lesions begin as macules, progress to pustules, and then rupture. This painful ulcer has a necrotic base and jagged edges. In contrast, the syphilitic chancre is nontender and indurated. Subsequent discharge can lead to further infection of self or others. On physical examination, lesions and regional lymphadenopathy (i.e., buboes) may be found. Secondary infection may cause significant tissue destruction.

Diagnosis usually is made clinically, but may be confirmed through culture. Gram stain rarely is used today because it is insensitive and nonspecific. PCR testing methods may soon be available commercially for definitive identification of *H. ducreyi*. The organism has shown resistance to treatment with sulfamethoxazole alone and to tetracycline. The CDC recommends treatment with azithromycin, erythromycin, or ceftriaxone.[9]

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is an acute and chronic venereal disease caused by *Chlamydia trachomatis* types L1, L2, and L3. The disease, although found worldwide, has a low incidence outside the tropics. Most cases reported in the United States are in men. There appears to be a new variant of L2 that is causing a resurgence of LGV in Europe and the United States, particularly in men who have sex with men.[16]

The lesions of LGV can incubate for a few days to several weeks and thereafter cause small, painless papules or vesicles that may go undetected. An important characteristic of the infection is the early (1 to 4 weeks later) development of large, tender, and sometimes fluctuant inguinal lymph nodes called *buboes*. There may be flulike symptoms with joint pain, rash, weight loss, pneumonitis, tachycardia, splenomegaly, and proctitis. In later stages of the disease, a small percentage of affected persons develop elephantiasis of the external genitalia, caused by lymphatic obstruction or fibrous strictures of the rectum or urethra from inflammation and scarring. Urethral involvement may cause pyuria and dysuria. Cervicitis is a common manifestation of primary LGV in women, and could extend to perimetritis or salpingitis, which are known to occur in other chlamydial infections.[16] Anorectal structures may be compromised to the point of incontinence. Complications of LGV may be minor or extensive, involving compromise of whole systems or progression to a cancerous state.

Diagnosis usually is accomplished by a complement fixation test for LGV-specific *Chlamydia* antibodies. High titers for this antibody differentiate this group from other chlamydial subgroups. PCR techniques, when more widely available, will provide a more practical, cost-effective tool for diagnosis.[16] Treatment involves 3 weeks of doxycycline, tetracycline, or erythromycin.[9] Surgery may be required to correct sequelae such as strictures or fistulas or to drain fluctuant lymph nodes.

In summary, sexually transmitted infections that primarily affect the external genitalia include HPV-induced genital warts, genital HSV infections, chancroid, and lymphogranuloma venereum. The lesions of these infections occur on the external genitalia of male and female sexual partners. Of recent concern is the relation between HPV infections and the development of genital neoplasms. Over 100 types of HPV have been

identified, including subtypes 6 and 11, which are typically associated with genital warts, and subtypes 16 and 18, which account for approximately two thirds of cervical dysplasia and cervical cancer. Genital herpes is an ulcerative disorder caused by the highly contagious HSV. There are two types of HSV that can cause genital herpes—HSV-1, which is usually associated with cold sores of the mouth, but may also cause genital lesions, and HSV-2. Both HSV-1 and HSV-2 are neurotrophic viruses that produce acute primary infections and latent recurrent episodes. During the primary infection, the HSV ascends through peripheral nerves to a sacral dorsal root ganglia. Recurrences occur when the virus is reactivated and travels down the nerve root to the affected area. There is no permanent cure for herpes infections. Chancroid and LGV produce external genital lesions with various degrees of inguinal lymph node involvement. These diseases are uncommon in the United States.

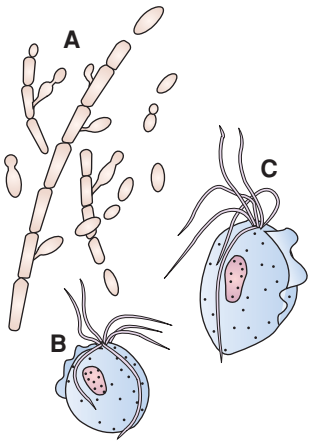


FIGURE 41-3. Organisms that cause vaginal infections. **(A)** *Candida albicans* (blastospores and pseudohyphae). **(B, C)** *Trichomonas vaginalis.*

Vaginal Infections

Candidiasis, trichomoniasis, and bacterial vaginosis are vaginal infections that can be associated with sexual activity. Trichomoniasis is the only form of vaginitis that is known to be sexually transmitted and requires partner treatment. The male partner usually is asymptomatic.

Candidiasis

Also called *yeast infection, thrush,* and *moniliasis, candidiasis* is the second leading cause of vulvovaginitis in the United States. Approximately 75% of reproductive-age women in the United States experience one episode in their lifetime; 40% to 45% experience two or more infections.[17]

Candida albicans is the most commonly identified organism in vaginal yeast infections, but other *Candida* species, such as *Candida glabrata* and *Candida tropicalis,* may also be present.[18] These organisms are present in 20% to 55% of healthy women without causing symptoms, and alteration of the host vaginal environment usually is necessary before the organism can cause pathologic effects.[17] Although vulvovaginal candidiasis usually is not transmitted sexually, it is included in the CDC STI treatment guidelines because it often is diagnosed in women being evaluated for STIs.[9] The possibility of sexual transmission has been recognized for many years; however, candidiasis requires a favorable environment for growth of the organism. The gastrointestinal tract also serves as a reservoir for this organism, and candidiasis can develop through autoinoculation in women who are not sexually active. Studies have documented the presence of *Candida* on the penis of male partners of women with vulvovaginal candidiasis, but few men develop balanoposthitis that requires treatment.

Reported risk factors for the overgrowth of *C. albicans* include recent antibiotic therapy, which suppresses the normal protective bacterial flora; high hormone levels owing to pregnancy or the use of oral contraceptives, which cause an increase in vaginal glycogen stores; and uncontrolled diabetes mellitus or HIV infection, which compromise the immune system.[19,20] Women with vulvovaginal candidiasis commonly complain of vulvovaginal pruritus accompanied by irritation, erythema, swelling, dysuria, and dyspareunia. The characteristic discharge, when present, is usually thick, white, and odorless. In obese persons, *Candida* may grow in skin folds underneath the breast tissue, the abdominal flap, and the inguinal folds.

Accurate diagnosis is made by identification of budding yeast filaments (i.e., hyphae) or spores on a wet-mount slide using 20% potassium hydroxide (Fig. 41-3A). The pH of the discharge, which is checked with litmus paper, typically is less than 4.5. When the wet-mount technique is negative but the clinical manifestations are suggestive of candidiasis, a culture may be necessary.

Antifungal agents such as clotrimazole, miconazole, butoconazole, and terconazole, in various forms, are effective in treating candidiasis. These drugs, with the exception of terconazole, are available without prescription for use by women who have had a previously confirmed diagnosis of candidiasis. Oral fluconazole has been shown to be as safe and effective as the standard intravaginal regimens.[9] Chronic vulvovaginal candidiasis, defined as four or more mycologically confirmed episodes within 1 year, affects approximately 5% of women and is difficult to manage. Subsequent prophylaxis (maintenance therapy) often is required for long-term management of this problem.[17]

Trichomoniasis

Trichomoniasis is credited with being a far more prevalent STI than either chlamydial infection or gonorrhea.[21–23]

Trichomonas vaginalis infections are commonly associated with other STIs and are therefore a marker for high-risk sexual behavior. The majority of women with trichomoniasis also have other STIs, particularly gonorrhea.[22] Although the infection is commonly transmitted by sexual contact, it can occur via fomites and the organism has been shown to survive in swimming pools and hot tubs.[4]

T. vaginalis is an anaerobic protozoan that is shaped like a turnip and has three or four anterior flagella (see Fig. 41-3B, C). Trichomonads can reside in the paraurethral glands of both sexes. Men harbor the organism in the urethra and prostate and are asymptomatic. Although 10% to 25% of women are asymptomatic, trichomoniasis is a common cause of vaginitis when some imbalance allows the protozoan to proliferate. This extracellular parasite feeds on the vaginal mucosa and ingests bacteria and leukocytes. The infection causes a copious, frothy, malodorous, green or yellow discharge. There commonly is erythema and edema of the affected mucosa, with occasional itching and irritation. Sometimes, small hemorrhagic areas, called *strawberry spots,* appear on the cervix.

Trichomoniasis can cause a number of complications.[21–23] It is a risk factor for HIV transmission and infectivity in both men and women.[23] In women, it increases the risk of tubal infertility and atypical pelvic inflammatory disease (PID; see Chapter 40), and it is associated with adverse outcomes such as premature birth in pregnant women. Trichomonads attach easily to mucous membranes. They may serve as vectors for the spread of other organisms, carrying pathogens attached to their surface into the fallopian tubes. In men, it is a common cause of nongonococcal urethritis and is a risk factor for infertility, altering sperm motility and viability. It has also been associated with chronic prostatitis.

Diagnosis is made microscopically by identification of the motile protozoan on a wet-mount slide preparation. The pH of the discharge usually is greater than 6.0. Newer point-of-care tests include an antigen-based diagnostic test (OSOM *Trichomonas* Rapid Test) and a DNA probe test (Affirm VP III). Both tests have greater sensitivity than a vaginal mount and results can be available in less than an hour.[9,23] PCR-based tests for *T. vaginalis* are currently under development.

Because the organism resides in other urogenital structures besides the vagina, systemic treatment is recommended. The treatment of choice is oral metronidazole or tinidazole, medications that are effective against anaerobic protozoans.[9] Both medications are chemically similar to disulfiram (Antabuse), a drug used in the treatment of alcohol addiction that causes nausea, vomiting, flushing of the skin, headache, palpitations, and lowering of the blood pressure when alcohol is ingested. Gastrointestinal disturbances and a metallic taste in the mouth are potential adverse effects of the drugs. Although metronidazole is considered safe for use during pregnancy, data on tinidazole use in pregnancy are limited. Sexual partners should be treated to avoid reinfection, and abstinence is recommended until the full course of therapy is completed.

Bacterial Vaginosis

Bacterial vaginosis is a polymicrobial infection characterized by lack of hydrogen peroxide–producing lactobacilli and an overgrowth of anaerobic organisms. It is the most prevalent vaginal disorder in women of reproductive age.[23] The disorder is associated with having multiple sex partners, a new sex partner, douching, and a lack of vaginal lactobacilli. Its relation to sexual activity is not clear. Sexual activity is believed to be a catalyst rather than a primary mode of transmission, and endogenous factors may play a role in the development of symptoms.

The predominant symptom of bacterial vaginosis is a thin, grayish-white discharge that has a foul, fishy odor. Burning, itching, and erythema usually are absent because the bacteria have only minimal inflammatory potential. Because of the lack of inflammation, the term *vaginosis* rather than *vaginitis* is used to describe the condition. The organisms associated with bacterial vaginosis may be carried asymptomatically by men and women.

The pathogenesis of bacterial vaginosis remains poorly understood. It is a complex disorder characterized by a shift in the vaginal flora from one dominated by hydrogen peroxide–producing lactobacilli to one with greatly reduced numbers of *Lactobacillus* species and an overgrowth of facultative anaerobic organisms, including *Gardnerella vaginalis, Mobiluncus* species, and *Mycoplasma hominis*.[4,23,24] The massive overgrowth of vaginal anaerobes is associated with the production of proteolytic enzymes that break down vaginal amines, which in a high pH become volatile and malodorous. The amines are associated with increased vaginal transudation and squamous epithelial cell exfoliation, creating the typical discharge.[24] In conditions of elevated pH, the vaginal anaerobes more efficiently adhere to the exfoliating epithelial cells, creating what are called *clue cells* (Fig. 41-4).

In addition to causing bothersome symptoms, bacterial vaginosis is associated with an increased risk of PID, preterm labor, premature rupture of membranes, and

FIGURE 41-4. Clue cells. Clue cells are epithelial cells with clumps of bacteria clustered to their surface. Clue cells indicate the presence of bacterial vaginosis. (Courtesy M. Rein, Centers for Disease Control and Prevention Public Health Image Library.)

postpartum endometritis linked to the organisms associated with bacterial vaginosis. Postoperative infections, including postabortion PID, posthysterectomy cuff cellulitis, and postcesarean endometritis, have been shown to be associated with asymptomatic bacterial vaginosis. It has also been associated with increased risk of acquisition of HIV and HSV infection.

The diagnosis of bacterial vaginosis is made when at least three of the following characteristics are present: abnormal gray discharge, vaginal pH above 4.5 (usually 5.0 to 6.0), positive whiff test on addition of 10% potassium hydroxide, and appearance of characteristic "clue cells" on wet-mount microscopic studies. Because *G. vaginalis* can be a part of the normal vaginal flora, cultures should not be done routinely.

Bacterial vaginosis may be treated with oral or topical metronidazole or oral or topical clindamycin. Symptomatic pregnant women can also be treated with these medications. Some studies have shown that screening for and treating bacterial vaginosis may reduce the incidence adverse pregnancy outcomes. However, studies do not confirm a benefit from universal testing of low- and medium-risk pregnant women.[25]

In summary, candidiasis, trichomoniasis, and bacterial vaginosis are common vaginal infections that become symptomatic because of changes in the vaginal ecosystem. Only trichomoniasis is spread through sexual contact. *Trichomoniasis*, which is caused by the anaerobic protozoan *T. vaginalis,* incites the production of a copious, frothy, yellow or green, malodorous discharge. It is a risk factor for HIV transmission and infectivity in both men and women. In women, it increases the risk of pelvic inflammatory disease, tubal infertility, and adverse outcomes such as premature birth in pregnant women. *Candidiasis*, also called a *yeast infection,* is a frequent cause of vulvovaginitis. Candida can be present without producing symptoms; usually some host factor, such as altered immune status, contributes to the development of vulvovaginitis. *Bacterial vaginosis* is a polymicrobial disorder characterized by a lack of hydrogen peroxide–producing lactobacilli and an overgrowth of anaerobic organisms, including *G. vaginalis, Mobiluncus* species, and *M. hominis*. It is the most prevalent vaginal disorder in women of reproductive age. The predominant symptom of bacterial vaginosis is a thin, grayish-white discharge that has a foul, fishy odor.

Vaginal-Urogenital-Systemic Infections

Some STIs infect male and female genital and extragenital structures. Among the infections of this type are chlamydial infections, gonorrhea, and syphilis. Many of these infections also pose a risk to infants born to infected mothers. Some infections, such as syphilis, may be spread to the infant while in utero, whereas others, such as chlamydial and gonorrheal infections, can be spread to the infant during the birth process.

Chlamydial Infections

Chlamydial infection is the most frequently reported bacterial STI in the United States, with an incidence estimated to be more than twice that of gonorrhea. Despite high numbers of reported cases, most cases of chlamydial infections go unreported. If untreated, up to 40% of women with chlamydial infection will develop pelvic inflammatory disease. It has been estimated that 20% of women become infertile, 18% experience chronic pelvic pain, and 9% have a tubal pregnancy.[26]

C. trachomatis is an obligate intracellular bacterial pathogen that is closely related to gram-negative bacteria.[11,12] It resembles a virus in that it requires tissue culture for isolation, but like bacteria, it has both DNA and ribonucleic acid (RNA) and is susceptible to some antimicrobial agents. Chlamydial infection exists in two morphologically distinct forms during its unique life—a small infectious elementary body and a large noninfectious reticulate body. Much like a spore, the *elementary body* is metabolically inactive and can survive outside the cell. It does not replicate. The *reticulate body* is metabolically active and cannot survive outside the cell. The 48-hour growth cycle starts with attachment of the elementary body to the susceptible host cell, after which it is ingested by a process that resembles phagocytosis (Fig. 41-5). Once inside the cell, the elementary body transforms in the larger *reticulate body*, which then commandeers the host cell's metabolic machinery to fuel its replication. The reticulate body divides repeatedly for up to 36 hours, forming new elementary bodies that are released when the infected cell bursts. Necrotic debris elicits inflammatory and immune processes that further damage infected tissue.

The signs and symptoms of chlamydial infection resemble those produced by gonorrhea. The most significant difference between chlamydial and gonococcal salpingitis is that chlamydial infections may be asymptomatic or clinically nonspecific. In women, chlamydial infections may cause urinary frequency, dysuria, and vaginal discharge.[27–29] The most common symptom is a mucopurulent cervical discharge. The cervix itself frequently hypertrophies and becomes erythematous, edematous, and extremely friable. This can lead to fallopian tube damage and increase the reservoir for further chlamydial infections. In men, chlamydial infections cause urethritis, including meatal erythema and tenderness, urethral discharge, dysuria, and urethral itching. Prostatitis and epididymitis with subsequent infertility may develop. The most serious complication of untreated chlamydial infection in men is the development of Reiter syndrome, a reactive arthritis that includes the triad of urethritis, conjunctivitis, and painless mucocutaneous lesions (see Chapter 44).[29]

Questions remain regarding screening for chlamydial infections.[25] At present, the CDC recommends annual

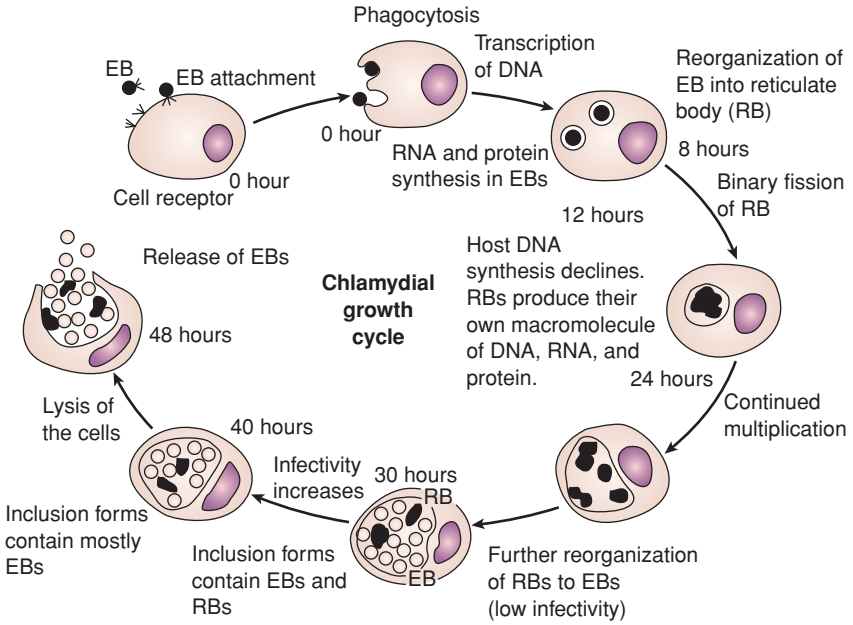


FIGURE 41-5. Chlamydial growth cycle. EB, elementary body; RB, reticulate body. (From Thompson S.E., Washington A.E. [1983]. Epidemiology of sexually transmitted *Chlamydia trachomatis* infections. *Epidemiologic Reviews* 5, 96–123.)

screening of women who are sexually active and younger than 25 years; women who are older than 25 years and having sex with more than one partner; women who are older than 25 years and having sex with a new partner; and women who are pregnant.[30]

Diagnosis of chlamydial infections takes several forms. The identification of polymorphonuclear leukocytes on Gram stain of penile discharge in the man or cervical discharge in the woman provides presumptive evidence. The direct fluorescent antibody test and the enzyme-linked immunosorbent assay, which use antibodies against an antigen in the *Chlamydia* cell wall, are rapid tests that are highly sensitive and specific. The positive predictive value of these tests is excellent among high-risk groups, but false-positive results occur more often in low-risk groups. The methodologic challenges of culturing this organism have led to the development of non–culture-based tests that amplify and detect *C. trachomatis*–specific DNA and RNA sequences.[29] One of the newest sets of nonculture techniques, the nucleic acid amplification tests (NAATs), do not require viable organisms for detection, and can produce a positive signal from as little as a single copy of the target DNA or RNA.[30] These amplification methods are highly sensitive and, if properly monitored, very specific. Because NAATs can be performed on urine and self-collected swab specimens from the distal vagina as well as the traditional endocervical and urethral specimens, this easy, convenient means of accurate detection has become the diagnostic method of choice.[9,28,29] Detection rates (specificity) for chlamydiae in urine and vaginal samples are nearly identical to those for cervical and urethral samples.[30]

The CDC recommends the use of azithromycin or doxycycline in the treatment of chlamydial infection; penicillin is ineffective. Azithromycin or amoxicillin is the preferred choice in pregnancy.[9] Simultaneous antibiotic treatment of both sexual partners is recommended. Abstinence from sexual activity is encouraged to facilitate cure. Retesting all women with chlamydial infection 3 to 4 months after treatment has been recommended to rule out recurrence.[9]

Gonorrhea

Gonorrhea is a reportable STI caused by the bacterium *Neisseria gonorrhoeae*. It is one of the oldest and still one of the most common STIs. Although the incidence of gonorrhea has declined steadily from its peak in 1975, rates in 2005 rose for the first time since 1999.[31] The emergence of antimicrobial-resistant strains and patterns of sexual behavior have contributed to a rise in its incidence. The highest rates are seen in adolescents and young adults.[4]

The gonococcus is a pyogenic (i.e., pus-forming), gram-negative diplococcus that evokes inflammatory reactions characterized by purulent exudates.[11,12] Humans are the only natural host for *N. gonorrhoeae*. The organism grows best in warm, mucus-secreting epithelia. The portal of entry can be the genitourinary tract, eyes, oropharynx, anorectum, or skin. Transmission usually is by heterosexual or homosexual intercourse. Autoinoculation of the organism to the conjunctiva is possible. Neonates born to infected mothers can acquire the infection during passage through the birth canal and are in danger of developing gonorrheal conjunctivitis, with resultant blindness, unless treated promptly. Genital gonorrhea in young children should raise the possibility of sexual abuse.

The infection commonly manifests 2 to 7 days after exposure. It typically begins in the anterior urethra, accessory urethral glands, Bartholin or Skene glands, and cervix. If untreated, gonorrhea spreads from its initial sites upward into the genital tract. In males, it spreads to the prostate and epididymis; in females, it commonly

FIGURE 41-6. Gonorrhea of the fallopian tube. Cross-section of a "pus tube" shows thickening of the wall and lumen swollen with pus. (From Schwartz D., Genta R.M., Conner D.H. [2005]. Infectious and parasitic diseases. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 386]. Philadelphia: Lippincott Williams & Wilkins.)

FIGURE 41-7. Purulent penile discharge due to gonorrhea with overlying pyodermal lesions. (From the Centers for Disease Control and Prevention Public Health Image Library.

moves to the fallopian tubes[31] (Fig. 41-6). Pharyngitis may follow oral–genital contact. The organism also can invade the bloodstream (i.e., disseminated gonococcal infection), causing serious sequelae such as bacteremic involvement of joint spaces, heart valves, meninges, and other body organs and tissues.

Persons with gonorrhea may be asymptomatic and may unwittingly spread the disease to their sexual partners. Men are more likely to be symptomatic than women.[32] In men, the initial symptoms include urethral pain and a creamy yellow, sometimes bloody, discharge (Fig. 41-7). The disorder may become chronic and affect the prostate, epididymis, and periurethral glands. Rectal infections are common in homosexual men. In women, recognizable symptoms include unusual genital or urinary discharge, dysuria, dyspareunia, pelvic pain or tenderness, unusual vaginal bleeding (including bleeding after intercourse), fever, and proctitis. Symptoms may occur or increase during or immediately after menses because the bacterium is an intracellular diplococcus that thrives in menstrual blood but cannot survive long outside the human body. There may be infections of the uterus and development of acute or chronic infection of the fallopian tubes (i.e., salpingitis), with ultimate scarring and sterility.

Diagnosis is based on the history of sexual exposure and symptoms. It is confirmed by identification of the organism on Gram stain or culture. A Gram stain usually is an effective means of diagnosis in symptomatic men (i.e., those with discharge). In women and asymptomatic men, a culture usually is preferred because the Gram stain often is unreliable. Culture has been the gold standard, particularly when the Gram stain is negative. An enzyme immunoassay for detecting gonococcal antigens (Gonozyme) is available but has several requirements that limit its usefulness. Detection by NAATs is possible using urine and urethral swab specimens.[33] The sensitivity of these tests is similar to that of culture, and they may be cost effective in high-risk populations.

Updated recommendations from the U.S. Preventive Services Task Force (USPSTF) suggest that clinicians screen all sexually active men and women for gonorrhea who are at increased risk for infection (i.e., younger than 25 years of age, new or multiple sexual partners, inconsistent condom use, sex work, or drug use).[34] Testing for other STIs, particularly syphilis and chlamydial infection, is suggested at the time of examination. Pregnant women are routinely screened at the time of their first prenatal visit; high-risk populations should have repeat cultures during the third trimester. Neonates are routinely treated with various antibacterial agents applied to the conjunctiva within 1 hour of birth to protect against undiagnosed gonorrhea and other diseases.

Penicillin-resistant strains of *N. gonorrhoeae* are prevalent worldwide and strains with other kinds of antibiotic resistance continue to evolve and spread. The current treatment recommendation to combat tetracycline- and penicillin-resistant strains of *N. gonorrhoeae* is ceftriaxone in a single injection or cefixime, ciprofloxacin, ofloxacin, or levofloxacin in a single oral dose.[9] All are equally effective and should be followed with azithromycin or doxycycline for chlamydiae. Quinolone-resistant strains are now common in Asia, the Pacific islands (including Hawaii), and California, so the CDC recommends avoiding the use of fluoroquinolones in those areas for infections in men who have sex with men or for individuals with a history of recent foreign travel.

All sex partners within 60 days prior to discovery of the infection should be contacted, tested, and treated. Test of cure is not required with observed single-dose therapy. Patients are instructed to refrain from intercourse until therapy is completed and symptoms are no longer present.[9]

Syphilis

Syphilis is a reportable STI caused by a spirochete, *Treponema pallidum*. After declining every year from 1990 to 2000, the rate of primary and secondary syphilis increased every year since 2001. Increased rates were primarily in men, although in 2005 the rates in women increased as well.[11] In 2006, 9756 cases of syphilis were reported in the United States (3.3 per 100,000 population). This increase in syphilis incidence has been demonstrated worldwide. The epidemiology of syphilis in the United States and Europe has changed over the years, and currently men who have sex with men represent the primary group affected.[35]

T. pallidum is spread by direct contact with an infectious moist lesion, usually through sexual intercourse. Bacteria-laden secretions may transfer the organism during kissing or intimate contact. Skin abrasions provide another possible portal of entry. There is rapid transplacental transmission of the organism from the mother to the fetus after 16 weeks' gestation, so that active infection in the mother during pregnancy can produce congenital syphilis in the fetus. Untreated syphilis can cause prematurity, stillbirth, and congenital defects and active infection in the infant. Because the manifestations of maternal syphilis may be subtle, testing for syphilis is mandatory in all pregnancies. Once treated for syphilis, a pregnant woman usually is followed throughout pregnancy by repeat testing of serum titers.

The clinical disease is divided into three stages: primary, secondary, and tertiary. Primary syphilis is characterized by the appearance of a chancre at the site of exposure.[11,36–38] Chancres typically appear within 3 weeks of exposure but may incubate for 1 week to 3 months. The primary chancre begins as a single, indurated, buttonlike papule up to several centimeters in diameter that erodes to create a clean-based ulcerated lesion on an elevated base. These lesions usually are painless and located at the site of sexual contact. Primary syphilis is readily apparent in the male, where the lesion is on the scrotum or penis (Fig. 41-8). Although chancres can develop on the external genitalia in females, they are more common on the vagina or cervix, and primary syphilis therefore may go untreated. There usually is an accompanying regional lymphadenopathy. The infection is highly contagious at this stage, but because the symptoms are mild, it frequently goes unnoticed. The chancre usually heals within 3 to 12 weeks, with or without treatment.

The timing of the second stage of syphilis varies even more than that of the first, lasting from 1 week to 6 months. The symptoms of a rash (especially on the palms [Fig. 41-9] and soles), fever, sore throat, stomatitis, nausea, loss of appetite, and inflamed eyes may come and go for a year but usually last for 3 to 6 months. Secondary manifestations may include alopecia and genital

FIGURE 41-8. Syphilitic chancre of the penis shaft. (From the Centers for Disease Control and Prevention Public Health Image Library.

FIGURE 41-9. Secondary syphilis. A maculopapular rash is present on the palm. (From Schwartz D., Genta R.M., Conner D.H. [2005]. Infectious and parasitic diseases. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 409]. Philadelphia: Lippincott Williams & Wilkins.)

condylomata lata.[35] Condylomata lata are elevated, red-brown lesions that may ulcerate and produce a foul discharge. They are 2 to 3 cm in diameter, contain many spirochetes, and are highly infectious.

After the second stage, syphilis frequently enters a latent phase that may last the lifetime of the person or progress to tertiary syphilis at some point. Persons can be infective during the first 1 to 2 years of latency.

Tertiary syphilis is a delayed response to the untreated disease. It can occur as long as 20 years after the initial infection. Only approximately one third of those with untreated syphilis progress to the tertiary stage of the disease, and symptoms develop in approximately one half of these. Approximately one third undergo spontaneous cure, and the remaining one third continue to have positive serologic tests but do not develop structural lesions.[31] When syphilis does progress to the symptomatic tertiary stage, it commonly takes one of three forms: development of localized destructive lesions called *gummas*, development of cardiovascular lesions, or development of central nervous system lesions. The syphilitic gumma is a peculiar, rubbery, necrotic lesion that is caused by noninflammatory tissue necrosis. Gummas can occur singly or multiply and vary in size from microscopic lesions to large, tumorous masses. They most commonly are found in the liver, testes, and bone. Central nervous system lesions can produce dementia, blindness, or injury to the spinal cord, with ataxia and sensory loss (i.e., tabes dorsalis). Cardiovascular manifestations usually result from scarring of the medial layer of the thoracic aorta with aneurysm formation. These aneurysms produce enlargement of the aortic valve ring with aortic valve insufficiency.

T. pallidum cannot be cultured. It does, however, evoke a humoral immune response and production of antibodies that provide the basis for serologic tests. Although PCR tests have been developed for syphilis, serology remains the mainstay for diagnosis.[11] Because the disease's incubation period may delay test sensitivity, serologic tests usually are repeated after 6 weeks if the initial test results were negative.

Two types of antibodies—nonspecific and specific—are produced.[11] Tests for nonspecific antibodies measure antibody to cardiolipin, a phospholipid that is present in both host cells and the *T. pallidum*. These antibodies are detected by flocculation tests such as the Venereal Disease Research Laboratory (VDRL) test or the rapid plasma reagin test. Because these tests are nonspecific, positive results can occur with diseases other than syphilis. The tests are easy to perform, rapid, and inexpensive and frequently are used as screening tests for syphilis. Results become positive 4 to 6 weeks after infection or 1 to 3 weeks after the appearance of the primary lesion. Because these tests are quantitative, they can be used to measure the degree of disease activity or treatment effectiveness. The VDRL titer usually is high during the secondary stage of the disease and becomes less so during the tertiary stage. A falling titer during treatment suggests a favorable response. The fluorescent treponemal antibody absorption test or microhemagglutinin test is used to detect specific antibodies to *T. pallidum*. These qualitative tests are used to determine whether a positive result on a nonspecific test such as the VDRL is attributable to syphilis. The test results remain positive for life.

The treatment of choice for syphilis is penicillin.[9,37] Because of the spirochetes' long generation time, effective tissue levels of penicillin must be maintained for several weeks. Long-acting injectable forms of penicillin are used. Tetracycline or doxycycline is used for treatment in persons who are sensitive to penicillin. Pregnant patients should be desensitized and treated with penicillin because erythromycin does not treat fetal infection. Sexual partners should be evaluated and treated prophylactically even though they may show no sign of infection. All treated individuals should be reexamined clinically and serologically at 6 and 12 months after completing therapy; more frequent monitoring (3-month intervals) is suggested for individuals with HIV infection.[9]

In summary, the vaginal-urogenital-systemic STIs—chlamydial infections, gonorrhea, and syphilis—can severely involve the genital structures and manifest as systemic infections. Gonorrheal and chlamydial infections can cause a wide variety of genitourinary complications in men and women, and both can cause ocular disease and blindness in neonates born to infected mothers. Syphilis is caused by a spirochete, *T. pallidum*. It can produce widespread systemic effects and is transferred to the fetus of infected mothers through the placenta.

REVIEW EXERCISES

1. A 25-year-old woman has been told that her Pap test indicates infection with HPV type 16.

- **A.** What are the possible implications of infection with HPV 16?
- **B.** How might she have acquired this infection?
- **C.** What treatments are currently available for treatment of this infection?

2. A 35-year-old woman presents with vulvar pruritus, dysuria, dyspareunia, and an odorless, thick, cheesy vaginal discharge. She has diabetes mellitus and has recently recovered from a respiratory tract infection, which required antibiotic treatment.

- **A.** Given that these manifestations are consistent with a Candida infection, what tests might be used to confirm the diagnosis?
- **B.** What risk factors does this woman have that predispose to this type of vaginitis?
- **C.** How might this infection be treated?

REFERENCES

1. Centers for Disease Control and Prevention. (2007). *Human papillomavirus: HPV information for clinicians*. [Online] Available: http://www.cdc.gov/std/hpv/common-clinicians/ClinicianBro-br.pdf. Accessed September 18, 2009.
2. Hsueh P-R. (2009). Human papillomavirus, genital warts, and vaccines. *Journal of Microbiology, Immunology and Infection* 42, 101–106.
3. Diaz M.L. (2008). Human papillomavirus—Prevention and treatment. *Obstetric and Gynecology Clinics of North America* 35, 199–217.
4. Beckmann C.R.B., Ling F.W., Barzansky B.M., et al., for American College of Obstetrics and Gynecology. (2010). *Obstetrics and gynecology* (3rd ed., pp. 241–258). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.
5. Kodner C.M., Nasraty S. (2004). Management of genital warts. *American Family Physician* 70, 2335–2342.
6. Krejci E.B., Sanchez M.L. (2005). Genital human papillomavirus infection. *Clinics in Family Practice* 7(1), 79–96.
7. Frenkl T.L., Potts J. (2008). Sexually transmitted diseases. *Urology Clinics of North America* 35, 33–46.
8. Moore S.L., Seybold V.K. (2007). HPV vaccine. *Clinician Reviews* 17(1), 36–41.
9. Centers for Disease Control and Prevention. (2006). Sexually transmitted diseases: Treatment guidelines 2006. *Morbidity and Mortality Weekly Report 55*(RR11), 1–94.
10. Baker D.A. (2006). Tip of the iceberg: The startling incidence and prevalence of HSV-2. *Primary Care Perspectives* March, 3–5.
11. McAdam A.J., Sharpe A.H. (2010). Infectious diseases. In Kumar V., Abbas A.K., Fausto N. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 351–352, 366, 374–377, 380). Philadelphia: Saunders Elsevier.
12. Schwartz D., Centra R.M., Conner D.H. (2005). Infectious and parasitic diseases. In Rubin E., Gorstein F., Rubin R., et al. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (4th ed., pp. 295–301, 309–312, 329–332, 336). Philadelphia: Lippincott Williams & Wilkins.
13. Beauman J.G. (2005). Genital herpes: A review. *American Family Physician* 72, 1527–1537, 1541–1542.
14. Kimberlin D.W., Rouse D.J. (2004). Genital herpes. *New England Journal of Medicine* 350, 1970–1977.
15. Burkhart C.G. (2006). A guide to recognizing and treating herpes. *The Clinical Advisor* November, 26–36.
16. Witt R. (2006). Emerging epidemic of lymphogranuloma venereum. *Clinician Reviews* 16(5), 56–64.
17. American College of Obstetricians and Gynecologists. (2006). ACOG practice bulletin: Vaginitis. *Obstetrics and Gynecology* 107, 1195–1205.
18. Nyirjesy P. (2008). Vulvovaginal candidiasis and bacterial vaginosis. *Infectious Disease Clinics of North America* 22, 637–652.
19. Owen M.K., Clenney T.L. (2004). Management of vaginitis. *American Family Physician* 70, 2125–2132, 2139–2140.
20. Eckert L.O. (2006). Acute vulvovaginitis. *New England Journal of Medicine* 355, 1244–1252.
21. Soper D. (2004). Trichomoniasis: Under control or undercontrolled? *American Journal of Obstetrics and Gynecology* 190, 281–290.
22. Schwebke J.R., Burgess D. (2004). Trichomoniasis. *Clinical Microbiology Reviews* 17, 794–803.
23. Sobel J.D. (2005). What's new in bacterial vaginosis and trichomoniasis? *Infectious Disease Clinics of North America* 19, 387–406.
24. Sobel J.D. (2000). Bacterial vaginosis. *Annual Review of Medicine* 51, 349–356.
25. Nygren P., Fu R., Freeman M., et al. (2008). Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: An update review of the U.S. Preventative Services Task Force. *Annals of Internal Medicine* 148, 220–233.
26. Meyers D.S., Halvorson H., Luckhaupt S. (2007). Screening for chlamydial infection: An evidence update for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 47, 135–142.
27. Grimshaw-Mulcahy L.J. (2006). Chlamydia: Diagnosing the hidden STD. *The Clinical Advisor* March, 32–42.
28. Miller K.E. (2006). Diagnosis and treatment of *Chlamydia trachomatis* infection. *American Family Physician* 73, 1411–1416.
29. Peipert J.F. (2003). Genital chlamydial infections. *New England Journal of Medicine* 349, 2424–2430.
30. Centers for Disease Control and Prevention. (2008). *Chlamydia: The facts*. [Online] Available: http://www.cdc.gov/std/chlamydia/the-facts/default.htm. Accessed October 12, 2009.
31. Miller W.C., Zenilman J.M. (2005). Epidemiology of chlamydial infection, gonorrhea, and trichomoniasis in the United States—2005. *Infectious Disease Clinics of North America* 19, 281–296.
32. Miller K.E. (2006). Diagnosis and treatment of *Neisseria gonorrhoeae*. *American Family Physician* 73, 1779–1784, 1786.
33. Cook R.L., Hutchison S.L., Ostergaard L., et al. (2005). Systematic review: Noninvasive testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Annals of Internal Medicine* 142, 914–925.
34. U.S. Preventive Services Task Force. (2005). Screening for gonorrhea: Recommendation statement. *American Journal for Nurse Practitioners* 9(10), 35–40.
35. Stevenson J. (2006). Syphilis and HIV infection: An update. *Dermatology Clinics of North America* 24, 497–507.
36. Centers for Disease Control and Prevention. (2003). Primary and secondary syphilis—United States, 2002. *Morbidity and Mortality Weekly Report* 52(46), 1117–1120.
37. Brown D.L., Frank J.E. (2003). Diagnosis and management of syphilis. *American Family Physician* 68, 283–290, 297.
38. Domantay-Apostol G.P., Handog E.B., Gabriel T.G. (2008). Syphilis: The international challenge of the great imitator. *Dermatology Clinics of North America* 26, 191–292.

UNIT 12

Musculoskeletal Function

Structures of the Skeletal System
- *Cartilage*
  - Types of Cartilage
  - Repair of Hyaline Cartilage
- *Bones and Bone Structure*
  - Types of Bone
  - Periosteum and Endosteum
  - Bone Marrow
  - Blood Supply
- *Bone Tissue*
  - Lamellar and Woven Bone
  - Bone Cells
- *Bone Formation, Growth, and Remodeling*
  - Bone Growth in Childhood
  - Bone Remodeling
  - Hormonal Control of Bone Formation and Metabolism

Joints
- *Synarthroses*
- *Synovial (Diarthrodial) Joints*
  - Ligaments and Tendons
  - Joint Vasculature and Innervation
  - Bursae and Tendon Sheaths
  - Intra-Articular Menisci

Chapter 42

Structure and Function of the Skeletal System

Without the skeletal system, movement in the external environment would not be possible. The bones of the skeletal system serve as a framework for skeletal muscle attachment and movement. The skeletal system protects and maintains vital structures in their proper position, provides stability for the body, and maintains the body's shape. Bones also serve as a reservoir for ions such as calcium, phosphorous, and magnesium, and it houses the hematopoietic connective tissue in which blood cells are formed.

Structures of the Skeletal System

The skeletal system can be divided into two functional parts—the axial and appendicular skeleton. The *axial skeleton* is composed of the bones of the skull, thorax, and vertebral column, and forms the axis of the body. The *appendicular skeleton* consists of the bones of the upper and lower extremities, including the shoulder and hip. In addition to bones, the skeletal system includes cartilage and ligaments that join bones together at joints. The joints give the body flexibility and allow movement to occur. Skeletal muscles, which are attached to bones by tendons, use bones as levers to move the body and its parts.

Two types of connective tissue are found in the skeletal system: cartilage and bone. They both have living cells that secrete the extracellular matrix in which the cells are housed. The extracellular matrix in cartilage is solid and

The Skeletal System

- The skeletal system consists of the bones of the skull, thorax, and vertebral column, which form the *axial skeleton,* and the bones of the upper and lower extremities, which form the *appendicular skeleton.*
- Two types of connective tissue are found in the skeletal system: (1) cartilage, a semirigid and slightly flexible structure that plays an essential role in prenatal and childhood development of the skeleton and as a surface for the articulating ends of skeletal joints; and (2) bone, which provides for the firm structure of the skeleton and serves as a reservoir for calcium and phosphate storage.
- Both bone and cartilage tissue are composed of living cells and a nonliving intercellular matrix that is secreted by the living cells.
- Bone matrix is maintained by four types of cells: osteoblasts, which synthesize and secrete the constituents of bone; osteoclasts, which resorb surplus bone and are required for bone remodeling; osteocytes, which make up the osteoid tissue of bone; and osteoprogenitor cells, which are the source of all bone cells, except osteoclasts.

firm but also somewhat pliable, which provides resilience for cushioning of bony structures. In contrast to cartilage, the extracellular matrix of bone is mineralized, producing a hard tissue capable of providing protection for body structures and rigid support for the extremities.

Cartilage

Cartilage is an avascular tissue that consists of cells, called *chondrocytes*, and an extensive extracellular matrix. More than 95% of cartilage volume is extracellular matrix, which is the functional element of this tissue. The chondrocytes are sparse, but are essential to the production and maintenance of the matrix. A connective tissue sheath, called the *perichondrium,* overlies the free surfaces of most cartilage. The perichondrium is vascular and its vessels supply nutrients to the cells of cartilage. In areas where the cartilage has no perichondrium, such as the articular surfaces of moving joints, the cartilage cells receive their nourishment from the synovial fluid that bathes the joint surfaces. The perichondrium also is the source of new cartilage cells.

Types of Cartilage

There are three types of cartilage, which differ in appearance and mechanical properties—hyaline cartilage, elastic cartilage, and fibrocartilage.

Hyaline Cartilage. Hyaline cartilage, a bluish-gray semitranslucent pliable substance, is the most abundant type of cartilage. It forms the costal cartilages that join the ribs to the sternum and vertebrae, many of the cartilages of the respiratory tract, and the articulating surfaces of movable joints of the body. It is also essential for growth before and after birth. In the embryo, most of the axial and appendicular skeleton is formed first as a cartilage model and then is replaced by bone. This process is known as *endochondral bone formation*. In postnatal life, cartilage continues to play an essential role in the growth of long bones and persists as articular cartilage in the adult.

The matrix of hyaline cartilage is composed of proteoglycans, multiadhesive glycoproteins, and collagen fibers. The collagen fibers of the cartilage matrix are embedded in a gel formed by the proteoglycans. Proteoglycans consist of polysaccharides, called *glycosaminoglycans,* linked to a core protein. Cartilage matrix contains three types of glycosaminoglycans: chondroitin sulfate, keratin sulfate, and hyaluronan. A proteoglycan may contain more than 100 glycosaminoglycans. Aggrecan, the most important proteoglycan in hyaline cartilage, contains 100 chondroitin sulfate chains and up to 50 keratin sulfate molecules. Hyaluronan is a single polypeptide chain, allowing it to associate with as many as 100 to 200 aggrecan molecules and form large proteoglycan aggregates. The negatively charged groups on the proteoglycans have a high affinity for water molecules. In this way, the cartilage matrix becomes hydrated to such an extent that up to 80% of the wet weight of cartilage is water. Both transient and regional changes occur in water content during joint movement and when the joint is subjected to pressure. This high degree of hydration and the movement of water in the matrix allow the cartilage matrix to respond to varying pressure loads and contribute to cartilage's weight-bearing properties.

The multiadhesive glycoproteins influence interactions between the chondrocytes and matrix molecules and have clinical value as markers of cartilage turnover and degeneration. Throughout life, cartilage undergoes continuous internal remodeling as the cells replace matrix molecules lost through degradation. Normal matrix turnover depends on the ability of the chondrocytes to detect changes in matrix composition. The chondrocytes then respond by synthesizing appropriate types of new molecules. In addition, the matrix acts as a signal transducer for the chondrocytes. Thus, pressure loads applied to the cartilage create mechanical and chemical signals that direct synthetic activity by the chondrocytes. As the body ages, however, the composition of the matrix changes and the chondrocytes lose their ability to respond to these signals.

Elastic Cartilage. Elastic cartilage resembles hyaline cartilage, except that it has a dense network of elastic fibers scattered throughout its matrix. It is found in areas where flexibility is important, such as in the auricle of the external ear, the auditory canal, the epiglottis, and the larynx. The cartilage in these locations is surrounded by a perichondrium.

Fibrocartilage. Fibrocartilage is a combination of dense connective tissue and cartilage. The chondrocytes are similar to those found in hyaline cartilage, but there is considerably less matrix associated with them, and there is no surrounding perichondrium. Fibrocartilage is typically present in intervertebral disks, the symphysis pubis, articular disks of the sternoclavicular and temporomandibular joints, menisci of the knee, and certain areas where tendons attach to bones. Fibrocartilage serves as a shock absorber, and its presence in these sites indicates that resistance to both compression and shearing forces is required.

Repair of Hyaline Cartilage

Hyaline cartilage can tolerate considerable amounts of intense and repetitive stress, but manifests a striking inability to heal from even the most minor injuries. This lack of response to injury is attributable to the avascular nature of cartilage, the immobility of chondrocytes, and the limited ability of chondrocytes to proliferate. Some repair can occur, but only if the defect involves the perichondrium, in which case chondrogenic cells from the perichondrium enter the defect and form new cartilage. If the defect is large, the cells form dense connective tissue to repair the scar. Hyaline cartilage is also subject to calcification, a process in which calcium phosphate crystals become embedded in the cartilage matrix. In most situations, given sufficient time, cartilage that calcifies will be replaced by bone. Chondrocytes normally derive all of their nutrients and dispose of waste materials through the matrix. When the matrix becomes heavily calcified, diffusion is impeded and the chondrocytes swell and die. The ultimate consequence of this event is removal of the calcified matrix and its replacement by bone.

Bones and Bone Structure

Bone is a connective tissue that, like other connective tissue, consists of cells and an extracellular matrix. The feature of bone that distinguishes it from other connective tissue is the mineralization of its matrix with calcium phosphate in the form of hydroxyapatite crystals, which produces an extremely hard tissue capable of providing support and protection. By virtue of its mineral content, bone also serves as a storage site for calcium and phosphorous, which can be mobilized and taken up by the blood to maintain appropriate levels throughout the body.

Types of Bone

There are two types of mature bones: cancellous and compact (Fig. 42-1B). Cancellous, or spongy, bone is found in the interior of bones and is composed of *trabeculae,* or *spicules,* of bone that form a latticelike pattern. These latticelike structures are lined with osteogenic cells and filled with red or yellow bone marrow. Cancellous bone is relatively light, but its structure is such that it has considerable tensile strength and weight-bearing

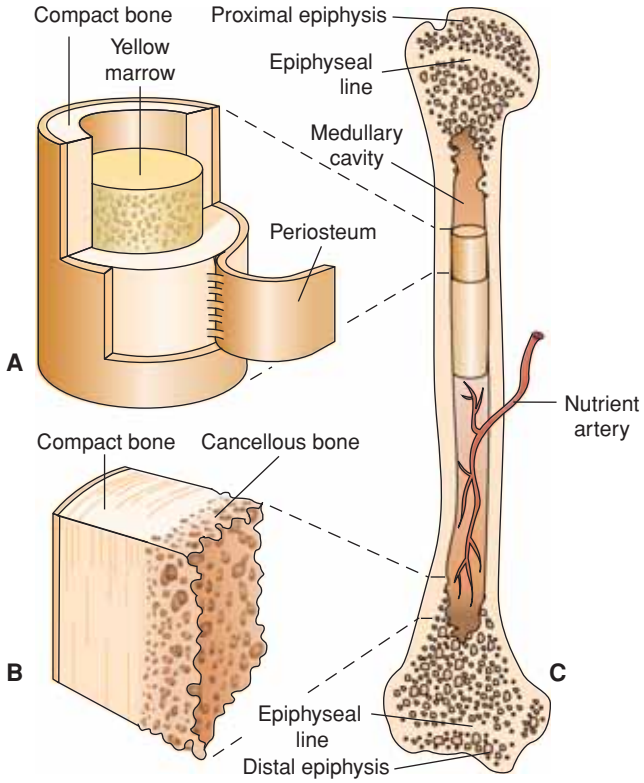


FIGURE 42-1. A long bone shown in longitudinal section. **(A)** Periosteum and bone marrow, **(B)** compact and cancellous bone, and **(C)** epiphysis and source of blood supply from epiphysial and nutrient arteries.

properties. Compact, or cortical, bone, which forms the outer shell of a bone, has a densely packed, calcified intercellular matrix that makes it more rigid than cancellous bone. Although bones contain both cancellous and compact elements, their proportions vary in different bones throughout the body and in different parts of the same bone, depending on the relative needs for strength and lightness. Compact bone, for example, is the major component of tubular bones and is also found along the lines of stress on long bones.

Bones are classified by shape as long, short, flat, and irregular. Long bones are found in the upper and lower extremities. Short bones are irregularly shaped bones located in the ankle and the wrist. Except for their surface, which is compact bone, these bones are spongy throughout. Flat bones are composed of a layer of cancellous bone between two layers of compact bone. They are found in areas such as the skull and rib cage, where extensive protection of underlying structures is needed, or, as in the scapula, where a broad surface for muscle attachment must be provided. Irregular bones, because of their shapes, cannot be classified in any of the previous groups. This group includes bones such as the vertebrae and the bones of the jaw.

A typical long bone has a shaft, or *diaphysis,* and two ends, called *epiphyses* (Fig. 42-2). Long bones usually are narrow in the midportion and broad at the ends so that the weight they bear can be distributed over a wider

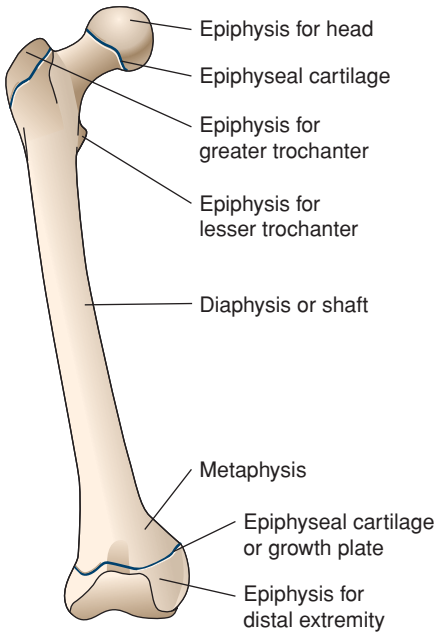


FIGURE 42-2. A femur, showing epiphyseal cartilages for the head, metaphysis, trochanters, and distal end of the bone.

surface. The shaft of a long bone is formed mainly of compact bone roughly hollowed out to form a marrow-filled medullary canal. The ends of long bones are covered with articular cartilage.

In growing bones, the part of the bone shaft that funnels out as it approaches the epiphysis is called the *metaphysis*. It is composed of bony trabeculae that have cores of cartilage. In the child, the epiphysis is separated from the metaphysis by the cartilaginous growth plate. After puberty, the metaphysis and epiphysis merge, and the growth plate is obliterated.

Periosteum and Endosteum

Bones are covered, except at their articular ends, by a membrane called the *periosteum* (see Fig. 42-1A). The periosteum has an outer fibrous layer and an inner layer that contains the osteoprogenitor cells needed for bone growth and development. The periosteum also contains blood vessels and acts as an anchorage point for vessels as they enter and leave the bone. The endosteum is the membrane that lines the spaces of spongy bone, the marrow cavities, and the haversian canals of compact bone. It is composed mainly of osteoprogenitor cells that contribute to the growth and remodeling of bone and are necessary for bone repair.

Bone Marrow

Bone marrow occupies the medullary cavities of the long bones throughout the skeleton and the cavities of cancellous bone in the vertebrae, ribs, sternum, and flat bones of the pelvis. The cellular composition of the bone marrow varies with age and skeletal location. Red bone marrow contains developing red blood cells and is the site of blood cell formation. Yellow bone marrow is composed largely of adipose cells. At birth, nearly all of the marrow is red and hematopoietically active. As the need for red blood cell production decreases during postnatal life, red marrow is gradually replaced with yellow bone marrow in most of the bones. In the adult, red marrow persists in the vertebrae, ribs, sternum, and ilia.

Blood Supply

The compact bone of long tubular bones is provided with blood supply from two sources, nutrient arteries and perforating arteries (Fig. 42-1C). The nutrient arteries enter the bone through a nutrient foramen and supply the marrow space and the internal one half of the cortex. The perforating arteries are small arteries that extend inward from the periosteal arteries on the external surface of the periosteum and anastomose in the cortex with branches of the nutrient arteries coming from the bone marrow. The distribution of blood in the cortex occurs through the haversian and Volkmann canals (Fig. 42-3). Haversian canals are spaces in the bone of the cortex that course parallel through the long axis of the bone for a short distance and then branch and communicate with other, similar canals. Each canal carries one or two blood vessels, lymphatics, and some nerve fibers. Volkmann canals, which also contain blood vessels, are spaces in the cortex that run perpendicular to the long axis of the cortex to connect adjacent haversian canals.

Cancellous bone is usually not penetrated by blood vessels. Instead, the bone cells of cancellous bone are nourished by diffusion from the endosteal surface through canaliculi, which interconnect their surrounding fluid-filled lacunae and extend to the bone surface.

Bone Tissue

Bone is connective tissue in which the intercellular matrix has been impregnated with inorganic calcium salts so that it has great tensile and compressive strength but is light enough to be moved by coordinated muscle contractions. The matrix is composed of two types of substances—organic matter and inorganic salts.

The organic matter, which constitutes approximately one-third the dry weight of bone, consists primarily of collagen fibers embedded in an amorphous ground substance. The inorganic matter consists of hydroxyapatite crystals and small amounts of calcium carbonate and calcium fluoride. Bone may also take up lead and other heavy metals, thereby removing these toxic substances from the circulation. This can be viewed as a protective mechanism. The antibiotic tetracycline is readily bound to calcium deposited in newly formed bones and teeth. When tetracycline is given during pregnancy, it can be deposited in the teeth of the fetus, causing discoloration and deformity. Similar changes can occur if the drug is given for long periods to children younger than 6 years of age.

Lamellar and Woven Bone

There are two types of bone tissue: lamellar and woven. Both forms of bone tissue can be mineralized or

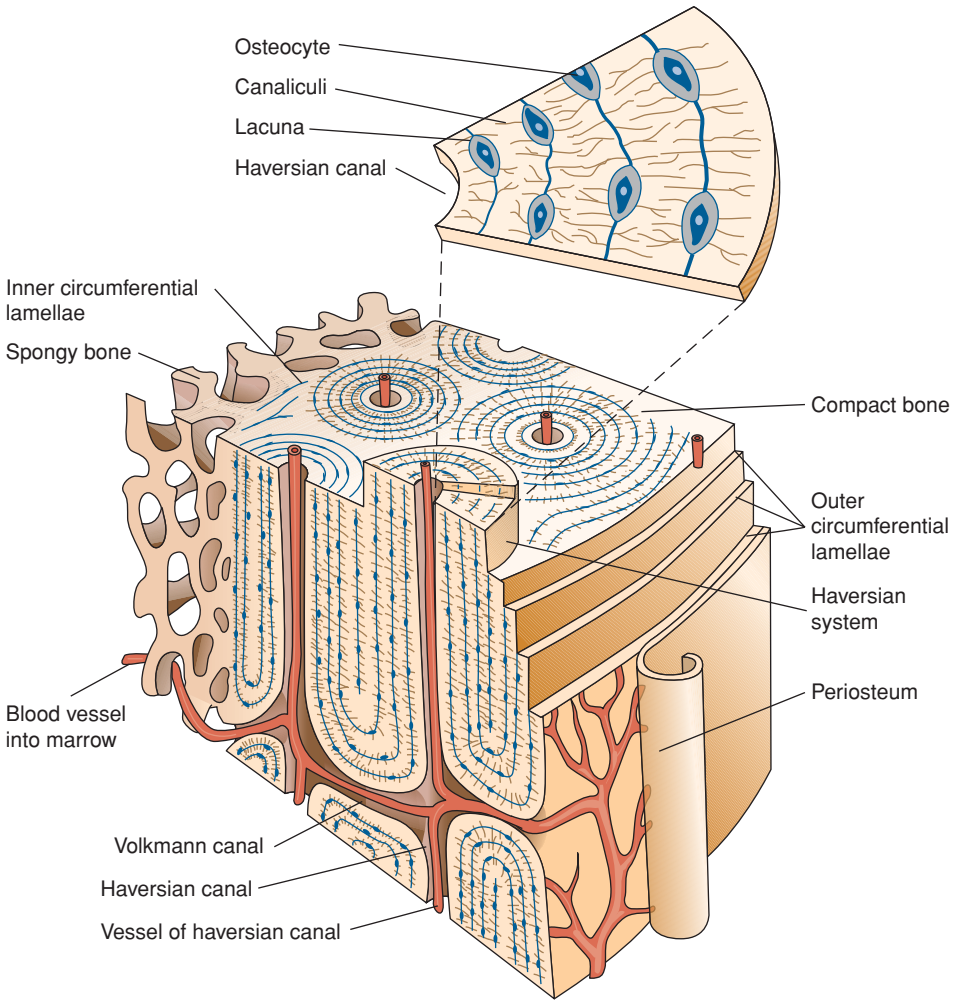


FIGURE 42-3. (Bottom) Haversian systems as seen in a wedge of compact bone tissue. The periosteum has been peeled back to show a blood vessel entering a Volkmann canal. **(Top)** Osteocytes lying within lacunae; canaliculi permit interstitial fluid to reach each lacuna.

unmineralized, the latter being referred to as *osteoid*. *Lamellar bone* is a strong, mature form of bone that is formed slowly and is highly organized. It is the mature bone found in the adult skeleton. Lamellar bone is composed largely of cylindrical units called *osteons* or *haversian systems*. The osteons consist of concentric lamellae of bone matrix, surrounding a central canal, called the *haversian canal*, that contains the blood vessels and nerve supply for the osteon (see Fig. 42-3). In compact bone, 4 to 20 lamellae are arranged concentrically around a central haversian canal, which runs essentially parallel to the long axis of the bone. Between the osteons are remnants of previous concentric lamellae, called the *interstitial lamella*. Circumferential lamellae follow the entire inner and outer shaft of a long bone, appearing much like the growth rings of a tree. Cancellous bone is also composed of lamellae, but, as mentioned previously, its trabeculae usually are not penetrated by blood vessels.

Woven bone is deposited more rapidly than lamellar bone. It is of low tensile strength, serving as temporary scaffolding for support. It is found in the developing fetus, in areas surrounding tumors and infections, and as part of a healing fracture.

Bone Cells

Four types of bone cells participate in the formation and maintenance of bone tissue: osteoprogenitor cells, osteoblasts, osteocytes, and osteoclasts (Table 42-1). With the exception of the osteoclast, each type of bone cell originates from the same basic cell type, undergoing transformation from a less mature to a more mature cell type.

Osteoprogenitor Cells. Osteoprogenitor cells are undifferentiated cells that are found in the periosteum, endosteum, and epiphyseal plate of growing bone. Derived from mesenchymal stem cells in the bone marrow, they have the potential to differentiate into many different cell types, including adipocytes, fibroblasts, muscle cells, and osteoblasts. When appropriately stimulated by bone morphogenic proteins (BMPs) and transforming growth factors, they undergo cell division and differentiate into osteoblasts.

Osteoblasts. Osteoblasts are bone-building cells that secrete bone matrix. Bone formation occurs in two stages: ossification and calcification. Ossification involves

TABLE 42-1 Function of Bone Cells

Type of Bone Cell	Function
Osteoprogenitor cells	Undifferentiated cells that differentiate into osteoblasts. They are found in the periosteum, endosteum, and epiphyseal growth plate of growing bones.
Osteoblasts	Bone-building cells that synthesize and secrete the organic matrix of bone. Osteoblasts also participate in the calcification of the organic matrix.
Osteocytes	Mature bone cells that function in the maintenance of bone matrix. Osteocytes also play an active role in releasing calcium into the blood.
Osteoclasts	Bone cells originating from mononuclear hematopoietic progenitor cells that are responsible for bone resorption.

the formation of the initial unmineralized bone, or osteoid. Osteoblasts secrete both type I collagen (which constitutes 90% of the protein of bone) and bone matrix proteins, forming the osteoid or prebone. They also are responsible for calcification of the bone matrix. The calcification process appears to be initiated by the osteoblast through the secretion of *alkaline phosphatase*, which is thought to act locally in bone tissue to raise calcium and phosphate levels to the point at which precipitation occurs. The activity of the osteoblasts undoubtedly contributes to the increase in serum levels of alkaline phosphatase that follows bone injury and fractures.

Osteocytes. Osteocytes are mature bone cells, derived from osteoblasts, that are housed in small lakes, or *lacunae*, within the calcified bony matrix (see Fig. 42-3). Extracellular fluid-filled passageways permeate the calcified matrix and connect with the lacunae of adjacent osteocytes. These passageways are called *canaliculi*. Because diffusion does not occur through the calcified matrix of bone, the canaliculi serve as communicating channels for the exchange of nutrients and metabolites between the osteocytes and the blood vessels on the surface of the bone layer.

Osteocytes are the cells responsible for maintaining the bone matrix. Osteocytes can synthesize new matrix, as well as participate in matrix degradation. Death of osteocytes, either through trauma, cell senescence, or apoptosis, results in resorption of the bone matrix by osteoclasts, followed by repair or remodeling of the bone tissue by osteoblasts.

Osteoclasts. Osteoclasts are large multinucleated "bone-chewing" cells that function in the resorption of bone, removing the mineral content and organic matrix. They are derived from the same mononuclear hematopoietic progenitor cells that give rise to blood monocytes and tissue macrophages. Osteoclast formation occurs in close association with the stromal cells of the bone marrow. These cells secrete essential cytokines that promote the differentiation of both osteoclasts and macrophages. These cytokines function either by stimulating osteoclast progenitor cells or by participating in a paracrine system in which osteoblasts and marrow stromal cells play a central role. Recent studies indicate that substances promoting osteoclast differentiation act through the RANK-RANKL signaling pathway (to be discussed).

Newly formed osteoclasts undergo activation to become a bone-resorbing cell. Once activated, they bind to the bone surface, where they form an underlying resorption pit. The cell membrane overlying the resorption pit is thrown into numerous folds, increasing its surface area, while the adjacent cell surface forms a tight seal with the bone that prevents leakage of digestion products. The osteoclast removes the bone mineral by generating an acidic environment utilizing a proton pump and digests the organic bone matrix by releasing proteolytic enzymes.

Bone Formation, Growth, and Remodeling

The development of skeletal structures begins in utero and continues to change throughout life. During childhood, skeletal structures grow in length and diameter and sustain a large increase in bone mass. The term *modeling* refers to the formation of the macroscopic skeleton resulting in a bone having adult form and shape. Once skeletal growth has ceased, the process of bone *remodeling* is responsible for skeletal maintenance. It involves both bone resorption and formation. With aging, bone resorption and formation are no longer perfectly coupled, and there is loss of bone.

Bone Growth in Childhood

During the first two decades of life, the skeleton undergoes general overall growth. The long bones of the skeleton, which grow at a relatively rapid rate, are provided with a specialized structure called the *epiphyseal growth plate*. As long bones grow in length, the deeper layers of cartilage cells in the growth plate multiply and enlarge, pushing the articular cartilage farther away from the metaphysis and diaphysis of the bone. As this occurs, the mature and enlarged cartilage cells at the metaphyseal end of the plate become metabolically inactive and are replaced by bone cells. This process allows bone growth to proceed without changing the shape of the bone or causing disruption of the articular cartilage. The cells in the growth plate stop dividing at puberty, at which time the epiphysis and metaphysis fuse.

Several factors can influence the growth of cells in the epiphyseal growth plate. Epiphyseal separation can occur in children as the result of trauma. The separation usually occurs in the zone of the mature enlarged cartilage cells, which is the weakest part of the growth plate. The blood vessels that nourish the epiphysis pass through the growth

plate. These vessels are ruptured when the growth plate separates. This can cause cessation of growth and a shortened extremity. The growth plate also is sensitive to nutritional and metabolic changes. Scurvy (i.e., vitamin C deficiency) impairs the formation of the organic matrix of bone, causing slowing of growth at the epiphyseal plate and cessation of diaphyseal growth. In rickets (i.e., vitamin D deficiency), calcification of the newly developed bone on the metaphyseal side of the growth plate is impaired. Thyroid and growth hormones are required for normal growth. Alterations in these and other hormones can also affect growth (see Chapter 32).

Growth in the diameter of bones occurs as new bone is added to the outer surface of existing bone along with an accompanying resorption of bone on the endosteal or inner surface. Such oppositional growth allows for widening of the marrow cavity while preventing the cortex from becoming too thick and heavy. In this way, the shape of the bone is maintained. As a bone grows in diameter, concentric rings are added to the bone surface, much as rings are added to a tree trunk; these rings form the lamellar structure of mature bone. Osteocytes, which develop from osteoblasts, become buried in the rings. Haversian channels form as periosteal vessels running along the long axis become surrounded by bone (see Fig 42-3).

Bone Remodeling

Peak bone mass is achieved during early adulthood after cessation of modeling. It is determined by a number of factors, including the type of vitamin D receptor inherited, nutrition, level of physical activity, age, and hormonal status. Once skeletal growth has attained its adult size, the breakdown and renewal of bone that is responsible for skeletal maintenance is initiated at sites that require replacement or repair. This process is called *bone remodeling*.

In bone remodeling, the processes of bone formation and resorption are tightly coupled, and their balance determines skeletal mass at any time. The sequence of bone resorption and bone formation begins with osteoclastic resorption of existing bone, during which the organic (protein matrix) and the inorganic (mineral) components are removed. The sequence proceeds to the formation of new bone by osteoblasts. In the adult, the length of one sequence (i.e., bone resorption and formation) is approximately 4 months. Ideally, the replaced bone should equal the absorbed bone. If it does not, there is a net loss of bone. In the elderly, for example, bone resorption and formation no longer are perfectly coupled, and bone mass is lost.

Recently, significant progress has been made in understanding the phenomenon of bone remodeling as it relates to the coupling of bone resorption with bone formation. The pivotal paracrine pathway linking these two processes consists of three factors: RANKL (for *r*eceptor *a*ctivator of *n*uclear factor-κB *l*igand); its receptor, RANK; and a soluble inhibitor receptor for RANKL called *osteoprotegerin* (OPG). RANKL is a member of the tumor necrosis factor (TNF) superfamily, and both RANK and OPG are members of the TNF receptor family. RANKL is expressed by osteoblasts and their immature precursors and is necessary for osteoclast differentiation and function. RANKL activates its receptor, RANK, which is expressed on osteoclasts and their precursors, thus promoting osteoclast differentiation and activation and prolonging osteoclast survival by suppressing apoptosis. The fact that RANKL is expressed on osteoblasts indicates that bone resorption and bone formation are linked through RANKL. The term *osteoprotegerin* was coined because of its protective effects against bone loss, detected in animal studies. The effects of RANKL are blocked by OPG, a soluble receptor protein, which acts as a decoy receptor that binds RANKL and prevents it from binding with RANK on osteoclasts.

It is now believed that dysregulation of the RANKL/RANK/OPG pathway plays a prominent role in the pathogenesis of bone diseases such as osteoporosis. For example, it has been shown that postmenopausal women express higher levels of RANKL on their marrow stromal cells and lymphocytes than premenopausal women or postmenopausal women taking estrogen. It has also been shown that estrogens and the selective estrogen receptor modulator, raloxifene, stimulate OPG production in osteoblasts. Glucocorticoid exposure, which can contribute to steroid osteoporosis, enhances RANKL expression and suppresses OPG levels, thus elevating the RANKL-to-OPG ratio. There is also evidence linking the pathogenesis of inflammatory conditions such as rheumatoid arthritis to dysregulation of the RANKL/OPG system. Based on animal models of rheumatoid arthritis, cytokines differentially regulate RANKL and OPG, producing an enhanced RANKL-to-OPG ratio that favors skeletal damage. There is also evidence that RANKL is expressed on T cells, and in vitro studies have shown that activated T cells can regulate the development and activation of osteoclasts through RANKL.

Hormonal Control of Bone Formation and Metabolism

The process of bone formation and mineral metabolism is complex. It involves the interplay among the actions of parathyroid hormone (PTH), calcitonin, and vitamin D (Table 42-2). Other hormones, such as cortisol, growth hormone, thyroid hormone, and the sex hormones, also influence bone formation directly or indirectly.

Parathyroid Hormone. Parathyroid hormone is one of the important regulators of calcium and phosphate levels in the blood. PTH prevents serum calcium levels from falling below and serum phosphate levels from rising above normal physiologic concentrations (see Chapter 8). The secretion of PTH is regulated through negative feedback related to serum levels of ionized calcium, with decreased levels of ionized calcium stimulating PTH release and increased levels inhibiting its release.

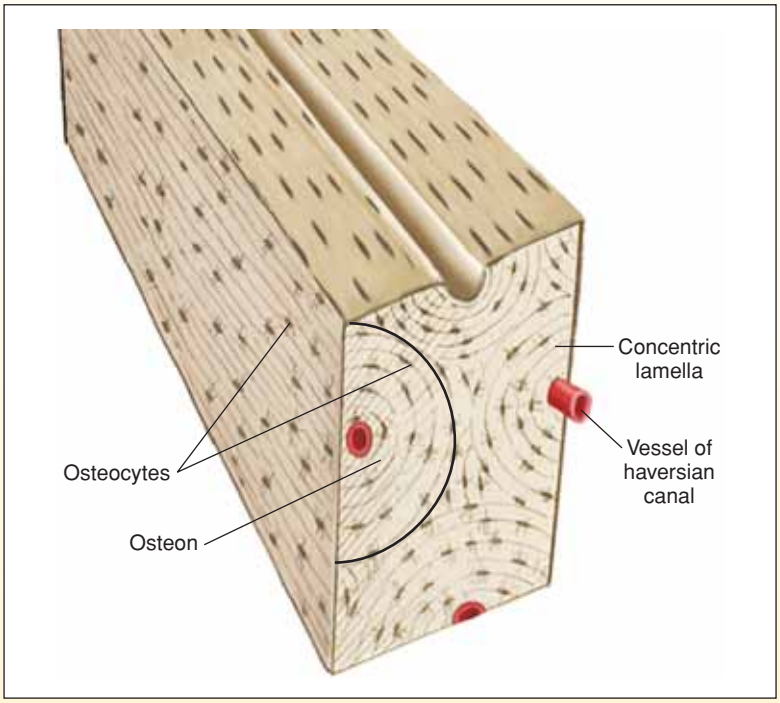
PTH maintains serum calcium levels by promoting bone resorption, by conserving calcium by the kidney, by enhancing intestinal absorption of calcium through

UNDERSTANDING → Bone Remodeling

Bone remodeling constitutes a process of skeletal maintenance once skeletal growth is complete. It takes place in the (1) osteons of mature bone and consists of a cycle of (2) bone resorption by osteoclasts, (3) followed by bone formation by osteoblasts. Bone remodeling is (4) controlled by cytokines and growth factors that interact with a paracrine system consisting of the RANK ligand (RANKL), the RANK receptor, and osteoprotegerin.

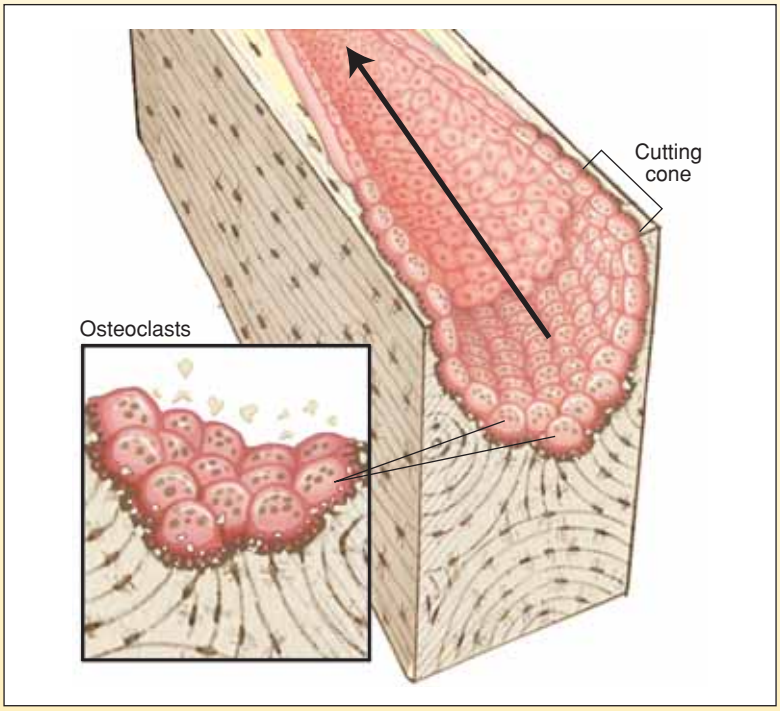
1

Bone Remodeling Cycle. Mature bone is made up of osteons or units of concentric lamellae (bone layers) and the haversian canal they surround. Bone remodeling consists of a sequence of bone resorption within an osteon by osteoclasts, followed by new bone formation by osteoblasts. In the adult, the length of one sequence (i.e., bone resorption and formation) is approximately 4 months. Ideally, the replaced bone should equal the resorbed bone. If it does not, there is net loss of bone. In the elderly, for example, bone resorption and formation no longer are perfectly coupled, and bone mass is lost.



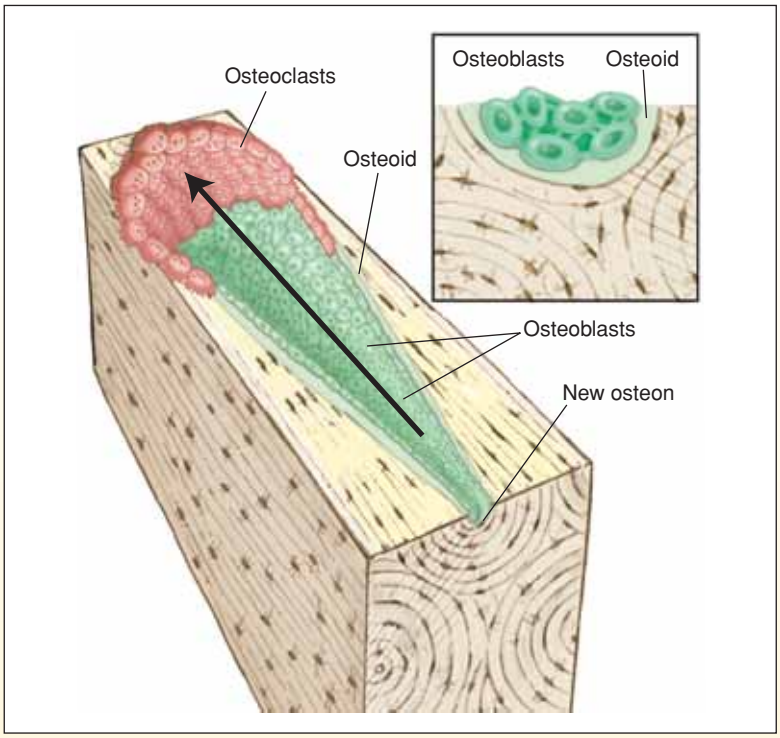
2

Bone Resorption. The osteoclasts, which are bone-resorbing cells derived from monocyte/macrophage precursors, are the cells involved in the initiation of bone remodeling. The sequence of bone resorption and bone formation is activated by many stimuli, including the action of parathyroid hormone and calcitonin. It begins with osteoclastic resorption of existing bone, during which the organic (protein matrix) and inorganic (mineral) components are removed, creating a tunnel-like space in the osteon. Soluble factors released during resorption aid in the recruitment of osteoblasts to the site, thereby linking bone resorption to bone formation.



3

Bone Formation. After osteoclastic activity has ceased, osteoblasts begin to deposit the organic matrix (osteoid) on the wall of the osteon canal. As successive lamellae of bone are deposited, the canal ultimately attains the relative proportions of the original osteon. In the formation and maintenance of bone, osteoblasts provide much of the local control because not only do they produce new bone matrix, they play an essential role in mediating osteoclast activity. Many of the primary stimulators of bone resorption, such as parathyroid hormone, have minimal or no direct effects on osteoclasts. Once the osteoblast, which has receptors for these substances, receives the appropriate signal, it releases a soluble mediator called *RANKL* that induces osteoclast activity.



4

Control of Bone Metabolism and Remodeling. The pivotal pathway linking osteoclast-mediated bone resorption with osteoblast-mediated bone formation consists of a paracrine system that includes RANKL, its receptor RANK, and a soluble protein called *osteoprotegerin* (OPG). RANKL, which is produced by osteoblasts and their precursors, binds to RANK, promoting osteoclast differentiation and proliferation. The soluble OPG molecule, which is produced by a number of tissues, acts as a decoy receptor to block the action of RANKL. This system ensures the tight coupling of bone formation and resorption, and provides a means whereby a wide variety of biologic mediators (e.g., hormones, cytokines, growth factors) influence the homeostasis of bone.

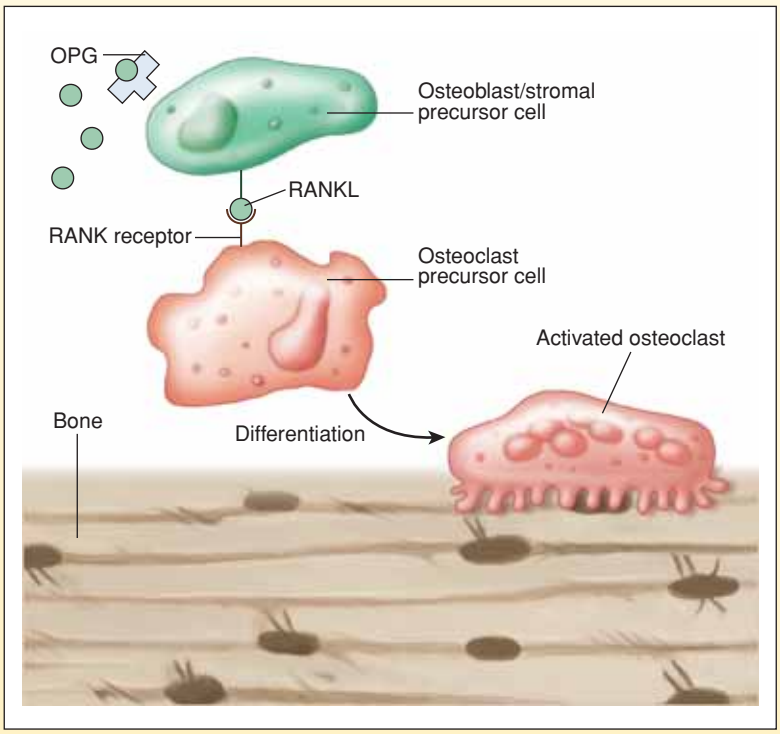


TABLE 42-2 Actions of Parathyroid Hormone, Calcitonin, and Vitamin D

Actions	Parathyroid Hormone	Calcitonin	Vitamin D
Intestinal absorption of calcium	Increases indirectly through increased activation of vitamin D	Probably not affected	Increases
Intestinal absorption of phosphate	Increases	Probably not affected	Increases
Renal excretion of calcium	Decreases	Minor effect	Probably increases, but less effect than PTH
Renal excretion of phosphate	Increases	Minor effect	Increases
Bone resorption	Increases	Decreases	$1,25\text{-}(OH)_2D_3$ increases
Bone formation	Decreases	Uncertain	$24,25\text{-}(OH)_2D_3$ increases (?)
Serum calcium levels	Produces a prompt increase	Decreases with pharmacologic doses	No effect
Serum phosphate levels	Prevents an increase	Decreases with pharmacologic doses	No effect

activation of vitamin D, and by reducing serum phosphate levels (Fig. 42-4). PTH also increases the movement of calcium and phosphate from bone into the extracellular fluid. Calcium is immediately released from the canaliculi and bone cells; a more prolonged release of calcium and phosphate is mediated by increased osteoclast activity. In the kidney, PTH stimulates tubular reabsorption of calcium while reducing the reabsorption of phosphate. The latter effect ensures that the increased release of phosphate from bone during mobilization of calcium does not produce an elevation in serum phosphate levels. This is important because an increase in calcium and phosphate levels could lead to crystallization in soft tissues. PTH also stimulates the activation of vitamin D by the kidney, thereby increasing the absorption of calcium from the intestine.

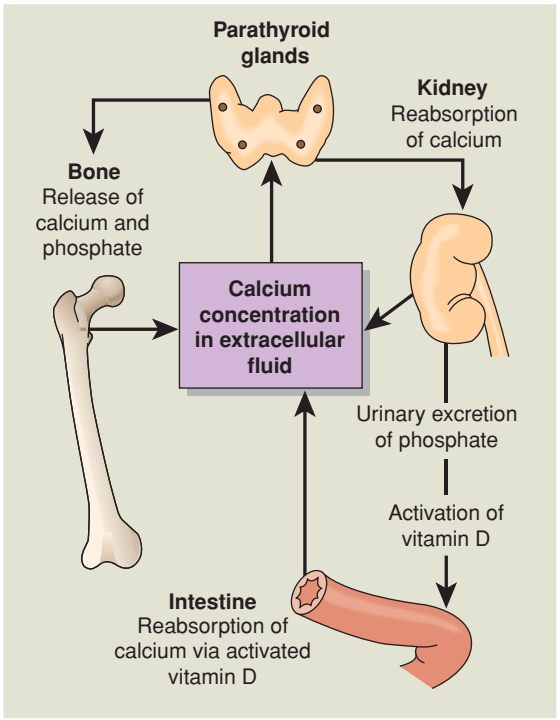


FIGURE 42-4. Regulation and actions of parathyroid hormone.

Calcitonin. Whereas PTH increases blood calcium levels, the hormone calcitonin lowers blood calcium levels. Calcitonin, sometimes called *thyrocalcitonin,* is secreted by the parafollicular, or C, cells of the thyroid gland. Calcitonin inhibits the release of calcium from bone into the extracellular fluid. It is thought to act by causing calcium to become sequestered in bone cells and by inhibiting osteoclast activity. Calcitonin also reduces the renal tubular reabsorption of calcium and phosphate; the decrease in serum calcium level that follows administration of pharmacologic doses of calcitonin may be related to this action.

The major stimulus for calcitonin synthesis and release is an increase in serum calcium. The role of calcitonin in overall mineral homeostasis is uncertain. There are no clearly definable syndromes of calcitonin deficiency or excess, which suggests that calcitonin does not directly alter calcium metabolism. It has been suggested that the physiologic actions of calcitonin are related to the postprandial handling and processing of dietary calcium. This theory proposes that after meals, calcitonin maintains PTH secretion at a time when it normally would be reduced by calcium entering the blood from the digestive tract. Although excess or deficiency states associated with alterations in physiologic levels of calcitonin have not been observed, it has been shown that pharmacologic doses of the hormone reduce osteoclast activity. Because of this action, calcitonin has proved effective in the treatment of Paget disease (see Chapter 44). The hormone is also used to reduce serum calcium levels during hypercalcemic crises.

Vitamin D. Vitamin D and its metabolites are not true vitamins but steroid hormones. There are two forms of vitamin D: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). The two forms differ by the presence of a double bond, but they have identical biologic activity. The term *vitamin D* is used to indicate both forms.

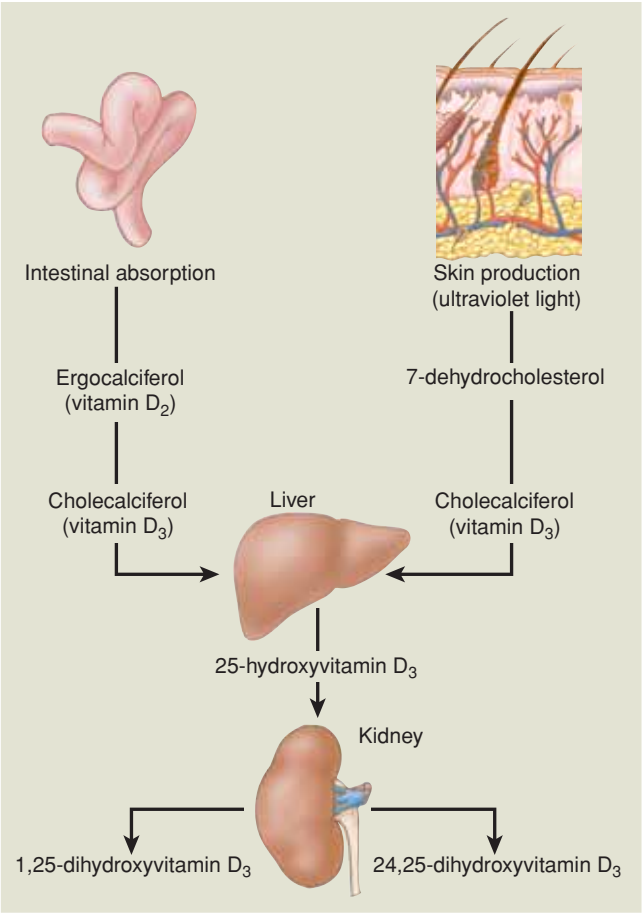


FIGURE 42-5. Sources and pathways for activation of vitamin D.

Vitamin D has little or no activity until it has been converted to physiologically active compounds. Figure 42-5 depicts sources of vitamin D and pathways for activation. The first step of the activation process occurs in the liver, where vitamin D is hydroxylated to form the metabolite 25-hydroxyvitamin D_3 [25-(OH)D_3]. From the liver, 25-(OH)D_3 is transported to the kidneys, where it undergoes conversion to 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] or 24,25-dihydroxyvitamin D_3 [24,25-$(OH)_2D_3$]. Other metabolites of vitamin D have been and are still being discovered.

There are two sources of vitamin D: intestinal absorption and skin production. Intestinal absorption occurs mainly in the jejunum and includes vitamin D_2 and vitamin D_3. The most important dietary sources of vitamin D are fish, liver, and irradiated milk. Because vitamin D is fat soluble, its absorption is mediated by bile salts and occurs by means of the lymphatic vessels. In the skin, ultraviolet radiation from sunlight spontaneously converts 7-dehydrocholesterol D_3 to vitamin D_3. A circulating vitamin D–binding protein provides a mechanism to remove vitamin D from the skin and make it available to the rest of the body.

With adequate exposure to sunlight, the amount of vitamin D that can be produced by the skin is usually sufficient to meet physiologic requirements. Modern conditions of dress, lifestyle, and recommendations regarding sun screens and avoidance of sun exposure to reduce skin cancer risk may prevent a large proportion of the population from producing adequate amounts of vitamin D. Elderly persons who are housebound or institutionalized frequently have low vitamin D levels. The deficiency often goes undetected until there are problems such as pseudofractures or electrolyte imbalances. Seasonal variations in vitamin D levels probably reflect changes in sunlight exposure.

The most potent of the vitamin D metabolites is 1,25-$(OH)_2D_3$. This metabolite increases intestinal absorption of calcium and promotes the actions of PTH on resorption of calcium and phosphate from bone. Bone resorption by the osteoclasts is increased, and bone formation by the osteoblasts is decreased; there is also an increase in acid phosphatase and a decrease in alkaline phosphatase. Intestinal absorption and bone resorption increase the amount of calcium and phosphorus available to the mineralizing surface of the bone. The role of 24,25-$(OH)_2D_3$ is less clear. There is evidence that 24,25-$(OH)_2D_3$, in conjunction with 1,25-$(OH)_2D_3$, may be involved in normal bone mineralization.

The regulation of vitamin D activity is influenced by several hormones. PTH and prolactin stimulate 1,25-$(OH)_2D_3$ production by the kidney. States of hyperparathyroidism are associated with increased levels of 1,25-$(OH)_2D_3$, and hypoparathyroidism leads to lowered levels of this metabolite. Prolactin may have an ancillary role in regulating vitamin D metabolism during pregnancy and lactation. Calcitonin inhibits 1,25-$(OH)_2D_3$ production by the kidney. In addition to hormonal influences, changes in the concentration of ions such as calcium, phosphate, hydrogen, and potassium exert an effect on 1,25-$(OH)_2D_3$ and 24,25-$(OH)_2D_3$ production. Under conditions of phosphate and calcium deprivation, 1,25-$(OH)_2D_3$ levels are increased, whereas hyperphosphatemia and hypercalcemia decrease the levels of metabolite.

In summary, the skeletal system is made up of two types of connective tissue—cartilage and bone. Cartilage is a firm, flexible type of skeletal tissue that is essential for growth before and after birth. There are three types of cartilage: hyaline, elastic, and fibrocartilage. Hyaline cartilage is the most abundant type of cartilage. It forms the costal cartilages that join the ribs to the sternum and vertebrae, many of the cartilages of the respiratory tract, the articulating surfaces of movable joints of the body, and the epiphyseal plates in growing bones.

There are two types of bone: compact bone, which forms the outer shell of a bone, and cancellous or spongy bone, which forms the interior. The endosteum is the membrane that lines the spaces of spongy bone, the marrow cavities, and the haversian canals of compact bone. The periosteum, the membrane that covers bones, contains blood vessels and acts as an anchor point for

vessels as they enter and leave the bone. Mature bone is largely made up of cylindrical units called *osteons,* formed from concentric layers or lamellae of bone matrix and surrounding a central *haversian canal.* The haversian canals contain the blood vessels and nerve supply for the osteon. There are four types of bone cells: osteocytes, or mature bone cells; osteoblasts, or bone-building cells; osteoclasts, which function in bone resorption; and osteoprogenitor cells, which differentiate into osteoblasts.

The process of bone formation and mineral metabolism involves the interplay among the actions of PTH, calcitonin, and vitamin D. PTH acts to maintain serum levels of ionized calcium; it increases the release of calcium and phosphate from bone, the conservation of calcium and elimination of phosphate by the kidney, and the intestinal reabsorption of calcium through vitamin D. Calcitonin inhibits the release of calcium from bone and increases renal elimination of calcium and phosphate, thereby serving to lower serum calcium levels. Vitamin D functions as a hormone in regulating body calcium. It increases absorption of calcium from the intestine and promotes the actions of PTH on bone.

Joints

Joints, or articulations, are places where adjacent bones or cartilages meet. Joints exhibit a variety of movements. Some joints have no movement; others allow only slight movement; and some such as the shoulder joint are freely moveable. There are two classes of joints based on their movement and the presence or absence of a joint cavity: synarthroses and synovial joints.

Skeletal Joints

- Articulations, or joints, are sites where two or more bones meet to hold the skeleton together and give it mobility.
- There are two types of joints: synarthroses, which are immovable joints, and synovial joints, which are freely movable joints.
- All limb joints are synovial diarthroidal joints, which are enclosed in a joint cavity containing synovial fluid.
- The articulating surfaces of synovial joints are covered with a layer of avascular cartilage that relies on oxygen and nutrients contained in the synovial fluid.
- Regeneration of articular cartilage of synovial joints is slow, and healing of injuries often is slow and unsatisfactory.

Synarthroses

Synarthroses are joints that lack a joint cavity and move a little or not at all. There are three types of synarthroses: synostoses, synchondroses, and syndesmoses. *Synostoses* are nonmovable joints in which the surfaces of the bones are joined by dense connective tissue or bone. The bones of the skull are joined by synostoses. They are joined by dense connective tissue in children and young adults and by bone in older persons. *Synchondroses* are joints in which bones are connected by hyaline cartilage and have limited motion. The ribs are attached to the sternum by this type of joint. *Syndesmoses* permit a certain amount of movement; they are separated by a fibrous disk and joined by interosseous ligaments. The symphysis pubis of the pelvis and the vertebral bodies joined by intervertebral disks are examples of syndesmoses.

Synovial (Diarthrodial) Joints

Synovial or *diarthrodial joints* are freely moveable joints in which the articulating bone ends are separated by a joint cavity containing synovial fluid. Most joints in the body are of this type. Although they are classified as freely movable, their movements range from those of *planar joints* with almost no movement (e.g., vertebrocostal joint), to *hinge joints* with angular movement in one plane (e.g., interphalangeal, knee, and ankle joint), to the *ball and socket joints* with movement in all directions (e.g., shoulder or hip joint).

All synovial joints are covered with articular cartilage, a feature that allows the surfaces of these joints to slide freely past each other during movement. The articular cartilage, which is typically hyaline cartilage, is unique in that its free surface is not covered with perichondrium. It has only a peripheral rim of perichondrium, and calcification of the portion of cartilage abutting the bone may limit or preclude diffusion from blood vessels supplying the subchondral bone. Regeneration of most cartilage is slow; it is accomplished primarily by growth that requires the activity of perichondrium cells.

In synovial joints, the articulating ends of the bones are not connected directly but are indirectly linked by a strong fibrous capsule (i.e., joint capsule) that surrounds the joint and is continuous with the periosteum (Fig. 42-6). The joint capsule consists of two layers: an outer fibrous layer and an inner membrane, the *synovium*. The outer fibrous layer of the capsule supports the joint and helps to hold the bones in place. Additional support is provided by ligaments that extend between the bones and by tendons that attach to muscles supplying the joint. The synovium secretes a slippery fluid with the consistency of egg white called *synovial fluid*. In addition to supplying nutrients and oxygen to the chondrocytes in the articular cartilage, this fluid serves as a lubricant for the joint. Moreover, macrophages in the synovial fluid act to phagocytize debris in the joint space.

Ligaments and Tendons

Ligaments and tendons are dense connective tissue structures that connect muscles and bone and support joint

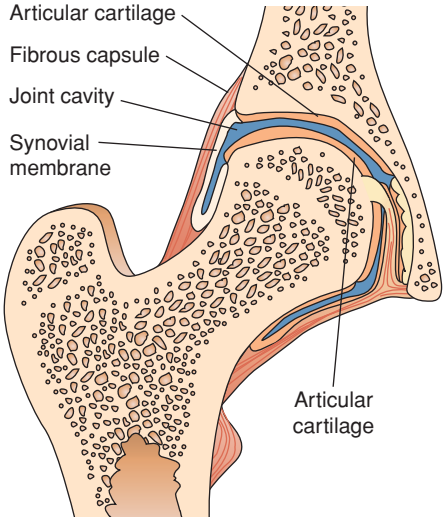


FIGURE 42-6. Synovial (diarthrodial) joint, showing the articular cartilage, fibrous joint capsule, joint cavity, and synovial membrane.

structures. The dense connective tissue found in tendons and ligaments has a limited blood supply and is composed largely of intercellular bundles of collagen fibers arranged in the same direction and plane. Collagen is an inelastic and insoluble fibrous protein. Because of its molecular configuration, collagen has great tensile strength; the breaking point of collagenous fibers found in human tendons is reached with a force of several hundred kilograms per square centimeter.

Ligaments are fibrous thickenings of the articular capsule that join one bone to its articulating mate. They vary in size and shape depending on their specific role. Although most ligaments are considered inelastic, they are pliable enough to permit movement at the joints. However, ligaments tear rather than stretch when exposed to excess stress. Torn ligaments are extremely painful and accompanied by local swelling.

Tendons, which attach skeletal muscles to bone, are relatively inextensible because of their richness in collagen fibers. The intercellular bands of collagen fibers aggregate into bundles that are enveloped by loose connective tissue, blood vessels, and nerves. Tendons that may rub against bone or other friction-generating surfaces are enclosed in double-layered sheaths. An outer connective tissue tube is attached to the structures surrounding the tendon, and an inner sheath encloses the tendon and is attached to it. The space between the inner and outer sheath is filled with a fluid similar to synovial fluid. Overuse can result in *tendonitis* or inflammation of the tendon.

Joint Vasculature and Innervation

All the tissues of synovial joints, except the surfaces of the articulating cartilage, receive nourishment either directly or indirectly from blood vessels. The articulating areas are nourished indirectly by the synovial fluid that is distributed over the surface of the articular cartilage.

The blood supply to a joint arises from blood vessels that enter the subchondral bone at or near the attachment of the joint capsule and form an arterial circle around the joint. The synovial membrane has a rich blood supply, and constituents of plasma diffuse rapidly between these vessels and the joint cavity. Because many of the capillaries are near the surface of the synovium, blood may escape into the synovial fluid after relatively minor injuries. Healing and repair of the synovial membrane usually are rapid and complete. This is important because synovial tissue is injured in many surgical procedures that involve the joint.

The nerve supply to joints is provided by the same nerve trunks that supply the muscles that move the joints. These nerve trunks also supply the skin over the joints. As a rule, each joint of an extremity is innervated by all the peripheral nerves that cross the articulation; this accounts for the referral of pain from one joint to another. For example, hip pain may be perceived as pain in the knee.

The synovial membrane is innervated only by autonomic fibers that control blood flow. It is relatively free of pain fibers, as evidenced by the fact that surgical procedures on the joint are often done under local anesthesia. The joint capsule and the ligaments have pain receptors; these receptors are more easily stimulated by stretching and twisting than are other joint structures. Pain arising from the capsule tends to be diffuse and poorly localized.

The tendons and ligaments of the joint capsule are sensitive to position and movement, particularly stretching and twisting. These structures are supplied by the large sensory nerve fibers that form proprioceptor endings for the deep tendon reflex (see Chapter 36). The proprioceptors function reflexively to adjust the tension of the muscles that support the joint and are particularly important in maintaining muscular support for the joint. For example, when a weight is lifted, there is a proprioceptor-mediated reflex contraction and relaxation of appropriate muscle groups to support the joint and protect the joint capsule and other joint structures. Loss of proprioception and reflex control of muscular support leads to destructive changes in the joint.

Bursae and Tendon Sheaths

In some diarthrotic joints, the synovial membrane forms closed sacs that are not part of the joint. These sacs, called *bursae,* contain synovial fluid. Their purpose is to prevent friction on a tendon. Bursae occur in areas where pressure is exerted because of close approximation of joint structures (Fig. 42-7). Such conditions occur when tendons are deflected over bone or where skin must move freely over bony tissue. Bursae may become injured or inflamed, causing discomfort, swelling, and limitation in movement of the involved area.

In addition to bursae, structures called tendon sheaths also reduce friction at joints. Tendon sheaths are tube-like bursae that wrap around tendons where there is considerable friction. This occurs where tendons pass through synovial cavities, such as the tendon of the

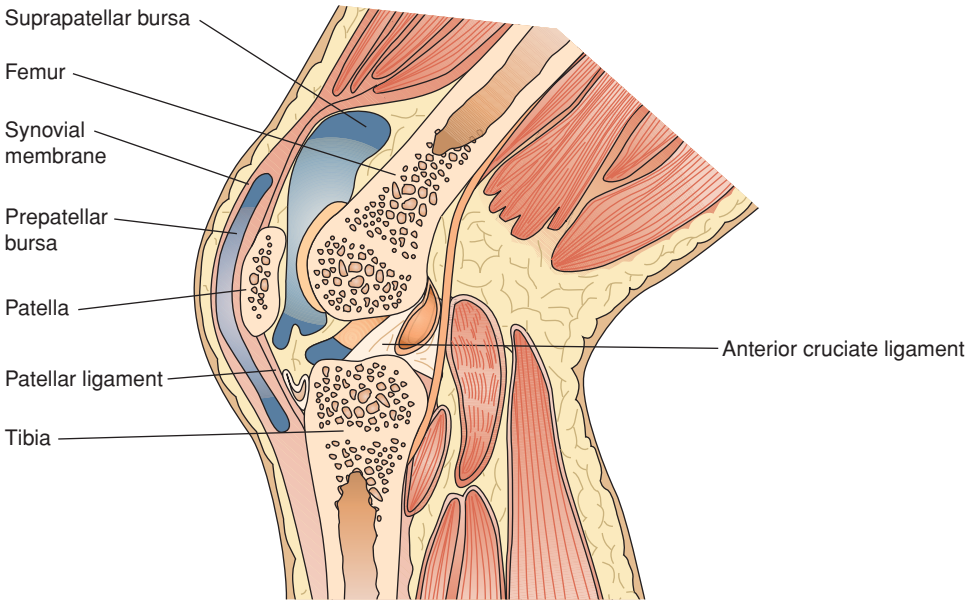


FIGURE 42-7. Sagittal section of knee joint, showing prepatellar and suprapatellar bursa.

biceps brachii muscle at the shoulder joint. Similar areas of friction are found at the wrist and ankle, where many tendons come together in a confined space.

Intra-Articular Menisci

Intra-articular menisci are fibrocartilage structures that develop from portions of the articular disk that occupied the space between articular cartilage surfaces during fetal development. Menisci may extend through the joint, separating it into two separate cavities, as in the sternoclavicular joint, or they may extend partway through the joint and have a free inner border, as at the lateral and medial articular surfaces of the knee. The menisci of the knee joint may be torn as the result of an injury (see Chapter 43).

In summary, joints or articulations are areas where two or more bones meet. Synarthroses are joints in which bones are joined together by fibrous tissue, cartilage, or bone; they lack a joint cavity and have little or no movement. Synovial or diarthrodial joints are freely movable. The surfaces of the articulating ends of bones in synovial joints are covered with a thin layer of articular cartilage, and they are enclosed in a fibrous joint capsule. The joint capsule consists of two layers: an outer fibrous layer and an inner membrane, the synovium. The synovial fluid, which is secreted by the synovium into the joint capsule, acts as a lubricant and facilitates movement of the joint's articulating surfaces. Tendons and ligaments are dense connective tissue structures that connect muscles and bones. Bursae, which are closed sacs containing synovial fluid, prevent friction in areas where tendons are deflected over bone or where skin must move freely over bony tissue. Menisci are fibrocartilaginous structures that develop from portions of the articular disk that occupied the space between articular cartilage surfaces during fetal development. The menisci may have a free inner border, or they may extend through the joint, separating it into two cavities.

REVIEW EXERCISES

1. Hyaline cartilage degenerates when the chondrocytes become metabolically inactive and die, causing the matrix to calcify and be replaced by bone.

A. Explain how this process can contribute to normal skeletal growth during childhood and adolescence, but cause joint pain and immobility when it occurs during adulthood.

2. Persons with end-stage kidney disease have a deficiency of activated vitamin D.

A. Explain why this occurs and what effect it would have on their bones.

3. Recent studies have revealed that estrogen deficiency as well as normal aging may produce a decrease in osteoblast activity.

A. Explain how this would contribute to a disruption in bone remodeling and the development of osteoporosis.

4. Often pain from injury to the knee is experienced as pain in the hip.

A. Explain why this might occur.

BIBLIOGRAPHY

Cohen S. (2006). Role of RANK ligand in normal and pathologic bone remodeling and therapeutic potential of novel inhibitory molecules in musculoskeletal disease. *Arthritis & Rheumatism* 55(1), 15–18.

Guyton A.C., Hall J.E. (2006). *Textbook of medical physiology* (11th ed., pp. 980–989). Philadelphia: Elsevier Saunders.

Hoch B.L., Klein M.J., Schiller A.L. (2008). Bones and joints. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1084–1092). Philadelphia: Lippincott Williams & Wilkins.

Hofbauer L.C., Schoppet M. (2004). Clinical implications of osteoprotegrin/RANKL/RANK system for bone and vascular disease. *Journal of the American Medical Association* 292(4), 490–495.

Holick M.F. (2007). Vitamin D deficiency. *New England Journal of Medicine* 357(3), 266–281.

Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* (5th ed., pp. 16–30). Philadelphia: Lippincott Williams & Wilkins.

Moore K.L., Persaud T.V.N. (2003). *The developing human: Clinically oriented embryology* (7th ed., pp. 381–399). Philadelphia: Saunders.

Rogers A., Eastell R. (2005). Review: Circulating osteoprotegerin and receptor activator for nuclear factor κB ligand: Clinical utility in metabolic bone disease assessment. *Journal of Clinical Endocrinology and Metabolism* 90, 6323–6331.

Rosenberg A. (2010). Bones, joints, and soft tissue tumors. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1205–1210). Philadelphia: Elsevier Saunders.

Ross M.H., Pawlina W. (2006). *Histology* (5th ed., pp. 146–237). Philadelphia: Lippincott Williams & Wilkins.

Seeman E., Delmas P.D. (2006). Bone quality—The material and structural basis of bone strength and fragility. *New England Journal of Medicine* 344(21), 2250–2261.

Vega D., Maalouf N.M., Sakhaee K. (2007). The role of receptor activator of nuclear factor-κB (Rank)/Rank ligand/osteoprotegerin: Clinical implications. *Journal of Clinical Endocrinology and Metabolism* 92(12), 4514–4521.

Injury and Trauma of Musculoskeletal Structures
Sports-Related Injuries
Soft Tissue Injuries
Joint (Musculotendinous) Injuries
Strains and Sprains
Dislocations
Shoulder and Rotator Cuff Injuries
Knee Injuries
Hip Injuries
Fractures
Classification
Manifestations
Diagnosis and Treatment
Bone Healing
Complications of Fractures and Other Injuries
Bone Infections and Osteonecrosis
Infections—Osteomyelitis
Pyogenic Osteomyelitis
Tuberculosis Osteomyelitis
Osteonecrosis
Neoplasms
Benign Bone Tumors
Malignant Bone Tumors
Osteosarcoma
Chondrosarcoma
Ewing Sarcoma
Metastatic Bone Disease
Skeletal Disorders in Children
Variations of Normal Growth and Development
Torsional and Angular Deformities
Genu Varum and Genu Valgum
Hereditary and Congenital Disorders
Osteogenesis Imperfecta
Developmental Dysplasia of the Hip
Congenital Clubfoot
Juvenile Osteochondroses
Legg-Calvé-Perthes Disease
Osgood-Schlatter Disease
Slipped Capital Femoral Epiphysis
Scoliosis
Congenital Scoliosis
Neuromuscular Scoliosis
Idiopathic Scoliosis

Chapter 43

Disorders of the Skeletal System: Trauma, Infections, Neoplasms, and Childhood Disorders

The musculoskeletal system includes the bones, joints, and muscles of the body together with associated structures such as ligaments and tendons. This system, which constitutes more than 70% of the body, is subject to a large number of disorders. These disorders affect persons in all age groups and walks of life and are a major cause of pain and disability. The main discussion in this chapter focuses on injuries, infections, necrosis, and neoplasms of the musculoskeletal system. At the end of the chapter, disorders of skeletal growth and development in children are discussed.

Injury and Trauma of Musculoskeletal Structures

A broad spectrum of musculoskeletal injuries results from numerous physical forces, including blunt tissue trauma, disruption of tendons and ligaments, and fractures of bony structures. Many of the forces that cause these injuries are typical for a particular age group, activity, or environmental setting.[1] The most common causes of childhood injuries are falls, bicycle-related injuries, and sports injuries. Trauma resulting from high-speed motor vehicle accidents is ranked as the number one killer of adults younger than 45 years of age. Falls are the most common cause of injury in people 65 years of age and older, with fractures of the hip and proximal humerus particularly common in this age group.

Sports-Related Injuries

Sports and athletic activities are particularly common causes of acute and overuse injuries of the musculoskeletal system. Acute injuries are caused by sudden trauma and include injuries to soft tissues (contusion, strains, and sprains) and to bone (fractures). Overuse injuries have been described as chronic injuries, including tendinopathies, stress fractures, compartment syndrome, and shin splints, that result from constant high levels of physiologic stress without sufficient recovery time.[2–4] They commonly occur in the elbow ("little league elbow" or "tennis elbow") and in tissue where tendons attach to the bone, such as the heel, knee, hip, and shoulder. Contact sports pose a greater threat for injury to the neck, spine, and growth plates in children and adolescents, who have not yet reached maturity. Injuries can often be prevented by proper training, use of safety equipment, and limiting the level of competition according to skill and size rather than chronologic age. Adequate warm-up time, hydration, and proper nutrition are also key factors in injury prevention.

Soft Tissue Injuries

Most skeletal injuries are accompanied by soft tissue (muscle, tendon, or ligament) injuries. These injuries include contusions and hematomas. They are discussed here because of their association with musculoskeletal injuries.

A contusion is an injury, or *bruise,* that results from direct trauma and is usually caused by striking a body part against a hard object.[5] Although the resulting disability is usually minor, some contusions can be quite painful. Muscle bruises are common in all athletic events, even the so-called noncontact sports. The thigh and upper portion of the arm are the most commonly involved. In contusions, the skin overlying the injury remains intact while the injured tissue undergoes a well-defined sequence of events including microscopic rupture of blood vessels and damage to muscle cells, swelling, and inflammation. The area often becomes ecchymotic (i.e., black and blue) because of local hemorrhage; later, the discoloration gradually changes to brown and then to yellow as the blood is reabsorbed. A large area of local hemorrhage is called a *hematoma*. Hematomas cause pain as blood accumulates and exerts pressure on nerve endings. The pain increases with movement or when pressure is applied to the area. The pain and swelling of a hematoma take longer to subside than those accompanying a contusion.

The treatment for a contusion and a hematoma consists of elevating the affected part and applying cold for the first 24 hours to reduce the bleeding into the area. A compression wrapping is sometimes helpful in the early stages. Reinjury is avoided by appropriately protecting the area and allowing for complete healing to occur before returning to activities.

Joint Injuries

- Joints are the weakest part of the skeletal system and common sites for injury due to mechanical overloading or forcible twisting or stretching.
- Injury can include damage to the tendons, which connect muscle to bone; ligaments, which hold bones together; or the cartilage that covers the articular surface.
- Healing of the dense connective tissue involved in joint injuries requires time to restore the structures so that they are strong enough to withstand the forces imposed on the joint. Ligamentous injuries may require surgical intervention with approximation of many fibrous strands to facilitate healing.
- Injuries involving the articular cartilage may predispose to later joint disease.

Joint (Musculotendinous) Injuries

Joints, or articulations, are sites where two or more bones meet. Joints (i.e., diarthrodial) are supported by tough bundles of collagenous fibers called *ligaments* that attach to the joint capsule and hold the articular ends of bones together, and by *tendons* that join muscles to the periosteum of the articulating bones (see Chapter 42). Joint injuries usually involve mechanical overloading or forcible twisting or stretching.

Strains and Sprains

Strains and sprains are both musculoskeletal injuries, but they differ in terms of the tissue that is affected.[5] Strains involve muscles, or more precisely the muscle–tendon unit. Sprains involve the supporting ligaments of a joint.

A *strain* is a stretching or partial tear in a muscle or a muscle–tendon unit. Strains commonly result from sudden stretch of a muscle that is actively contracting. Although there usually is no external evidence of a specific injury, an inflammatory response develops at the injured site, followed by fibrous tissue replacement of the damaged muscle fibers. Muscle strains are usually characterized by pain, stiffness, swelling, and local tenderness. Pain is increased with stretching of the muscle group. Strains can occur at any age, but are more common in middle-aged and older adults. With aging, the collagen fibers in the muscle–tendon unit change; as result, muscles have decreased elasticity and are more susceptible to injury. Common sites of muscle strains are the lower back and the cervical region of the spine. The elbow and the shoulder are also supported by muscle–tendon units that are subject to strains. Strains of muscle units around the hip, hamstring, and quadriceps are commonly associated with athletic activities. Proper warm-up exercises increase the flexibility of muscle–tendon units and help prevent these types of injuries.

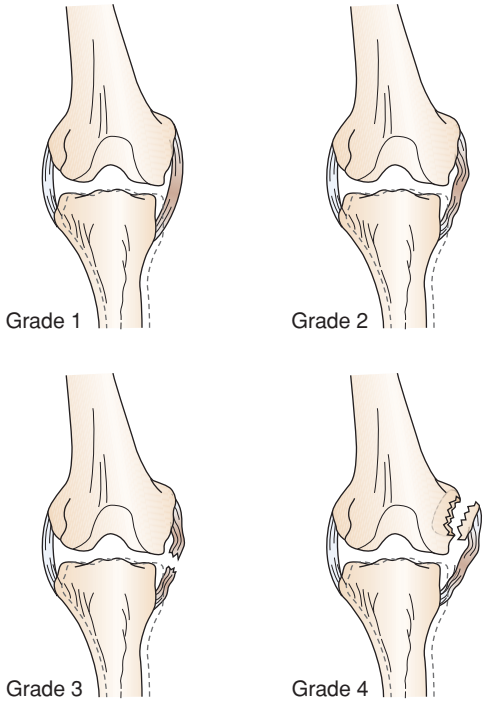


FIGURE 43-1. Degrees of sprain on the medial side of the right knee: grade 1, mild sprain of the medial collateral ligament; grade 2, moderate sprain with hematoma formation; grade 3, severe sprain with total disruption of the ligament; and grade 4, severe sprain with avulsion of the medial femoral condyle at the insertion of the medial collateral ligament.

A *sprain,* which involves the joint ligaments or capsule surrounding the joint, resembles a strain, but the pain and swelling subside more slowly. It usually is caused by abnormal or excessive movement of a joint. With a sprain, the ligaments may be incompletely torn or, as in a severe sprain, completely torn or ruptured (Fig. 43-1). The signs of sprain are pain, rapid swelling, discoloration, and limitation of function. Any joint may be sprained, but the ankle joint is most commonly involved, especially in high-risk sports such as basketball. Most ankle sprains occur in the lateral ankle when the foot is turned inward under a person, forcing the ankle into inversion beyond its structural limits. Other common sites of sprain are the knee (the collateral ligament and anterior cruciate ligament) and elbow (the ulnar side). As with a strain, the soft tissue injury that occurs with a sprain is not evident on the radiograph. However, occasionally a chip of bone is evident when the entire ligament, including part of its bony attachment, has been ruptured or torn from the bone.

The treatment of muscle strains and ligamentous sprains involves rest, ice, compression, and elevation (RICE).[5] For an injured extremity, such as the ankle, elevation of the part followed by local application of cold may be sufficient. Compression, accomplished through the use of adhesive wraps, helps to reduce swelling and provide support. Immobilization may be required for severe sprains, especially those severe enough to warrant surgical repair. Immobilization for a muscle strain is continued until the pain and swelling have subsided. In a sprain, the affected joint is immobilized for several weeks. Immobilization may be followed by graded active exercises. Early diagnosis, treatment, and rehabilitation are essential in preventing chronic ligamentous instability.

Healing of the dense connective tissues in tendons and ligaments is similar to that of other soft tissues. If properly treated, injuries usually heal with the restoration of the original tensile strength. Repair is accomplished by fibroblasts from the inner tendon sheath or, if the tendon has no sheath, from the loose connective tissue that surrounds the tendon.[6,7] Capillaries infiltrate the injured area during the initial healing process and supply the fibroblasts with the materials they need to produce large amounts of collagen. Formation of the long collagen bundles occurs within the first 2 weeks, and although tensile strength increases steadily thereafter, it is not sufficient to permit strong tendon pulls for 6 to 8 weeks.[6] During the healing process, there is a danger that muscle contraction will pull the injured ends apart, causing the tendon to heal in the lengthened position. There is also a danger that adhesions will develop in areas where tendons pass through fibrous channels, such as in the distal palm of the hands, rendering the tendon useless.

Dislocations

A dislocation is the abnormal displacement of the articulating surfaces of a joint such that surfaces are not in contact. It usually follows a severe trauma that disrupts the holding ligaments. Dislocations are seen most often in the shoulder and acromioclavicular joints. A *subluxation* is a partial dislocation in which the bone ends in the joint are still in partial contact with each other.

Dislocations can be congenital, traumatic, or pathologic. Congenital dislocations occur in the hip or knee. Traumatic dislocations occur after falls, blows, or rotational injuries. For example, auto accidents often cause dislocations of the hip and accompanying acetabular fractures because of the direction of impact. In the shoulder and patella, dislocations may become recurrent, especially in athletes. They recur with the same motion but require less and less force each time. Less common sites of dislocation, seen mainly in young adults, are the wrist and midtarsal region. They usually are the result of direct force, such as a fall on an outstretched hand. Pathologic dislocation in the hip is a late complication of infection, rheumatoid arthritis, paralysis, and neuromuscular diseases.

Diagnosis of a dislocation is based on history, physical examination, and radiologic findings. The symptoms are pain, deformity, and limited movement. The treatment depends on the site, mechanism of injury, and associated injuries such as fractures. Dislocations that do not reduce spontaneously usually require manipulation or surgical repair. Immobilization is necessary for several weeks after reduction of a dislocation to allow healing of the joint structures. In dislocations affecting the knee, alternatives to surgery are isometric quadriceps-strengthening exercises and a temporary brace.

Shoulder and Rotator Cuff Injuries

The shoulder is a complex series of joints that produce extraordinary range of motion. The extreme mobility is accomplished at the expense of instability. This instability, combined with its relatively exposed position, makes the shoulder extremely vulnerable to injuries including fractures, dislocations, and degenerative processes such as rotator cuff disorders.[5,8,9]

The shoulder is composed of three bones: the scapula, the clavicle, and the humerus (Fig. 43-2). The scapula is a thin bone that articulates widely and closely with the chest wall. It also articulates with the humerus by way of its small, shallow glenoid cavity and with the clavicle at the acromion process. The clavicle, which is held firmly in place by ligaments at the sternum and acromion, forms the only bony connection between the axial skeleton and the upper extremity. Clavicle fractures are among the most common fractures of childhood.[9] The typical mechanism of fracture is a fall on the lateral shoulder, or less commonly by a direct blow or by falling on an outstretched arm. Most clavicle fractures are treated nonoperatively, with either a simple arm sling or figure-of-eight clavicle strap.[5,8]

Three articulations form the shoulder joint—the acromioclavicular joint, which joins the clavicle to the acromion of the scapula; the glenohumeral joint, which connects the head of the humerus to the relatively shallow glenoid cavity in the scapula; and the sternoclavicular joint, which joins the sternum to the clavicle. The stability of these joints is provided by a series of muscles and tendons. The acromioclavicular joint is a common site of sprains in athletes and physically active persons. The classic cause of an acromioclavicular joint injury is a direct blow to the acromion with the humerus in an adducted position. This force drives the acromion medially and inferiorly. Acromioclavicular joint injuries also may be caused by indirect trauma, such as falling on an outstretched arm or elbow. The glenohumeral joint is one of the most commonly dislocated joints. It is also the joint most likely to develop problems with instability. Most acute dislocations involve anterior displacement of the humeral head with respect to the glenoid cavity, the result of the shoulder being abducted and forcefully extended and rotated. Other mechanisms include a fall on an outstretched arm or a blow to the posterior shoulder.

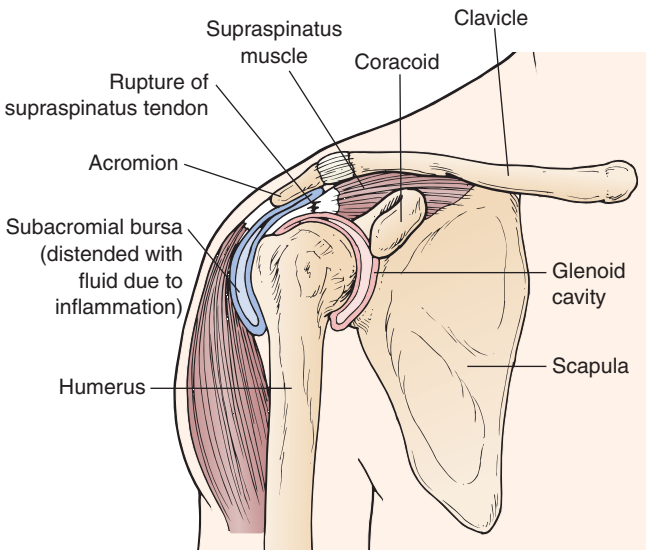


FIGURE 43-2. Structures of the glenohumeral shoulder joint, showing the location of common rotator cuff injuries. The supraspinatus muscle is the most commonly injured part of the rotator cuff. (Adapted from Moore K.L., Dalley A.F. (2006). *Clinically oriented anatomy* [5th ed., p. 763]. Philadelphia: Lippincott Williams & Wilkins.)

Movement of the shoulder results from the coordinated efforts the muscles of the rotator cuff: the supraspinous, teres minor, infraspinatus, and subscapularis.[5,8,9] These muscle and their musculotendinous attachments form a cover around the head of the humerus and function to rotate the arm and stabilize the humoral head against the glenoid. The rotator cuff muscles are separated from the overlying "coracoacromial arch" by the subdeltoid and subcoracoid bursae. Disorders of the rotator cuff, such as tendinitis, subacromial bursitis, and partial and complete tears, account for a substantial majority of shoulder problems (Fig. 43-2). Rotator cuff injuries can result from excessive use, a direct blow, or stretch injury, usually involving throwing or swinging, as with baseball pitchers or tennis players. While rotator cuff injuries sometimes occur with acute injury, most are the result of a combination of factors, including altered blood supply to the tendons, repeated mechanical insult as the tendon passes under the coracoacromial arch, and age-related degeneration. Repetitive overhead throwing, which produces significant stress on the glenohumeral complex of the rotator cuff, is a common cause of rotator cuff tendinitis. Full-thickness tears are more common in persons older than 40 years of age, although they can occur in athletes.[5,8] Tears generally originate in the supraspinous tendon and may progress posteriorly and anteriorly. Inflammation of the subacromial bursa and underlying rotator cuff tendons is a common cause of impingement and shoulder pain in middle-aged persons. The major clinical features of rotator cuff disorders are pain (especially at night), tenderness, and occasionally muscle atrophy. Pain and impingement may be noted when motions of the arm squeeze and pinch cuff tendons between the humerus and the overlying arch. With rotator cuff tears there may be difficulty abducting and rotating the arm.

Several physical examination maneuvers, including assessment of active and passive range of motion, are used to define shoulder pathology. The history and mechanism of injury are important. In addition to standard radiographs, an arthrogram or magnetic resonance imaging (MRI) scan may be obtained. Arthroscopic examination under anesthesia may be done for diagnostic purposes. Conservative treatment with anti-inflammatory agents, corticosteroid injections, and physical therapy often is used. A period of rest is followed by a customized exercise and rehabilitation program to improve strength, flexibility, and endurance. Surgical repair may be considered for persons with an acute traumatic rotator

cuff tear or those with significant symptoms and failed rehabilitation.

Knee Injuries

The knee is a common site of injury, particularly sports-related injuries in which the knee is subjected to abnormal twisting and compression forces.[10] These forces can result in injury to the ligaments and menisci, patellar subluxation and dislocation, and the patellofemoral pain syndrome. Many knee injuries can predispose to osteoarthritis in later life.

The knee joint consists of medial and lateral, femoral and tibial condyles, and the patella (Fig. 43-3). It is essentially a round bone (femoral condyles) sitting on a flat bone (tibial condyles) with no intrinsic bony stability, and depends on its ligaments and menisci for support.[8] The most important ligaments are the medial and lateral collateral ligament along with their associated posterior capsular structures and the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL).

Ligamentous Injuries. Ligamentous injuries of the knee are among the most serious of all knee injuries. The mechanism is usually one of forceful stress against the knee when the extremity is bearing weight. A "pop" or tearing sensation along with sudden pain is often described, especially with ACL ruptures. After injury, the ability to bear weight on the extremity is often lost, and the knee becomes swollen because of hemorrhaging into the joint.

Initial treatment includes rest, ice, and use of crutches until the person is able to ambulate without a limp. A knee immobilizer or range-of-motion brace may be used for comfort until the acute pain subsides. Range-of-motion exercises are important. Definitive treatment depends on the ligaments that are involved, the person's age and activity level, and any associated injuries. Most isolated lateral ligament injuries are treated nonsurgically. Isolated ACL and PCL ruptures are generally treated nonsurgically, at least initially. Surgical reconstruction is usually required in young, active persons. Older and less active individuals may be treated with physical therapy aimed at controlling the instability. A well-constructed brace may provide an option in some persons.

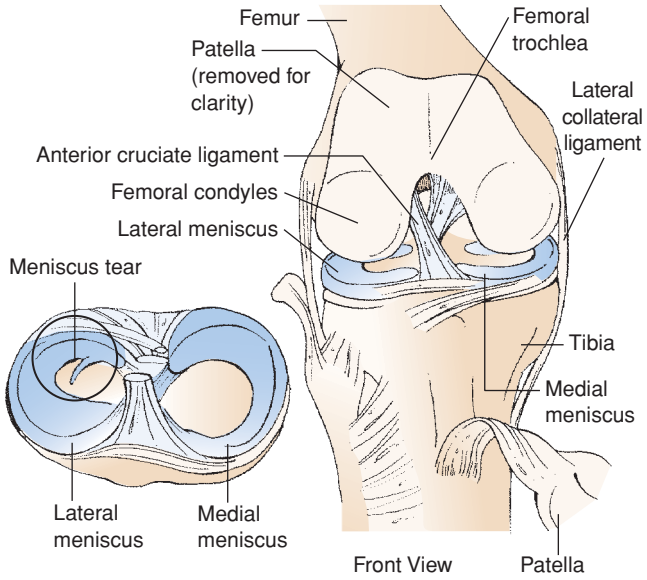


FIGURE 43-3. The knee, showing the lateral and medial meniscus (with the patella removed for clarity). *Inset* (*lower left*) shows meniscus tear.

Meniscus Injuries. The menisci are C-shaped plates of fibrocartilage that are superimposed between the condyles of the femur and tibia. There are two menisci in each knee, a lateral and medial meniscus[5,8] (see Fig. 44-3). The menisci are thicker at their external margins and taper to thin, unattached edges at their interior margin. They are firmly attached at their ends to the intercondylar area of the tibia and are supported by the coronary and transverse ligaments of the knee. The menisci play a major role in load bearing and shock absorption. They also help to stabilize the knee by deepening the tibial socket and maintaining the femur and tibia in proper position. In addition, the meniscus assists in joint lubrication and serves as a source of nutrition for articular cartilage in the knee.

Meniscus injury commonly occurs as the result of a rotational injury from a sudden or sharp pivot or a direct blow to the knee, as in hockey, basketball, or football. It is often associated with other injuries, such as a torn ACL. The type and location of the meniscal tear are determined by the magnitude and direction of the force that acts on the knee and the position of the knee at the time of injury. Meniscus tears can be described by their appearance (e.g., parrot-beak, bucket handle) or their location (e.g., posterior horn, anterior horn). The injured knee is edematous and painful, especially with hyperflexion and hyperextension. A loose fragment may cause knee instability and locking.

Diagnosis is made by examination and confirmed by MRI. A regular radiograph may be needed to rule out osteoarthritis. Initial treatment of meniscal injuries may be conservative. The knee may be placed in a removable knee immobilizer. Isometric quadriceps exercises may be prescribed. Activity usually is restricted until complete motion is recovered. Arthroscopic meniscectomy may be performed when there is recurrent or persistent locking, recurrent effusion, or disabling pain.

There is evidence that loss of meniscal function is associated with progressive deterioration of knee function and osteoarthritic changes.[11] Damaged articular cartilage has a limited capacity to heal because of its avascular nature and inadequate mobilization of regenerative cells. Meniscal reconstruction procedures have been developed to preserve these functions before significant degenerative changes develop, thus preventing the need for a total joint replacement later in life.

Patellar Subluxation and Dislocations. Recurrent subluxation and dislocation of the patella are common injuries in young adults.[5,8] Sports such as skiing or tennis may cause stress on the patella. These sports involve

external rotation of the foot and lower leg with knee flexion, a position that exerts rotational stresses on the knee. Congenital knee variations are also a predisposing factor. There is often a sensation of the patella "popping out" when the dislocation occurs. Other complaints include the knee giving out, swelling, crepitus, stiffness, and loss of range of motion. Treatment measures include immobilization with the knee extended, bracing, administration of anti-inflammatory agents, and isometric quadriceps-strengthening exercises. Surgical intervention often is necessary.

Patellofemoral Pain Syndrome. Patellofemoral pain syndrome is the most common cause of anterior knee pain.[5,12] It is caused by imbalances in the forces controlling movement of the patella during knee flexion and extension, particularly with overloading of the joint. The patellofemoral joint is composed of the patella and central groove (trochlea) in the proximal femur (see Fig. 43-3). Stability of the joint involves dynamic and static stabilizers, which control the movement of the patella within the trochlea, referred to as *patellar tracking*.[12] The disorder, also called "runner's knee," occurs most frequently in young adults, and is often associated with jogging, volleyball, and basketball. Persons with this disorder typically complain of pain, particularly when climbing stairs or sitting with the knees bent. The pain is usually difficult to localize and swelling of the knee is not characteristic of the disorder. Occasionally, the person experiences weakness of the knee.

Diagnosis is usually based on history and physical examination. Radiography may be used as an adjunct to the history and physical. Treatment consists of relative rest and physical therapy.[12] Reduction of loading of the patellofemoral joint and surrounding tissues is the first step to reduce pain. Inappropriate or excessively worn footwear may contribute to the problem and need to be replaced. Although a variety of braces, sleeves, and straps have been used in treatment of the disorder, studies have found no significant benefit from their use.[12]

Hip Injuries

The hip is a ball-and-socket joint in which the femoral head articulates deeply in the acetabulum.[8] The proximal part of the femur consists of a head, neck, and greater trochanter. The vascular anatomy of the femoral head, which receives its main blood supply from the lateral and medial circumflex femoral arteries and the obturator artery, is of critical importance in any disorder of the hip (Fig. 43-4). Disease or injuries that compromise blood flow may damage the viability of the femoral head and lead to avascular necrosis or osteonecrosis.

Dislocations of the Hip. Dislocations of the hip in which the femoral head is displaced from the acetabulum are commonly the result of severe trauma and are usually posterior in direction. They typically result from the knee being struck while the hip and knee are in a flexed position.[8] This force drives the femoral head out of the acetabulum posteriorly. Anterior dislocations are less common and usually result from a force on the knee with the thigh abducted.

Hip dislocation is an emergency.[5,8] The disorder is typically accompanied by severe pain and inability to move the lower extremity. In the dislocated position, great tension is placed on the blood supply to the femoral head and avascular necrosis may result. To prevent this complication, early reduction is indicated. Weight bearing is usually limited after reduction to prevent the dislocation from reoccurring and allow healing to occur.

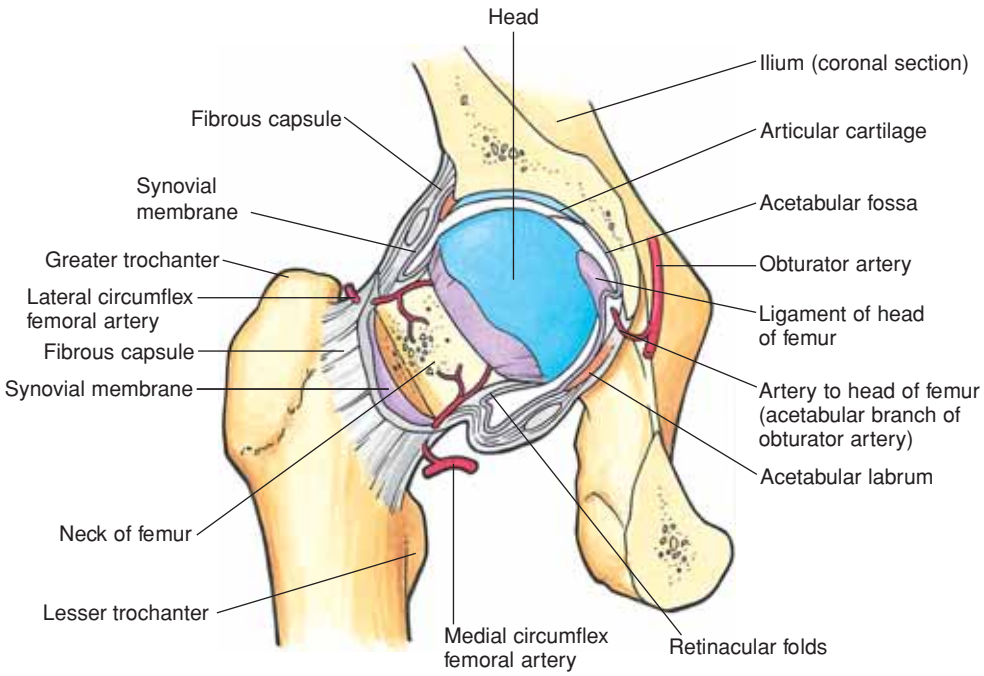


FIGURE 43-4. Blood supply of the head and neck of the femur (anterior view). A section of the bone has been removed from the femoral neck. (Modified from Moore K., Agur A.M.R. [2002]. *Essential clinical anatomy* [2nd ed., p. 381]. Philadelphia: Lippincott Williams & Wilkins.)

Fractures of the Hip. Hip fracture is a major public health problem in the Western world, particularly among the elderly. It results in hospitalization, disability, and loss of independence. The incidence of hip fractures increases with age, doubling for each decade after 50 years of age, and is two to three times higher in women than men.[13] Risk factors for hip fracture include physical inactivity, excessive consumption of alcohol, use of certain psychotropic drugs, residence in an institution, visual impairment, and dementia.[13] Osteoporosis is an important contributing factor.

Most hip fractures result from falls. Occasionally, the person may actually fracture the hip before falling, the fracture representing the completion of an incomplete fracture. The characteristics of the fall (the direction, site of impact, and protective response) and environmental factors are recognized as important influences for the risk of hip fracture from a fall.

A hip fracture is usually a fracture of the proximal femur. Such fractures are commonly categorized according to the anatomic site in which they occur.[13,14] Femoral neck fractures are located in the area distal to the femoral head but proximal to the greater and lesser trochanters and are considered intracapsular because they are located within the capsule of the hip joint. Intertrochanteric fractures occur in the metaphyseal region between the greater and lesser trochanter. Subtrochanteric fractures are those that occur just below the greater trochanter. Femoral neck and intertrochanteric fractures account for over 90% of hip fractures.[14]

The location of a hip fracture is important in terms of blood flow to the femoral head, which receives its blood supply from vessels that course proximally up the femoral neck (see Fig. 43-4). Subtrochanteric and intertrochanteric fractures that occur distal to these vessels do not usually disturb the blood supply to the femoral head, whereas femoral neck fractures, particularly those involving marked displacement, often disrupt the blood supply to the femoral head and are therefore associated with an increased incidence of complications (nonunion and avascular necrosis).

Most hip fractures are diagnosed based on clinical findings and standard radiographs. A bone scan or MRI may be done when the radiograph is negative but the clinical findings support the diagnosis of hip fracture.

The primary goal of treatment for a hip fracture is a return to the preinjury level of function as soon as possible.[8] Undisplaced or impacted fractures have a better prognosis in terms of healing and are often treated nonoperatively or by simple internal fixation to provide stability. Displaced intracapsular fractures in the elderly are usually best treated by surgical hip replacement and early mobilization. Young, healthy people are treated by reduction of the fracture (if needed) and internal fixation. This method allows for preservation of the femoral head, which in this age group is desirable because the long-term results are better than with prosthetic replacement. Intertrochanteric fractures are usually treated with open reduction and internal fixation. This allows for early ambulation by eliminating pain at the fracture site.

Fractures

A fracture represents a disruption in the continuity of a bone.[8,15,16] Normal bone can withstand considerable compression and shearing forces and, to a lesser extent, tension forces. A fracture occurs when more stress is placed on the bone than it is able to absorb. Grouped according to cause, fractures can be divided into three major categories: (1) fractures caused by sudden injury, (2) fatigue stress fractures, and (3) pathologic stress fractures. The most common fractures are those resulting from sudden injury. The force causing the fracture may be direct, such as a fall or blow, or indirect, such as a massive muscle contraction or trauma transmitted along the bone. For example, the head of the radius or clavicle can be fractured by the indirect forces that result from falling on an outstretched hand.

Stress fractures are incomplete fractures.[8] They may be described as either fatigue or pathologic fractures. *Fatigue stress fractures* occur when excess stress is applied to normal bone. They may occur in any weight-bearing bone, but they are most common in the metatarsal, neck of the femur, calcaneus, tibia, fibula, and pelvis. Fatigue stress fractures typically occur in unconditioned athletes. Clinically, a history of unusual stress with subsequent pain over a bone is common in fatigue fractures. *Stress fractures* in the tibia may be confused with "shin splints," a nonspecific term for pain in the lower leg from overuse in walking and running, because they frequently are not apparent on x-ray films until 2 weeks after the onset of symptoms.[3,4]

Pathologic stress fractures occur when normal stress is applied to bones that have been weakened by disease or tumors.[8] Fractures of this type may occur spontaneously with little or no stress. The underlying disease state can be local, as with infections, cysts, or tumors, or it can be generalized, as in osteoporosis, Paget disease, or disseminated tumors.

Classification

Fractures usually are classified according to location, type, and direction or pattern of the fracture line[14–16] (Fig. 43-5). A fracture of the long bone is described in relation to its position in the bone—proximal, midshaft, and distal. Other descriptions are used when the fracture affects the head or neck of a bone, involves a joint, or is near a prominence such as a condyle or malleolus.

The type of fracture is determined by its communication with the external environment, the degree of break in continuity of the bone, and the character of the fracture pieces. A fracture can be classified as open or closed. When the bone fragments have broken through the skin, the fracture is called an *open* or *compound fracture*. In a closed fracture, there is no communication with the outside skin.

The degree of a fracture is described in terms of a complete or incomplete break in the continuity of bone.[5,8] A *greenstick fracture,* which is seen in children, is an example of a partial break in bone continuity and resembles that seen when a young sapling is broken. This kind of break occurs because children's bones, especially

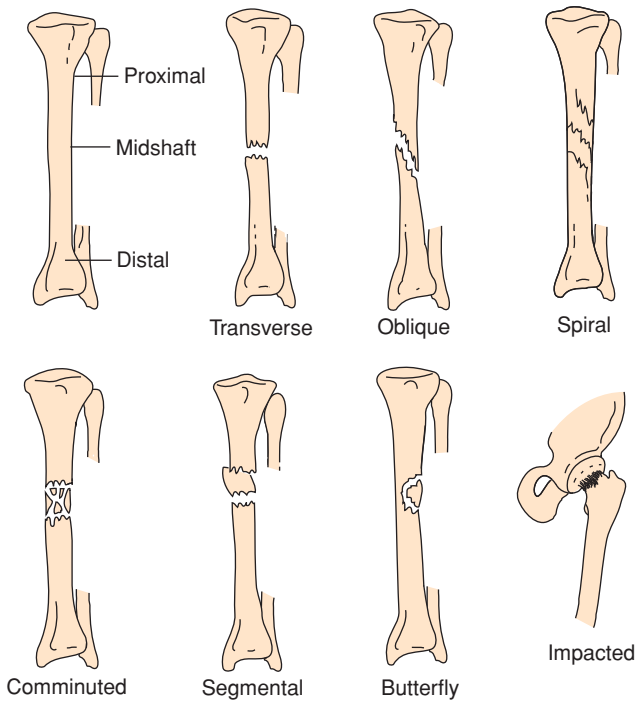


FIGURE 43-5. Classification of fractures. Fractures are classified according to location (proximal, midshaft, or distal), the direction of fracture line (transverse, oblique, spiral), and type (comminuted, segmental, butterfly, or impacted).

until approximately 10 years of age, are more resilient than the bones of adults.

The character of the fracture pieces may also be used to describe a fracture. A *comminuted fracture* has more than two pieces. A *compression fracture,* as occurs in the vertebral body, involves two bones that are crushed or squeezed together. A fracture is called *impacted* when the fracture fragments are wedged together. This type usually occurs in the humerus, often is less serious, and usually is treated without surgery.

The direction of the trauma or mechanism of injury produces a certain configuration or pattern of fracture. *Reduction* is the restoration of a fractured bone to its normal anatomic position. The pattern of a fracture indicates the nature of the trauma and provides information about the easiest method for reduction. *Transverse fractures* are caused by simple angulatory forces. A *spiral fracture* results from a twisting motion, or torque. A transverse fracture is not likely to become displaced or lose its position after it is reduced. On the other hand, spiral, oblique, and comminuted fractures often are unstable and may change position after reduction.

Manifestations

The signs and symptoms of a fracture include pain, tenderness at the site of bone disruption, swelling, loss of function, deformity of the affected part, and abnormal mobility. The deformity varies according to the type of force applied, the area of the bone involved, the type of fracture produced, and the strength and balance of the surrounding muscles.

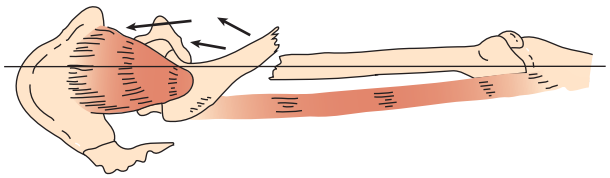


FIGURE 43-6. Displacement and overriding of fracture fragments of a long bone (femur) caused by severe muscle spasm.

In long bones, three types of deformities—angulation, shortening, and rotation—are seen. Severely angulated fracture fragments may be felt at the fracture site and often push up against the soft tissue to cause a tenting effect on the skin. Bending forces and unequal muscle pulls cause angulation. Shortening of the extremity occurs as the bone fragments slide and override each other because of the pull of the muscles on the long axis of the extremity (Fig. 43-6). Rotational deformity occurs when the fracture fragments rotate out of their normal longitudinal axis; this can result from rotational strain produced by the fracture or unequal pull by the muscles that are attached to the fracture fragments. A crepitus, or grating sound, may be heard as the bone fragments rub against each other. In the case of an open fracture, there is bleeding from the wound where the bone protrudes. Blood loss from a pelvic fracture or multiple long bone fractures can cause hypovolemic shock in a trauma victim.

Shortly after the fracture has occurred, nerve function at the fracture site may be temporarily lost. The area may become numb, and the surrounding muscles may become flaccid. This condition has been called *local shock*. During this period, which may last for a few minutes to half an hour, fractured bones may be reduced with little or no pain. After this brief period, the pain sensation returns and, with it, muscle spasms and contractions of the surrounding muscles.

Diagnosis and Treatment

Diagnosis is the first step in the care of fractures and is based on history and physical manifestations. X-ray examination is used to confirm the diagnosis and direct the treatment. The ease of diagnosis varies with the location and severity of the fracture. In the trauma patient, the presence of other, more serious injuries may make diagnosis more difficult.

Treatment depends on the general condition of the person, the presence of associated injuries, the location of the fracture and its displacement, and whether the fracture is open or closed. A *splint* is a device for immobilizing the movable fragments of a fracture. When a fracture is suspected, the injured part always should be splinted before it is moved. This is essential for preventing further injury.[8]

There are three objectives for treatment of fractures: (1) reduction of the fracture, (2) immobilization, and (3) preservation and restoration of the function of the injured part.[8] Reduction of a fracture is directed toward replacing the bone fragments to as near-normal an anatomic position as possible. This can be accomplished

by closed manipulation or surgical (open) reduction. Closed manipulation uses methods such as manual pressure and traction. Fractures are held in reduction by external or internal fixation devices. Surgical reduction involves the use of various types of hardware to accomplish internal fixation of the fracture fragments.

Immobilization prevents movement of the injured parts and is the single most important element in obtaining union of the fracture fragments. Immobilization can be accomplished through the use of external devices, such as splints, casts, external fixation devices, or traction, or by means of internal fixation devices inserted during surgical reduction of the fracture. Preservation and restoration of the function of muscles and joints is an ongoing process in the unaffected and affected extremities during the period of immobilization required for fracture healing. Exercises designed to preserve function, maintain muscle strength, and reduce joint stiffness should be started early.

Bone Healing

Bone healing occurs in a manner similar to soft tissue healing. However, it is a more complex process and takes longer. There are essentially four stages involved in bone healing: hematoma formation, fibrocartilaginous callus development, ossification, and remodeling.[15–17] The degree of response during each of these stages is in direct proportion to the extent of trauma.

Hematoma formation occurs during the first 1 to 2 days after fracture. It develops from torn blood vessels in the periosteum and adjacent muscles and soft tissue. Disruption of blood vessels also leads to death of bone cells at the fracture site. In 2 to 5 days, the hemorrhage forms a large blood clot. Neovascularization begins to occur peripheral to the blood clot. By the end of the first week, most of the clot is organized by invasion of blood vessels and early fibrosis. Hematoma formation is thought to be necessary for the initiation of the cellular events essential to bone healing.[15] As the result of hematoma formation, clotting factors remain in the injured area to initiate the formation of a fibrin meshwork, which serves as a framework for the ingrowth of fibroblasts and new capillary buds. At the same time, degranulated platelets and migrating inflammatory cells release growth factors, which stimulate osteoclast and osteoblast proliferation.[15]

The next event in fracture healing is formation of granulation tissue or *soft tissue callus*. During this stage of bone healing, fibroblasts and osteoblasts migrate into the fracture site from the nearby periosteal and endosteal membranes and begin reconstruction of bone. The fibroblasts produce collagen that spans the break and connects the broken bone ends, and some differentiate into chondrocytes that secrete collagen matrix. At about the same time, osteoblasts begin depositing bone into this matrix. After a few days, a fibrocartilage "collar" becomes evident around the fracture site. The collar edges on either side of the fracture eventually unite to form a bridge, which connects the bone fragments. The earliest bone, in the form of woven bone, begins its formation sometime after the first week. In an uncomplicated fracture, the repair tissue reaches its maximum girth at the end of the second to third week, which helps stabilize the fracture, but it is not yet strong enough for weight bearing.

Ossification represents the deposition of mineral salts into the callus. This stage usually begins during the third to fourth week of fracture healing. During this stage, mature bone gradually replaces the fibrocartilaginous callus, and the excess callus is gradually resorbed by the osteoclasts. The fracture site feels firm and immovable and appears united on the radiograph. At this point, it is usually safe to remove the cast.

Remodeling involves resorption of the excess bony callus that develops in the marrow space and encircles the external aspect of the fracture site. As the callus matures and transmits weight-bearing forces, the portions that are not stressed are resorbed. It is in this manner that the callus is reduced in size until the shape and outline of the bone have been reestablished. The medullary cavity of the bone is also restored. After this is completed, the bone usually appears as it did before the injury.

Healing Time. Healing time depends on the site of the fracture, the condition of the fracture fragments, hematoma formation, and other local and host factors. In children, fractures usually heal within 4 to 6 weeks; in adolescents, they heal within 6 to 8 weeks; and in adults, they heal within 10 to 18 weeks. The increased rate of healing among children compared with adults may be related to the increased cellularity and vascularity of the child's periosteum.[15] In general, fractures of long bones, displaced fractures, and fractures with less surface area heal more slowly. Function usually returns within 6 months after union is complete. However, return to complete function may take longer.

Impaired Bone Healing. Factors that influence bone healing are specific to the person, the type of injury sustained, and local factors that disrupt healing. Individual factors that may delay bone healing are the patient's age; current medications; debilitating diseases, such as diabetes and rheumatoid arthritis; local stress around the fracture site; circulatory problems and coagulation disorders; and poor nutrition.

Malunion is healing with deformity, angulation, or rotation that is visible on x-ray films.[18] Early and aggressive treatment, especially of the hand, can help prevent malunion and result in earlier alignment and return of function. *Delayed union* is the failure of a fracture to unite within the normal period (e.g., 20 weeks for a fracture of the tibia or femur in an adult). Intra-articular fractures (i.e., those through a joint) may heal more slowly and may eventually produce arthritis. *Nonunion* is failure to produce union and cessation of the processes of bone repair. It is seen most often in the tibia, especially with open fractures or crushing injuries. It is characterized by mobility of the fracture site and pain on weight bearing. Muscle atrophy and loss of range of motion may occur. Nonunion usually is established

TABLE 43-1 Complications of Fracture Healing

Complication	Manifestations	Contributing Factors
Delayed union	Failure of fracture to heal within predicted time as determined by x-ray	Large displaced fracture Inadequate immobilization Large hematoma Infection at fracture site Excessive loss of bone Inadequate circulation
Malunion	Deformity at fracture site Deformity or angulation on x-ray	Inadequate reduction Malalignment of fracture at time of immobilization
Nonunion	Failure of bone to heal before the process of bone repair stops Evidence on x-ray Motion at fracture site Pain on weight bearing	Inadequate reduction Mobility at fracture site Severe trauma Bone fragment separation Soft tissue between bone fragments Infection Extensive loss of bone Inadequate circulation Malignancy Bone necrosis Noncompliance with restrictions

6 to 12 months after the time of the fracture.[18] The complications of fracture healing are summarized in Table 43-1.

Treatment methods for impaired bone healing encompass surgical interventions, including bone grafts, bracing, external fixation, or electrical stimulation of the bone ends. Electrical stimulation is thought to stimulate the osteoblasts to lay down a network of bone. Three types of commercial bone growth stimulators are available: a noninvasive model, which is placed outside the cast; a semi-invasive model, in which pins are inserted around the fracture site; and a totally implantable type, in which a cathode coil is wound around the bone at the fracture site and operated by a battery pack implanted under the skin.[8]

Complications of Fractures and Other Injuries

The complications of fractures and other orthopedic injuries are associated with loss of skeletal continuity, injury from bone fragments, pressure from swelling and hemorrhage (e.g., fracture blisters, compartment syndrome), or development of fat emboli. The complex regional pain syndrome or reflex sympathetic dystrophy, caused by involvement of nerve fibers, is discussed in Chapter 35.

Fracture Blisters. Fracture blisters are skin bullae and blisters representing areas of epidermal necrosis with separation of the epidermis from the underlying dermis by edema fluid. They are seen with more severe, twisting types of injuries (e.g., motor vehicle accidents and falls from heights) but can also occur after excessive joint manipulation, dependent positioning, and heat application, or from peripheral vascular disease. They can be solitary, multiple, or massive, depending on the extent of injury. Most fracture blisters occur in the ankle, elbow, foot, knee, or areas where there is little soft tissue between the bone and the skin. The development of fracture blisters reportedly is reduced by early surgical intervention in persons requiring operative repair.[19] This probably reflects the early operative release of the fracture hematoma, reapproximation of the disrupted soft tissues, ligation of bleeding vessels, and fixation of bleeding fracture surfaces. Prevention of fracture blisters is important because they pose an additional risk of infection.

Compartment Syndrome. The compartment syndrome has been described as a condition of increased pressure within a limited space (e.g., abdominal and limb compartments) that compromises the circulation and function of the tissues within the space.[20–23] The abdominal compartment syndrome alters cardiovascular hemodynamics, respiratory mechanics, and renal function. The discussion in this chapter is limited to a discussion of the limb compartment syndromes.

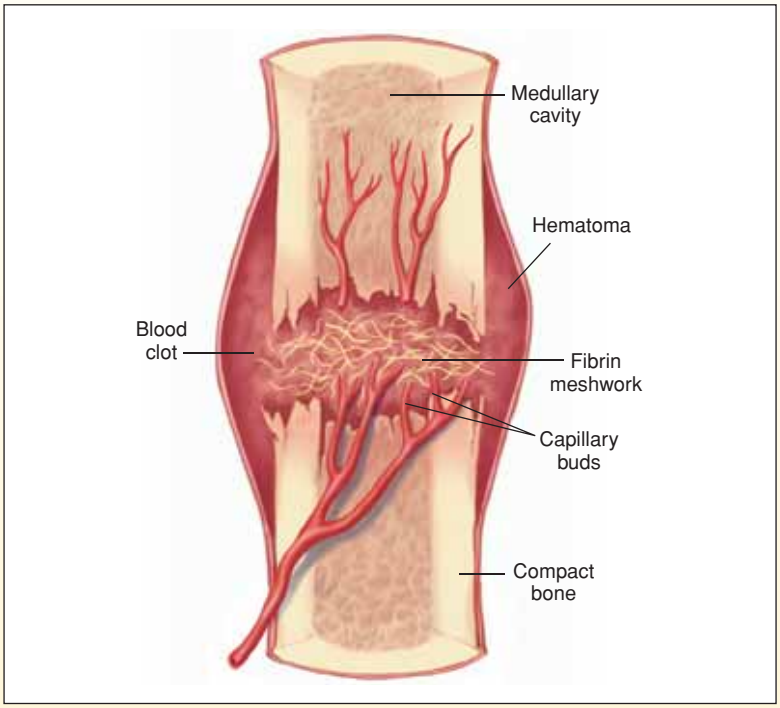
The muscles and nerves of an extremity are enclosed in a tough, inelastic fascial envelope called a *muscle compartment* (Fig. 43-7). If the pressure in the compartment is sufficiently high, tissue circulation is compromised, causing death of nerve and muscle cells. Permanent loss of function may occur. The amount of pressure required to produce a compartment syndrome depends on many factors, including the duration of the pressure elevation, the metabolic rate of the tissues, vascular tone, and local blood pressure. Less tissue pressure is required to impair circulation when hypotension or vasoconstriction is present. Intracompartmental pressures greater than 30 mm Hg (normal is approximately 6 mm Hg) are considered sufficient to impair capillary blood flow.[5]

UNDERSTANDING → Fracture Healing

A fracture, which is any break in a bone, undergoes a healing process to reestablish bone continuity and strength. The repair of simple fractures is commonly divided into four phases: (1) hematoma formation, (2) fibrocartilaginous callus formation, (3) bony callus formation, and (4) remodeling.

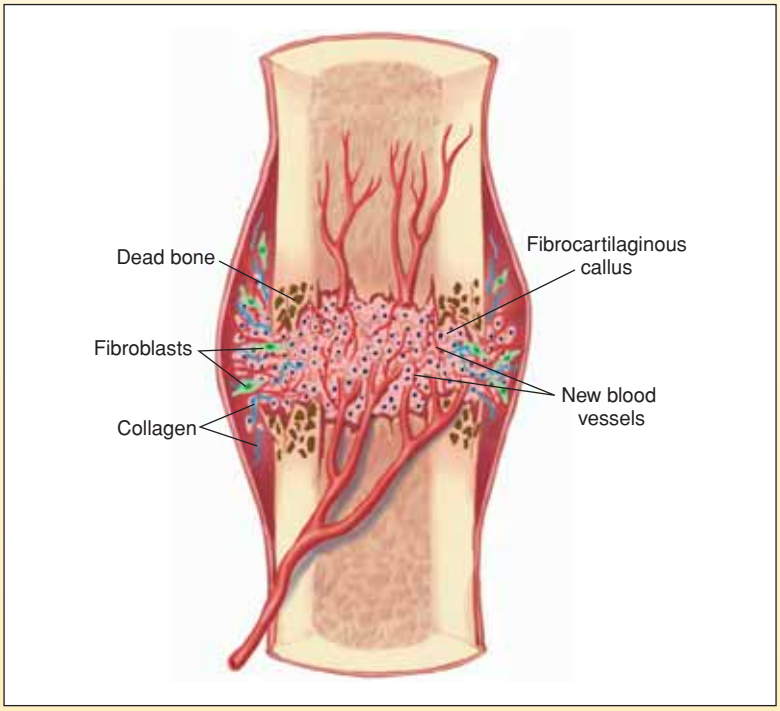
1

Hematoma Formation. When a bone breaks, blood vessels in the bone and surrounding tissues are torn and bleed into and around the fragments of the fractured bone, forming a blood clot, or hematoma. The hematoma facilitates the formation of the fibrin meshwork that seals off the fracture site and serves as a framework for the influx of inflammatory cells, the ingrowth of fibroblasts, and the development of new capillary buds (vessels). It is also the source of signaling molecules that initiate the cellular events that are critical to the healing process.



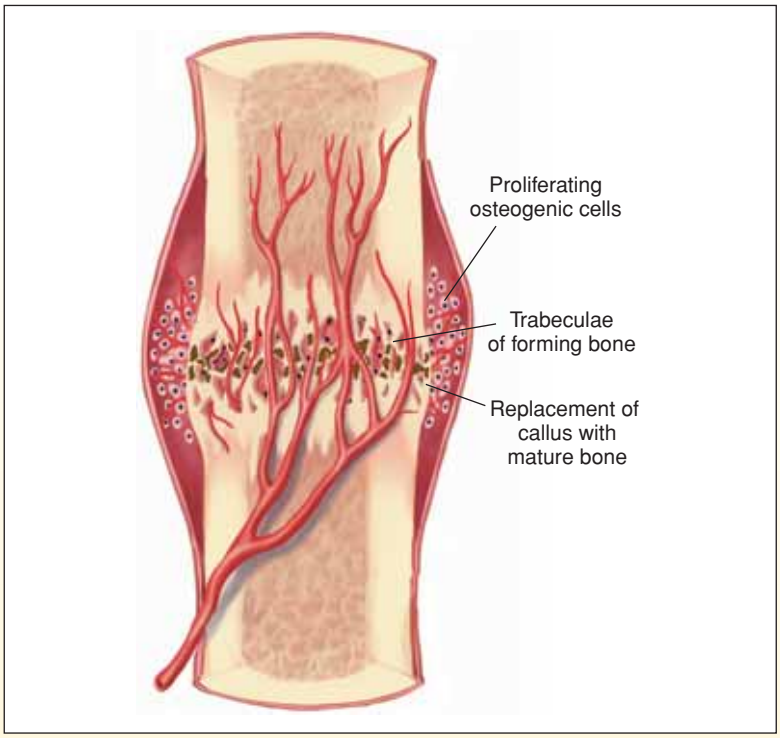
2

Fibrocartilaginous Callus Formation. As new capillaries infiltrate the hematoma at the fracture site, it becomes organized into a form of granulation tissue, called *procallus*. Fibroblasts from the periosteum, endosteum, and red bone marrow proliferate and invade the procallus. The fibroblasts produce a fibrocartilaginous soft callus bridge that connects the bone fragments. Although this repair tissue usually reaches its maximum girth at the end of the second or third week, it is not strong enough for weight bearing.



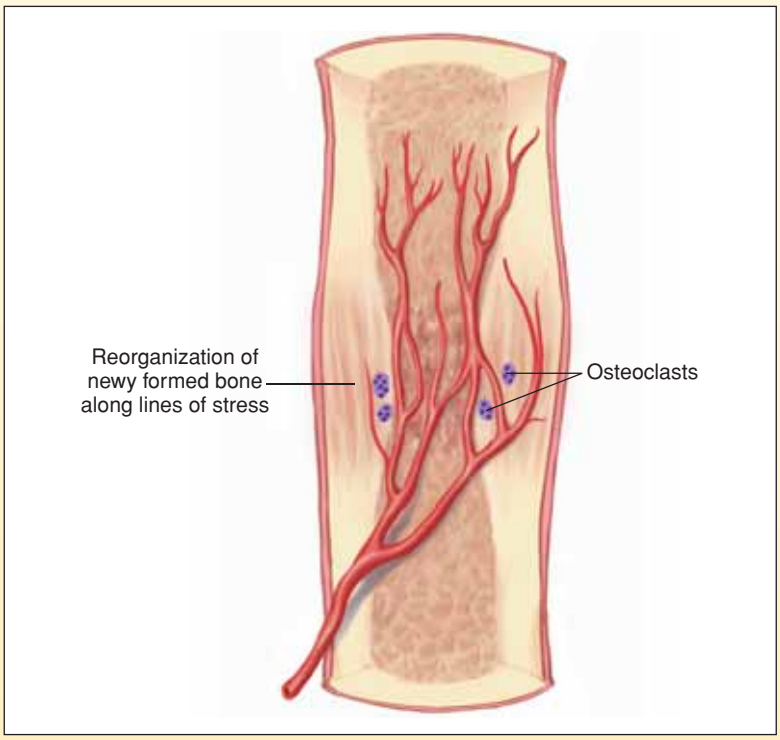
3

Bony Callus Formation. Ossification represents the conversion of the fibrocartilaginous cartilage to bony callus. In areas close to well-vascularized bone tissue, osteogenic cells develop into osteoblasts, or bone-building cells, which produce spongy bone trabeculae. The newly formed osteoblasts first deposit bone on the outer surface of the bone some distance from the fracture site. The formation of bone progresses toward the fracture site until a new bony sheath covers the fibrocartilaginous callus. In time, the fibrocartilage is converted to spongy bone, and the callus is then referred to as bony callus. Gradually, the bony callus calcifies and is replaced by mature bone. Bony callus formation begins 3 to 4 weeks after injury and continues until a firm bony union is formed months later.



4

Remodeling. During remodeling of the bony callus, dead portions of the bone are gradually removed by osteoclasts. Compact bone replaces spongy bone around the periphery of the fracture, and there is reorganization of mineralized bone along the lines of mechanical stress. During this period, the excess material on the outside of the bone shaft and within the medullary cavity is removed and compact bone is laid down to reconstruct the shaft. The final structure of the remodeled area resembles that of the original unbroken bone; however, a thickened area on the surface of the bone may remain as evidence of a healed fracture.



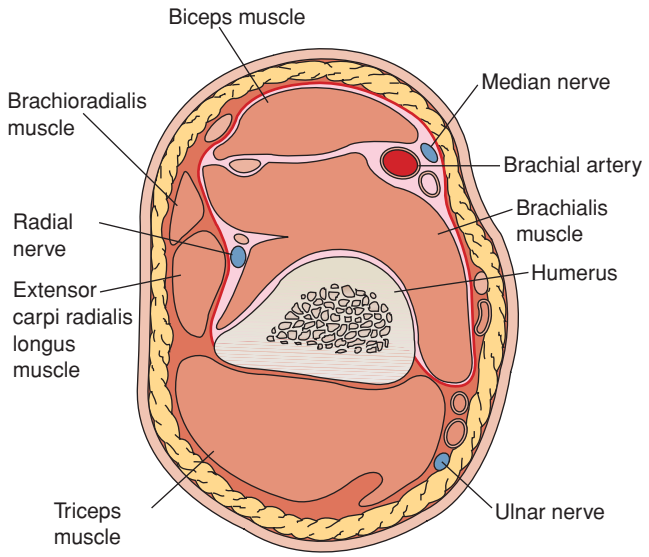


FIGURE 43-7. The proximal muscle compartment of the arm, showing the location of fascia, muscles, nerves, and blood vessels.

Compartment syndrome can result from a decrease in compartment size, an increase in the volume of its contents, or a combination of the two factors. Among the causes of decreased compartment size are constrictive dressings and casts, closure of fascial defects, and burns. In persons with circumferential third-degree burns, the inelastic and constricting eschar decreases the size of the underlying compartments.

An increase in compartment volume can be caused by trauma, swelling, vascular injury and bleeding, and venous obstruction. One of the most important causes of compartment syndrome is bleeding and edema caused by fractures and bone surgery. Contusions and soft tissue injury also are common causes of compartment syndrome. Increased compartment volume may also follow ischemic events, such as arterial occlusion, that are of sufficient duration to produce capillary damage, causing increased capillary permeability and edema. Infiltration of intravenous fluids or bleeding from an arterial puncture can also cause compartment swelling and ischemia. During unattended coma caused by drug overdose or carbon monoxide poisoning, high compartment pressures are produced when an extremity is compressed by the weight of the overlying head or torso.

Compartment syndrome can be acute or chronic. Acute compartment syndrome can occur after a fracture or crushing injury, when excessive swelling around the site of injury results in increased pressure in a closed compartment. Chronic compartment syndrome may develop in long-distance runners and others involved in a major change in activity level. In this case, the symptoms are less severe and tend to improve with rest. Several factors are thought to contribute to an increase in compartmental pressure during exercise including an inelastic facial sheath, an increase in volume of the skeleton muscles due to increased blood flow and edema, and muscle hypertrophy.[2]

The hallmark symptom of an acute compartment syndrome is severe pain that is out of proportion to the original injury or physical findings. Nerve compression may cause changes in sensation (e.g., paresthesias such as burning or tingling or loss of sensation), diminished reflexes, and eventually the loss of motor function. Symptoms usually begin within a few hours but can be delayed as long as 64 hours.[21]

Because muscle necrosis can occur in as little as 4 to 8 hours, it is important that persons at risk for compartment syndrome be identified and proper treatment methods instituted.[5] Assessment should include pain assessment, examination of sensory (i.e., light touch and two-point discrimination) and motor function (i.e., movement and muscle strength), tests of passive stretch, and palpation of the muscle compartments. Peripheral pulses frequently are normal in the presence of compartment syndrome because the major arteries are located outside the muscle compartments. Although edema may make it difficult to palpate the pulse, the increased compartment pressure seldom is sufficient to occlude flow in a major artery. Doppler methods usually confirm the existence of a pulse. Direct measurements of tissue pressure can be obtained using a needle or wick catheter inserted into the muscle compartment. This method is particularly useful in persons who are unresponsive and in those with nerve deficits.

Treatment consists of reducing compartmental pressures. This entails cast splitting or removal of restrictive dressings. These procedures often are sufficient to relieve most of the underlying pressure and symptoms. Elevating the extremity on pillows can help to reduce edema. However, excessive elevation should be avoided because the effects of gravity can lower the arterial pressure in the limb, thereby decreasing compartment perfusion.[5] When compartment syndrome cannot be relieved by conservative measures, a fasciotomy may become necessary. During this procedure, the fascia is incised longitudinally and separated so that the compartment volume can expand and blood flow can be reestablished. Because of potential problems with wound infection and closure, this procedure is usually performed as a last resort.

Fat Embolism Syndrome. The fat embolism syndrome (FES) refers to a constellation of clinical manifestations resulting from the presence of fat droplets in the small blood vessels of the lung or other organs after a long bone fracture or other major trauma.[20,24–26] The fat emboli are thought to be released from the bone marrow or adipose tissue at the fracture site into the venous system through torn veins. It is important to point out that FES is not synonymous with fat embolization, which involves the presence of fat particles in the circulation.[25] Although fat embolization occurs in many persons with fractures or operative fixation of fractures, FES occurs in only a small percentage of cases, supporting the hypothesis that factors other than fat embolization may be necessary in the development of FES.

The main clinical features of FES are respiratory failure, cerebral dysfunction, and skin and mucosal petechiae.[20,26] Cerebral manifestations include encephalopathy, seizures, and focal neurologic deficits unrelated to head injury. Initial symptoms begin within a few hours to 3 to 4 days after injury and do not appear beyond 1 week after the injury. The first symptoms include a subtle change in

behavior and signs of disorientation resulting from emboli in the cerebral circulation combined with respiratory depression. There may be complaints of substernal chest pain and dyspnea accompanied by tachycardia and a low-grade fever. Diaphoresis, pallor, and cyanosis become evident as respiratory function deteriorates. A petechial rash that does not blanch with pressure often occurs 2 to 3 days after the onset of symptoms. This rash usually is found on the anterior chest, axillae, neck, and shoulders. It also may appear on the soft palate and conjunctiva. The rash is thought to be related to embolization of the skin capillaries or thrombocytopenia.

Three degrees of severity are seen: subclinical, overt clinical, and fulminating. Although the subclinical and overt clinical forms of FES respond well to treatment, the fulminating form often is fatal. An important part of the treatment of FES is early diagnosis. Arterial blood gases should be assayed immediately after recognition of clinical manifestations. Treatment is directed toward correcting hypoxemia and maintaining adequate fluid balance. Mechanical ventilation may be required. Corticosteroid drugs are administered to decrease the inflammatory response of lung tissues, decrease edema, stabilize the lipid membranes to reduce lipolysis, and combat bronchospasm. Corticosteroids are also given prophylactically to high-risk persons. The only preventive approach to FES is early stabilization of the fracture.

In summary, many external physical agents can cause trauma to the musculoskeletal system. Particular factors, such as environment, activity, or age, can place a person at greater risk for injury. Some soft tissue injuries such as contusions, hematomas, and lacerations are relatively minor and easily treated. Muscle strains and ligamentous sprains are caused by mechanical overload on the connective tissue. They heal more slowly than the minor soft tissue injuries and require some degree of immobilization. Healing of soft tissue begins within 4 to 5 days of the injury and is primarily the function of fibroblasts, which produce collagen. Joint dislocation is caused by trauma to the supporting structures. The knee and shoulder are common sites for injuries in athletes. The rotator cuff is a common site for shoulder injuries. Knee injuries include injury to the ligaments and menisci, anterior cruciate ligament tears, patellar subluxation and dislocation, and patellofemoral pain syndrome. Hip injuries include dislocations and fractures. The blood supply to the head of the femur travels through the femoral neck. Thus, dislocations and hip fractures affecting the femoral neck often disrupt blood flow to the femoral head, predisposing to fracture malunion and avascular necrosis.

Fractures occur when more stress is placed on a bone than the bone can absorb. The nature of the stress determines the type of fracture and the character of the resulting bone fragments. Healing of fractures is a complex process that takes place in four stages: hematoma formation, fibrocartilaginous callus formation, ossification, and remodeling. For satisfactory healing to take place, the affected bone has to be reduced and immobilized. This is accomplished with external fixation devices (e.g., splints, casts, or traction) or surgically implanted internal fixation devices.

The complications of fractures include a loss of skeletal continuity (malunion or nonunion), pressure from swelling and hemorrhage (fracture blisters and compartment syndrome), and development of fat emboli. Compartment syndrome is a condition of increased pressure in a muscle compartment that compromises blood flow and potentially leads to death of nerve and muscle tissue. The fat embolism syndrome refers to a constellation of symptoms including a petechial skin rash, respiratory failure, and cerebral dysfunction due to the presence of fat droplets in small blood vessels after a fracture.

Bone Infections and Osteonecrosis

Infections—Osteomyelitis

Osteomyelitis represents an acute or chronic infection of the bone and marrow.[15,16] Despite the common use of antibiotics, these infections remain difficult to treat and eradicate. All types of organisms, including parasites, viruses, bacteria, and fungi, can cause osteomyelitis, but certain pyogenic bacteria and mycobacteria are the most common.[16]

Pyogenic Osteomyelitis

Pyogenic osteomyelitis is almost always caused by bacteria. Organisms may reach the bone by seeding through the bloodstream (hematogenous spread), direct penetration or contamination of an open fracture or wound (exogenous origin), or extension from a contiguous site.

The specific agents isolated in pyogenic bacterial osteomyelitis are often associated with the age of the person or the inciting condition (e.g., trauma or surgery).

Bone Infections

- Bone infections may be caused by a wide variety of microorganisms introduced during injury, during operative procedures, or from the bloodstream.
- Once established in bone, the microorganisms proliferate, produce cell death, and spread within the bone shaft, inciting a chronic inflammatory response with further destruction of bone.
- Bone infections are difficult to treat and eradicate. Measures to prevent infection include careful cleaning and debridement of skeletal injuries and strict operating room protocols.

Staphylococcus aureus is the most common cause, but organisms such as *Escherichia coli, Neisseria gonorrhoeae, Haemophilus influenzae,* and *Salmonella* species are also seen. *S. aureus* has two characteristics that favor its ability to produce osteomyelitis: (1) it has the ability to produce a collagen-binding adhesion molecule that allows it to adhere to the connective tissue elements of bone, and (2) it has the ability to evade host defenses, attack host cells, and colonize bone persistently. Also, infection caused by methicillin-resistant *S. aureus* is becoming an increasingly common problem.[27]

Hematogenous Osteomyelitis. Hematogenous osteomyelitis originates with infectious organisms that reach the bone through the bloodstream.[8,15,16,27–29] Acute hematogenous osteomyelitis occurs predominantly in children. In adults, it is seen most commonly in debilitated persons and in those with a history of chronic skin infections, chronic urinary tract infections, and intravenous drug use and in those who are immunologically suppressed. Intravenous drug users are especially at risk for infections with *Streptococcus* and *Pseudomonas*.

The pathogenesis of hematogenous osteomyelitis differs in children and adults.[27,29] In children, the infection usually affects the long bones of the appendicular skeleton. It starts in the metaphyseal region close to the growth plate, where termination of nutrient blood vessels and sluggish blood flow favor the attachment of bloodborne bacteria (Fig. 43-8). With advancement of the infection, purulent exudate collects in the rigidly enclosed bony tissue. Because of the bone's rigid structure, there is little room for swelling and the purulent exudate finds its way beneath the periosteum, shearing off the perforating arteries that supply the cortex with blood, thereby leading to necrosis of cortical bone. The necrotic bone that is formed may separate from the viable surrounding bone to form devascularized fragments, called *sequestra*.[15,16] Eventually, the purulent drainage may penetrate the periosteum and skin to form a draining sinus. In children 1 year of age and younger, the adjacent joint is often involved because the periosteum is not firmly attached to the cortex.[15,16] From 1 year of age to puberty, subperiosteal abscesses are more common. As the process continues, periosteal new bone formation and reactive bone formation in the marrow tend to wall in the infection.

In adults, the long bone microvasculature no longer favors seeding, and hematogenous infection rarely affects the appendicular skeleton. Instead, vertebrae, sternoclavicular and sacroiliac joints, and the symphysis pubis are involved. Infection typically first involves subchondral bone, then spreads to the joint space. With vertebral osteomyelitis, this causes sequential destruction of the endplate, adjoining disk, and contiguous vertebral body. Infection less commonly begins in the joint and spreads to the adjacent bone.

The signs and symptoms of acute hematogenous osteomyelitis are those of bacteremia accompanied by symptoms referable to the site of the bone lesion. Bacteremia is characterized by chills, fever, and malaise. There often is pain on movement of the affected extremity, loss of movement, and local tenderness followed by redness and swelling. X-ray studies may appear normal initially, but they show evidence of periosteal elevation and increased osteoclast activity after an abscess has formed. Radiographic bone scans and MRI can usually detect subtle changes at an earlier stage.

The treatment of hematogenous osteomyelitis begins with identification of the causative organism through blood and bone aspiration cultures. Antimicrobial agents are given first parenterally and then orally. The length of time the affected limb needs to be rested and the pain control measures used are based on the person's symptoms. Débridement and surgical drainage also may be necessary.

Chronic Osteomyelitis. Chronic osteomyelitis usually occurs in adults. Generally, these infections occur secondary to an open wound, most often to the bone or surrounding tissue. It may be the result of delayed or inadequate treatment of acute hematogenous osteomyelitis or osteomyelitis caused by direct contamination of bone by exogenous organisms. Chronic osteomyelitis can persist for years; it may appear spontaneously following a minor trauma, or when resistance is lowered.

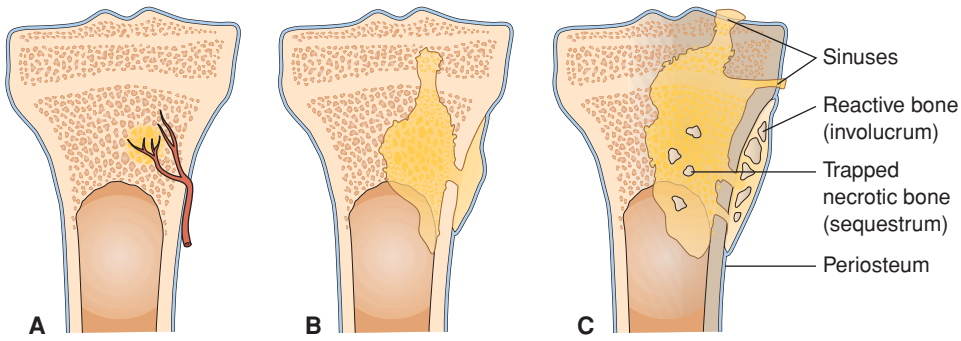


FIGURE 43-8. Hematogenous osteomyelitis. **(A)** Infectious organisms reach the metaphysis through a nutrient blood vessel. **(B)** Bacterial growth results in bone destruction and abscess formation. From the abscess cavity, the infection spreads between the trabeculae into the medullary cavity of compact bone and then through the cortex to the outside. **(C)** The purulent exudate finds its way beneath the periosteum, shearing off the perforating arteries that supply the cortex with blood, thereby leading to necrosis of cortical bone and formation of devascularized fragments, called *sequestra.*

The hallmark feature of chronic osteomyelitis is the presence of infected dead bone, a *sequestrum,* that has separated from the living bone.[8,15,16] A sheath of new bone, called the *involucrum,* forms around the dead bone. Radiologic techniques such as x-ray films, bone scans, and sinograms are used to identify the infected site. Chronic osteomyelitis or infection around a total joint prosthesis can be difficult to diagnose because the classic signs of infection are not apparent and the blood leukocyte count may not be elevated. A subclinical infection may exist for years. Bone scans are used with bone biopsy for a definitive diagnosis.

The treatment of chronic bone infections begins with wound cultures to identify the microorganism and its sensitivity to antibiotic therapy.[28] Initial antibiotic therapy is often followed by surgery to remove foreign bodies (e.g., metal plates, screws) or sequestra and by long-term antibiotic therapy. Immobilization of the affected part usually is necessary, with restriction of weight bearing on a lower extremity. External fixation devices are sometimes used.

Direct Penetration and Contiguous Spread Osteomyelitis. Direct penetration or extension of bacteria from an outside (exogenous) source is now the most common cause of osteomyelitis in the United States.[15] Bacteria may be introduced directly into the bone by a penetrating wound, an open fracture, or surgery. Iatrogenic bone infections are those inadvertently brought about by surgery or other treatments. These complications include pin tract infection in skeletal traction, septic (infected) joints in joint replacement surgery, and wound infections after surgery. In persons with vascular insufficiency, osteomyelitis may develop from a skin lesion. It is most commonly associated with chronic or ischemic foot ulcers in persons with long-standing diabetes.

The pathogenesis of osteomyelitis resulting from direct penetration or contiguous spread differs from hematogenous infection in that virtually any traumatized bone may be involved. Although healthy bone is highly resistant to infection, injury from local inflammation and trauma may devitalize bone and surrounding tissue, providing an inert matrix on which microorganisms introduced during trauma thrive.

Osteomyelitis after trauma or bone surgery usually is associated with persistent or recurrent fever, increased pain at the operative or trauma site, and poor incisional healing, which often is accompanied by continued wound drainage and wound separation. Prosthetic joint infections often present with joint pain, fever, and cutaneous drainage.

Treatment includes the use of antibiotics and selective use of surgical interventions. The choice of agents and method of administration depend on the microorganisms causing the infection. In acute osteomyelitis that does not respond to antibiotic therapy, surgical decompression is used to release intramedullary pressure and remove drainage from the periosteal area. Prosthesis removal may be necessary in cases of an infected prosthetic joint. The joint is left out while a 2- to 6-week course of therapy is given, after which another joint is implanted.[29]

Tuberculosis Osteomyelitis

A resurgence of tuberculosis osteomyelitis is occurring in industrialized countries of the world, attributed to the influx of immigrants from developing countries and the greater numbers of immunocompromised people.[30] Tuberculosis can spread from one part of the body, such as the lungs or the lymph nodes, to the musculoskeletal system. Any bone, joint, or bursa may be affected, but the spine is the most common site, followed by the knees and hips.[16,30] Tubercular osteomyelitis tends to be more destructive and difficult to control than pyogenic osteomyelitis. The infection spreads through large areas of the medullary cavity and causes extensive necrosis. In tuberculosis of the spine, also known as *Pott disease,* the infection spreads through the intervertebral disks to involve multiple vertebrae and extends into the soft tissue, forming abscesses.

Local symptoms include pain, immobility, and muscle atrophy; joint swelling, mild fever, and leukocytosis also may occur. The most feared complication of spinal tuberculosis is neurologic compromise due to spinal deformity and epidural abscess formation. Because there are no specific radiographic findings in tubercular osteomyelitis, the diagnosis is usually made by tissue biopsy or culture findings. In spinal tuberculosis, a computed tomography (CT)-guided biopsy is often used. The mainstay of treatment for tubercular osteomyelitis remains the appropriate three- or four-drug antimicrobial therapy based on current guidelines.[30] Conservative treatment is usually as effective as surgery, especially for earlier and milder cases.

Osteonecrosis

Osteonecrosis is an aseptic destruction of a segment of bone that is due to an interruption in blood flow rather than an infection.[15,16,31,32] It is a relatively common disorder and can occur in the medullary cavity of the metaphysis and the subchondral region of the epiphysis, especially in the proximal femur, distal femur, and proximal humerus. Destruction of bone frequently is severe enough to require joint replacement surgery.

Bone has a rich blood supply that varies from site to site. The flow in the medullary portion of bone originates in nutrient vessels from an interconnecting plexus that supplies the marrow, trabecular bone, and endosteal half of the cortex. The outer cortex receives its blood supply from periosteal, muscular, metaphyseal, and epiphyseal vessels that surround the bone. Some bony sites, such as the head of the femur, have only limited collateral circulation so that interruption of the flow, such as with a hip fracture, can cause necrosis and irreversible damage to a substantial portion of medullary and cortical bone.

Although bone necrosis results from ischemia, the mechanisms producing the ischemia are varied and include mechanical interruption such as occurs with a fracture; thrombosis and embolism (e.g., sickle cell

disease, nitrogen bubbles caused by inadequate decompression during deep sea diving); vessel injury (e.g., vasculitis, radiation therapy); and increased intraosseous pressure with vascular compression. Chart 43-1 lists some of the conditions associated with osteonecrosis. Other than vessel injury and obstruction, the most common causes of bone necrosis are idiopathic (i.e., those of unknown cause) and prior steroid therapy. Despite numerous studies, the mechanism of steroid-induced osteonecrosis remains unclear. The condition may develop after the administration of very high, short-term doses; during long-term treatment; or even from intra-articular injection. Although the risk increases with the dose and duration of treatment, it is difficult to predict who will be affected. Of recent concern is the development of osteonecrosis of the jaw with long-term use of bisphosphonates, drugs that are widely used for the treatment of postmenopausal osteoporosis, Paget disease of the bone, and cancer-related conditions.[33] The pathogenesis of bisphosphonate-associated osteonecrosis of the jaw remains largely unknown. The complication has mainly been reported in patients receiving the drugs intravenously for treatment of malignancies.

The pathologic features of bone necrosis are the same, regardless of cause. The site of the lesion is related to the vessels involved. There is necrosis of cancellous bone and marrow. The cortex usually is not involved because of collateral blood flow. In persons with subchondral infarcts (i.e., ischemia below the cartilage), a triangular or wedge-shaped segment of tissue that has the subchondral bone plate as its base and the center of the epiphysis as its apex undergoes necrosis (Fig. 43-9). In cases where medullary infarcts occur in fatty marrow, death of bone results in calcium release and necrosis of fat cells with the formation of free fatty acids. Released calcium forms an insoluble "soap" with free fatty acids. Because bone lacks mechanisms for resolving the infarct, the lesions remain for life.

The symptoms associated with osteonecrosis are varied and depend on the site and extent of infarction. Typically, subchondral infarcts cause chronic pain that is initially associated with activity but that gradually becomes more progressive until it is experienced at rest. Subchondral infarcts often collapse and predispose the patient to severe secondary osteoarthritis.

Diagnosis of osteonecrosis is based on history, physical findings, radiographic findings, and the results of special imaging studies, including CT scans and technetium-99m bone scans. Treatment depends on the underlying pathologic process. In some cases, only short-term immobilization, nonsteroidal anti-inflammatory drugs, exercises, and limitation in weight bearing are used. Osteonecrosis of the hip is particularly difficult to treat. In persons with early disease, limitation of weight bearing through the use of crutches may allow the condition to stabilize. Although several surgical approaches have been used, the most definitive treatment of advanced osteonecrosis of the knee or hip is total joint replacement.

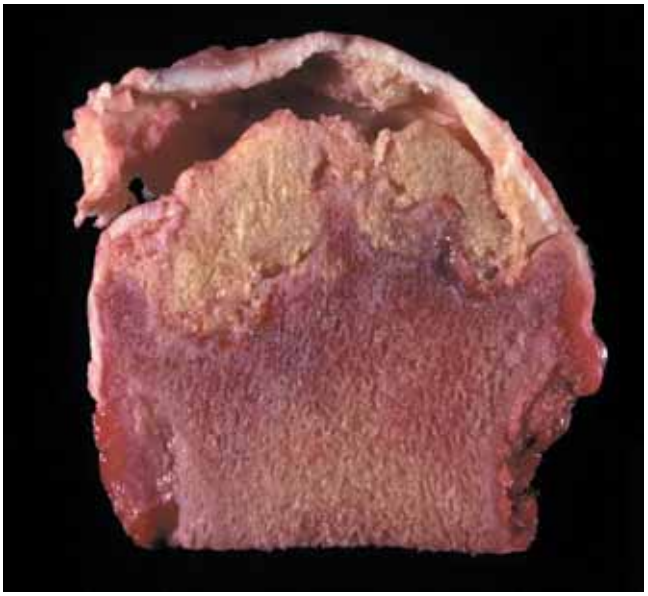


FIGURE 43-9. Osteonecrosis of the head of the femur. A coronal section shows a circumscribed area of subchondral infarction with partial detachment of the overlying articular cartilage and subarticular bone. (From Hoch B.L., Klein M.J., Schiller A.L. [2008]. Bones and joints. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1100]. Philadelphia: Lippincott Williams & Wilkins.)

CHART 43-1 Causes of Osteonecrosis

- Mechanical disruption of blood vessels
  - Fractures
  - Legg-Calvé-Perthes disease
  - Blount disease
- Thrombosis and embolism
  - Sickle cell disease
  - Nitrogen bubbles in decompression sickness
- Vessel injury
  - Vasculitis
  - Connective tissue disease
    - Systemic lupus erythematosus
    - Rheumatoid arthritis
  - Radiation therapy
  - Gaucher disease
- Corticosteroid therapy
- Biphosphonate therapy (jaw osteonecrosis)

In summary, bone infections occur because of the direct or indirect invasion of the musculoskeletal system by microorganisms, most commonly *S. aureus*. Osteomyelitis, or infection of the bone and marrow, can be an acute or chronic disease. Acute osteomyelitis is seen most often as a result of the direct contamination of bone by a foreign object. Chronic osteomyelitis represents an infection that continues beyond 6 to 8 weeks and may persist for years. The incidence of all types of bone infection has been dramatically reduced since the

advent of antibiotic therapy. Iatrogenic infections are those inadvertently brought about by surgery or other treatments. Tuberculosis osteomyelitis, which is characterized by bone destruction and abscess formation, is caused by spread of the infection from the lungs or lymph nodes.

Osteonecrosis, or death of a segment of bone, is due to an interruption in blood flow rather than an infection. The mechanisms producing interruption of blood flow are varied and include mechanical interruption such as occurs with a fracture, vessel injury, increased intraosseous pressure with vascular compression, and steroid therapy. Sites with poor collateral circulation, such as the femoral head, are most commonly affected. Of recent concern is the development of osteonecrosis of the jaw in persons receiving long-term treatment with bisphosphonate drugs. Symptoms include pain that varies in severity, depending on the extent of infarction. Total joint replacement is the most frequently used treatment for advanced osteonecrosis.

Neoplasms

Neoplasms of the skeletal system, often referred to as *bone tumors*, may be benign or malignant, and in the case of malignant neoplasms, may represent a primary tumor or secondary metastatic lesion.[5,8,15,16,34] Benign tumors greatly outnumber their malignant counterparts and occur with the greatest frequency in the first three decades of life, whereas in the elderly, a bone tumor is more likely to be malignant.

Both benign and malignant tumors can develop from the cartilage (chondrogenic), bone (osteogenic), and supporting (fibrogenic) elements of bone, and bone tumors are generally classified according to their tissue counterpart. As a group, these tumors affect all age groups and arise in virtually every bone. Most develop during the first several decades of life and have a propensity to originate in the long bones of the extremities; however, certain types of tumors target specific age groups and anatomic sites. Thus, the location of the tumor provides important diagnostic information.

There are three major manifestations of bone tumors: pain, presence of a mass, and impairment of function.[5,8] Although benign tumors are frequently asymptomatic and are detected as an incidental finding, many tumors produce pain. Malignant tumors are associated with constant, deep aching pain that does not go away with rest and is present at night. However, certain benign tumors also cause night pain. A mass or hard lump may be the first sign of a bone tumor. A malignant tumor is suspected when a painful mass exists that is enlarging or eroding the cortex of the bone. The ease of discovery of a mass depends on the location of the tumor; a small lump arising on the surface of the tibia is easy to detect, whereas a tumor that is deep in the medial portion of the femur may grow to a considerable size before it is noticed. Benign and malignant tumors may cause the bone to erode to the point where it cannot withstand the strain of ordinary use. A sudden increase in pain followed by trivial trauma that is preceded by a history of mild, dull aching pain is suggestive of a pathologic fracture. A tumor also may produce pressure on a peripheral nerve, causing a decreased sensation, numbness, a limp, or limitation in movement.

The diagnosis of bone tumors relies on the history and physical examination, as well radiography, CT, and MRI.[35] Radiographs give the most general diagnostic information, such as malignant versus benign and primary versus metastatic status. The radiograph demonstrates the region of bone involvement, extent of destruction, and amount of reactive bone formed. CT scans further aid diagnosis and anatomic localization and can identify small pulmonary metastases not seen by conventional radiographs. MRI is the most accurate method of evaluating the intramedullary extent of bone tumor and can demarcate the soft structures in relation to neurovascular structures without the use of contrast media. It is best used in conjunction with a CT scan. Radionuclide bone scans are used to assess for metastasis. A biopsy may be done to determine the histologic characteristics of the tumor.

Bone Tumors

- Bone tumors include both primary neoplasms that arise from the cartilage, osseous, or fibrous tissue elements of bone and metastatic tumors that arise from other primary sites.
- Most primary bone tumors, both benign and malignant, develop during the first several decades of life and have a propensity to originate in the long bones of the extremities.
- The more common benign tumors are often asymptomatic and are detected as an incidental finding.
- Malignant tumors tend to grow rapidly and extend beyond the confines of the bone, and typically present as painful enlarging masses.

Benign Bone Tumors

Benign bone tumors usually are limited to the confines of the bone, have well-demarcated edges, and are surrounded by a thin rim of sclerotic bone. The most common benign tumors are of either fibrous or cartilaginous tissue origin. Benign fibrous tumors of the bone are common in growing bones. They are usually asymptomatic, resolve in 2 to 3 years, and do not require treatment.[8] Common cartilaginous tumors include chondromas and osteochondromas. Giant cell tumors, which contain mononuclear and osteoclast-type giant cells, are often classified

as "intermediate" in nature between malignant and benign.

Chondromas are benign tumors of hyaline cartilage that usually occur in bones of endochondral origin. They can arise within the medullary cavity, where they are known as *endochondromas*, or on the surface of bone, where they are called *subperiosteal* or *juxtacortical chondromas*. The endochondromas are the most common of the intraosseous cartilage tumors and are usually diagnosed in persons between the ages of 20 and 40 years.[16] They are usually solitary lesions of tubular bone, and are most commonly found in short tubular bones of hands and feet. Most endochondromas are asymptomatic and detected incidentally. Occasionally they are painful and cause fractures. Treatment is usually simple observation, with surgical intervention reserved for cases in which pain or danger of fracture is present.

An *osteochondroma,* also known as an *exostosis,* is a benign cartilage-capped tumor that is attached to the underlying bone by a bony stalk. It is the most common benign bone tumor, about 85% of which occur as solitary tumors.[16] The remaining tumors are seen as part of a multiple hereditary exostosis syndrome, which is inherited as an autosomal dominant disorder. Solitary exostoses are usually first diagnosed in late adolescence or early adulthood, but multiple exostoses become apparent in childhood. Exostoses develop only in bones of endochondral origin, arising from the metaphysis near the growth plate of tubular bones, especially about the knee. Clinically, osteochondromas present as slow-growing masses, which can be painful if they impinge on a nerve or if the stalk is fractured. In many cases they are discovered incidentally. In multiple hereditary exostosis, the underlying bone may be bowed and shortened, reflecting an associated disturbance in epiphyseal growth. Osteochondromas usually stop growing at the time of growth plate closure. Malignant changes are rare, and excision of the tumor is done only when necessary.

A *giant cell tumor,* or *osteoclastoma,* is an aggressive tumor that often behaves like a malignant tumor, metastasizing through the bloodstream and recurring locally after excision.[16,36] The tumor is a mixture of mononuclear and multinucleated osteoclast-type giant cells. The mononuclear cells in the tumor express RANKL, and the giant osteoclast-like cells are believed to form via the RANK/RANKL signaling pathway (see Chapter 42).

Giant cell tumors usually arise in people in their twenties to forties.[16] The majority of tumors arise around the knee (distal femur and proximal tibia), but virtually any bone can be involved. The tumor begins in the metaphyseal region, grows into the epiphysis, and may extend into the joint surface. Pathologic fractures are common because the tumor destroys the bone substance. Clinically, pain may occur at the tumor site, with gradually increasing swelling. X-ray films show destruction of the bone with expansion of the cortex. The biologic unpredictability of these tumors complicates their management. Conservative surgery such as curettage is associated with a 40% to 60% recurrence rate; up to 4% metastasize to the lung.[16]

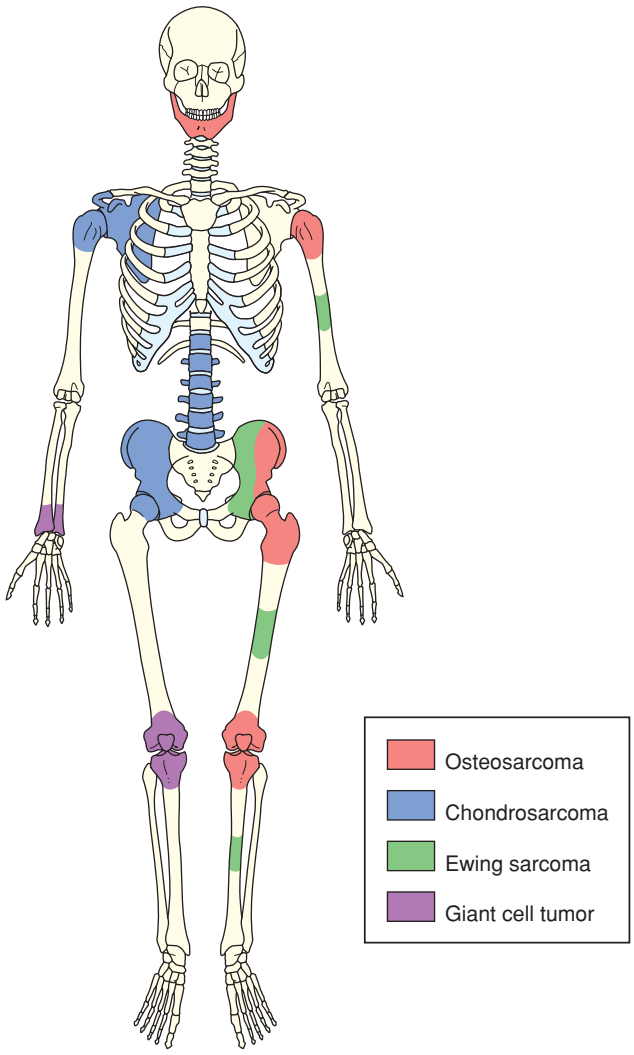


FIGURE 43-10. Common sites of primary malignant bone tumors (chondrosarcoma, osteosarcoma, and Ewing sarcoma) and giant cell tumor, a locally aggressive benign tumor.

Malignant Bone Tumors

In contrast to benign tumors, primary malignant tumors tend to be ill defined, lack sharp borders, and extend beyond the confines of the bone. Primary malignant bone tumors occur in all age groups and may arise in any part of the skeleton. However, certain types of tumors tend to target certain age groups and anatomic sites (Fig. 43-10). For example, most osteogenic sarcomas occur in adolescents and are particularly common around the knee joint. Also, people with certain conditions such as Paget disease are at increased risk for development of bone cancer.

Osteosarcoma

Osteosarcoma is an aggressive and highly malignant bone tumor. It is the most common malignant bone tumor, representing one fifth of all primary bone tumors.[16] The tumor has a bimodal distribution, with

75% occurring in persons younger than 20 years of age.[15] A second peak occurs in the elderly with predisposing factors such as Paget disease, bone infarcts, or prior irradiation. Overall, men are more commonly affected than women.

The cause of osteosarcoma is unknown. The correlation of age and location of most of the tumors with the period of maximum growth suggests some relation to increased osteoblastic activity. In younger persons, the primary tumor most often is located at the anatomic sites associated with maximum growth velocity—the distal femur, proximal tibia, and proximal humerus. Bone tumors in the elderly are more common in the humerus, pelvis, and proximal femur. There are known genetic factors associated with osteosarcoma. Mutations in two genes are reported to increase the susceptibility to the development of osteosarcoma: the retinoblastoma gene (*RB*), a critical cell cycle generator, and the p53 gene, which regulates deoxyribonucleic acid (DNA) repair and certain aspects of cellular metabolism[16] (see Chapter 7).

Osteosarcomas are aggressive tumors that grow rapidly in a circular, ball-like mass in the bone tissue. They often are eccentrically placed in the bone and move from the metaphysis of the bone out into the periosteal surface, with subsequent spread to adjacent soft tissues (Fig. 43-11). These tumors spread through the blood stream; most often, the tumor cells exit the primary tumor through the venous end of the capillary, and early metastasis to the lung is common. Lung metastases, even if massive, usually are relatively asymptomatic. The prognosis for a person with osteosarcoma depends on the aggressiveness of the disease, presence or absence of pathologic fractures, size of the tumor, and rapidity of tumor growth.

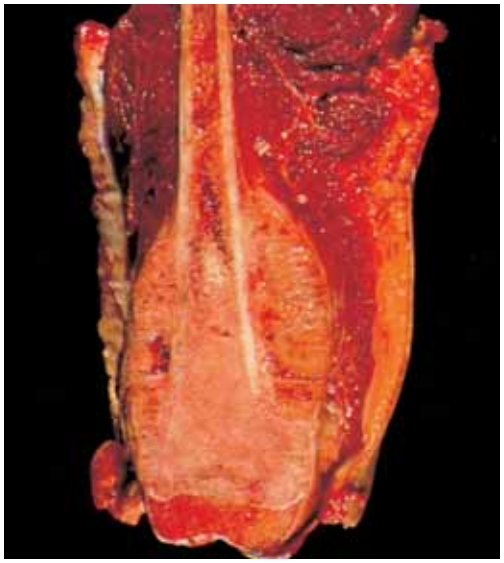


FIGURE 43-11. Osteosarcoma. The distal femur contains a dense osteoblastic malignant tumor that extends through the center in the soft tissue and epiphysis. (From Hoch B.L., Klein M.J., Schiller A.L. [2008]. Bones and joints. In Rubin R., Strayer D.E. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1126]. Philadelphia: Lippincott Williams & Wilkins.)

The primary clinical feature of osteosarcoma is deep, localized pain with nighttime awakening and swelling in the affected bone. Because the pain is often of sudden onset, patients and their families often associate the symptoms with recent trauma.[34] The skin overlying the tumor may be warm, shiny, and stretched, with prominent superficial veins. The range of motion of the adjacent joint may be restricted.

The treatment of osteosarcoma is surgery in combination with multiagent chemotherapy, both before and after surgery.[35,37] In the past, treatment usually entailed amputation above the level of the tumor. Limb salvage surgical procedures, using a metal prosthesis or cadaver allograft, are now a standard alternative. In younger children who undergo arthroplasty, an expandable internal prosthesis is used to allow for bone growth. Amputation is another surgical option. It involves either the removal of expendable bones such as the fibula, toes, or ulna, or the complete removal of the tumor and the affected limb.

Chondrosarcoma

Chondrosarcoma consists of malignant tumors of cartilaginous lineage and is commonly subclassified according to site of origin as central (intramedullary) or peripheral (juxtacortical and surface). Chondrosarcomas can arise as a primary tumor from preexisting benign cartilage tumors such as osteochondroma or chondroblastoma.[38] They commonly arise in the central portions of the skeleton, including the pelvis, shoulder, and ribs.

Chondrosarcomas develop about half as frequently as osteosarcomas. They occur primarily in middle or later life; however, there are chondromas that occur in younger persons. Chondrosarcomas are slow growing and metastasize late, and often are painless. They can remain hidden in an area such as the pelvis for a long period of time. This type of tumor, like many primary malignancies, tends to destroy bone and extend into the soft tissues beyond the confines of the bone of origin.

Early diagnosis is important because chondrosarcomas responds well to early radical surgical excision. It usually is resistant to radiation therapy and available chemotherapeutic agents. Not infrequently, these tumors transform into a highly malignant tumor, mesenchymal chondrosarcoma, which requires a more aggressive treatment, including combination chemotherapy.

Ewing Sarcoma

Ewing sarcoma is a member of a family of tumors that includes Ewing sarcoma and primitive neuroectodermal tumor (PNET). Both tumors are characterized by densely packed, regularly shaped, small cells with round or oval nuclei; and both share a specific reciprocal translocation of chromosomes 11 and 31, or variants thereof.[16,39]

Ewing sarcoma is primarily a disease of children and young adults and is rarely seen in older adults.[39] Males are affected slightly more frequently than females, and white children have an approximately ninefold higher incidence rate than black children.[39] The most frequent

site of Ewing sarcoma is the femur, usually in the diaphysis. The pelvis represents the second most common site; other sites include the pubis, sacrum, humerus, vertebrae, ribs, skull, and other flat bones. Manifestations of Ewing tumor include bone pain, limitation of movement, and tenderness over the involved bone or soft tissue. It often is accompanied by systemic manifestations such as fever or weight loss, which may serve to confuse the diagnosis. There may be a delay in diagnosis when the pain and swelling associated with the tumor are attributed to a sports injury or when the tumor is located in the pelvis and the pain is not localized and the mass is not apparent. Pathologic fractures are common because of bone destruction. The most common sites of metastasis are the lungs, bone marrow, and other bones. Because Ewing sarcoma is a difficult diagnosis to establish, the diagnostic biopsy is very important.

Treatment methods incorporate a combination of multiagent chemotherapy, surgery, and radiation therapy.[39] Multiagent chemotherapy can shrink the tumor rapidly, and is generally given before local control measures are initiated. Ewing sarcoma is considered to be a radiosensitive tumor, and local control may be achieved through radiation or surgery. Patients with small, nonmetastatic, distally located tumors generally have the best prognosis.

Metastatic Bone Disease

Skeletal metastases are the most common malignancy of osseous tissue.[40,41] Approximately half of all people with cancer have bone metastasis at some point in their disease. Metastatic lesions are seen most often in the spine, femur, pelvis, ribs, sternum, proximal humerus, and skull, and are less common in anatomic sites more distant from the trunk of the body. Tumors that frequently spread to the skeletal system are those of the breast, lung, prostate, kidney, and thyroid, although any cancer can ultimately involve the skeleton.

The major symptom of bone metastasis is pain with evidence of an impending pathologic fracture. It usually develops gradually, over weeks, and is more severe at night. Pain is caused by stretching of the periosteum of the involved bone or by nerve entrapment, as when the nerve roots of the spinal cord are compressed by the vertebral body. Symptoms of hypercalcemia may occur in cases of bony destruction.

Radiographic examinations are used along with CT or bone scans to detect, diagnose, and localize metastatic bone lesions. A bone biopsy usually is done when there is a question regarding the diagnosis or treatment. Serum levels of alkaline phosphatase and calcium often are elevated in persons with metastatic bone disease.

The primary goals in treatment of metastatic bone disease are to prevent pathologic fractures and promote survival with maximum functioning, allowing the person to maintain as much mobility and pain control as possible. Standard treatment methods include chemotherapy, irradiation, and surgical stabilization. Radiation therapy is primarily used as a palliative treatment to alleviate pain and prevent pathologic fractures. After a pathologic fracture has occurred, bracing, intramedullary nailing of the femur, or spine stabilization may be done. Because adequate fixation often is difficult, bone cement often is used with internal fixation devices to stabilize the bone.

Recent research has focused on the role of osteoclastic and osteoblastic activity in the pathogenesis of metastatic bone disease and on the use of the bisphosphonates (e.g., pamidronate disodium, zoledronic acid) for its treatment.[40,41] The bisphosphonates, which are now well-established agents for the prevention and treatment of osteoporosis, have recently been shown to decrease symptoms associated with bone metastasis secondary to breast and prostate cancer. These agents bind preferentially to bone at sites of active bone metabolism, are released from the bone matrix during bone resorption, and potentially inhibit osteoclast activity and survival, thereby reducing osteoclast-mediated bone resorption. Recent studies suggest that besides their strong antiosteoclastic activity, these agents may also have some direct antitumor effects.[42]

In summary, bone tumors, like any other type of neoplasm, may be benign or malignant. Both benign and malignant tumors can develop from the cartilage (chondrogenic), bone (osteogenic), and supporting (fibrogenic) elements of bone, and bone tumors are generally classified according to their tissue counterpart. Benign bone tumors grow slowly and usually do not destroy the surrounding tissues. Malignant tumors can be primary or metastatic. Primary bone tumors are rare, grow rapidly, metastasize to the lungs and other parts of the body through the bloodstream, and have a high mortality rate. They include osteosarcoma, which begins in osteogenic cells of the bone and is the most common type of bone cancer; chondrosarcoma, which has its origin in the cartilaginous elements of bone; and Ewing sarcoma, which is characterized by small round cell tumors of bone and soft tissue origin. Advances in chemotherapy, radiation therapy, and surgical procedures have substantially increased the survival and cure rates for many types of bone cancers. Metastatic bone tumors usually are multiple in occurrence, originating primarily from cancers of the breast, lung, and prostate. A primary goal in metastatic bone disease is the prevention of pathologic fractures.

Skeletal Disorders in Children

During childhood, skeletal structures grow in length and diameter and sustain a large increase in bone mass. Alterations in musculoskeletal structure and function may develop as a result of normal growth and developmental processes or as a result of impairment of skeletal development caused by hereditary or congenital influences.

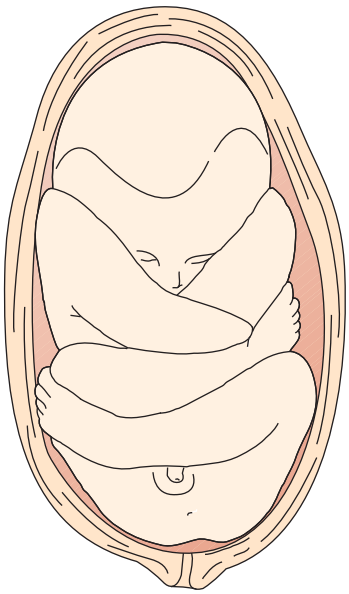


FIGURE 43-12. Position of fetus in utero, with tibial bowing and legs folded. (From Dunne K.B., Clarren S.K. [1986]. The origin of prenatal and postnatal deformities. *Pediatric Clinics of North America* 33, 1282; with permission from Elsevier Science.)

Variations of Normal Growth and Development

Infants and children undergo changes in muscle tone and joint motion during growth and development. Intoeing, outtoeing, bowlegs, and knock-knees occur frequently in infancy and childhood. They usually cause few problems and are corrected during normal growth processes. The normal folded position of the fetus in utero causes physiologic flexion contractures of the hips and a froglike appearance of the lower extremities[43] (Fig. 43-12). The hips are externally rotated and the patellae point outward, whereas the feet appear to point forward because of the internal pulling force of the tibiae. During the first year of life, the lower extremities begin to straighten out in preparation for walking. Internal and external rotations become equal, and the hips extend.

Musculoskeletal assessment of the newborn is important to identify abnormalities that require early intervention, facilitate treatment, establish baselines for future reference, and educate and counsel parents.[44–47] There are many clinical deviations that are easily correctable in a newborn. Many others correct spontaneously as the child grows.

Torsional and Angular Deformities

All infants and toddlers have lax ligaments that become tighter with age and assumption of the weight-bearing posture. The hypermobility that accompanies joint laxity coupled with the torsional, or twisting, forces exerted on the limbs during growth are responsible for a number of variants seen in young children. Torsional forces caused by intrauterine positions or sleeping and sitting patterns twist the growing bones and can produce deformities as a child grows and develops.

Developmental Skeletal Disorders

- Many disorders of early infancy are caused by intrauterine positions and resolve as the child grows.
- All infants and toddlers have lax ligaments that predispose to skeletal disorders caused by twisting or torsional forces.
- Bone growth in infants and children occurs at the epiphysis. Separation of the epiphyseal growth plate ruptures the blood vessels that nourish the epiphysis, causing cessation of growth and shortened extremity length.

In infants, the femur normally is rotated to an anteverted or forward position with the femoral head and neck rotated anteriorly with respect to the femoral condyles. Normally this angle is approximately 30 degrees at birth and declines to 15 degrees by age 10.[48] A second source of rotation is found in the tibia. The normal tibia is externally rotated approximately 5 degrees at birth and 15 degrees at maturity. The abnormalities may be excessive adduction (turning in or toward the body) or abduction (turning out or away from the body).

Intoeing and Outtoeing. The foot progression angle describes the angle between the axis of the foot and the line of progression.[45] It is determined by watching the child walking and running, although it is usually less noticeable when the child is running or barefoot. Figure 43-13 illustrates the position of the foot in intoeing and outtoeing. Inward rotation of the foot is assigned a negative value and outward rotation is assigned a positive value. The normal value in children and adolescents is 10 degrees (range –3 to 20 degrees). The foot progression value serves only to define whether there is an intoeing or outtoeing gait.

Intoeing may be secondary to foot deformities or may be due to inward rotation of the femur or tibia, or a combination of the two.[45] Increased internal torsion of the femur (femoral anteversion) is the most common finding. In many cases intoeing is a variation of normal development. Outtoeing is a common problem in children and is caused by external femoral torsion.[45] Because the femoral torsion persists when a child habitually sleeps in the prone position, an external tibial torsion also may develop. External tibial torsion rarely causes outtoeing; it only intensifies the condition. Outtoeing usually corrects itself as the child becomes proficient in walking.

Intoeing due to a condition called *metatarsus adductus* is a common congenital deformity characterized by forefoot adduction with a normal hindfoot, giving the foot a kidney-shaped appearance[49–51] (Fig. 43-14). It may occur in one foot or both feet. Diagnostic methods

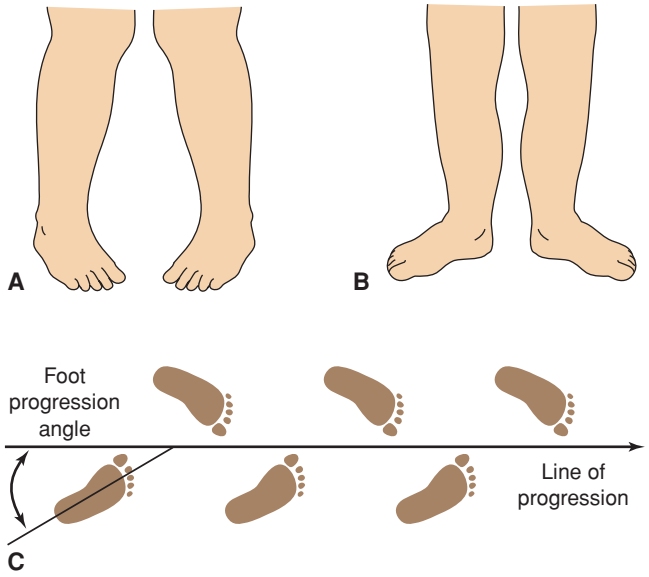


FIGURE 43-13. **(A)** Toeing-in. **(B)** Toeing-out. **(C)** Toeing-in and toeing-out can be determined by watching a child walk and comparing the long axis of the foot with the direction in which the child is walking. If the foot is directed inward, the angle is negative and indicative of in toeing; if it is positive, it is indicative of out toeing.

include examination of the plantar aspect of the foot, noting the overall shape of the foot and the presence or absence of an arch. The severity of the deformity can be determined by assessing the flexibility of the foot and using a heel bisection line. Normally, a line bisecting the heel crosses the forefoot between the second and third toes. In mild metatarsus adductus, the foot is flexible and can be passively manipulated and the line crosses the third toe; in a moderate deformity, the foot is less flexible and the line falls between the third and fourth toes; and in a severe deformity, the foot is more rigid and the line crosses between the fourth and fifth toes. Most infants do not require treatment, although parents are advised to avoid positioning the infant in the prone position with the feet turned in, a position that accentuates metatarsus adductus. Because the condition often corrects itself spontaneously, treatment is usually not instituted until the infant is 6 months of age.[50] When needed, treatment consists of serial long leg casting or a brace that pushes the metatarsals (not the hindfoot) into abduction.

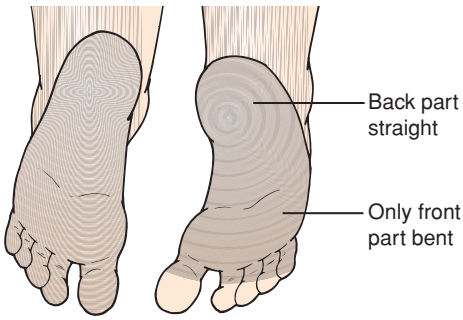


FIGURE 43-14. Shape of foot. The left foot is normal, whereas the right foot has metatarsus adductus.

Femoral Torsion. *Femoral torsion* refers to abnormal variations in hip rotation.[45,48] Hip rotation is measured at the pelvic level with the child in the prone position and the knees flexed at a 90-degree angle (Fig. 43-15A). In this position, the hip is in a neutral position. Rotating the lower leg outward produces internal or medial femoral rotation; rotating it inward produces external or lateral rotation. During measurement of hip rotation, the legs are allowed to fall to full internal rotation by gravity alone; lateral rotation is measured by allowing the legs to fall inward and cross. Hip rotation in flexion and extension also can be measured with CT.

Excessive *internal femoral anteversion* is a normal variant commonly seen during the first 6 years of life, especially in 3- and 4-year-old girls.[45] Characteristically, there is 80 to 90 degrees of internal rotation of the hip in the prone position.[46] The condition is thought to be related to increased laxity of the anterior capsule of the

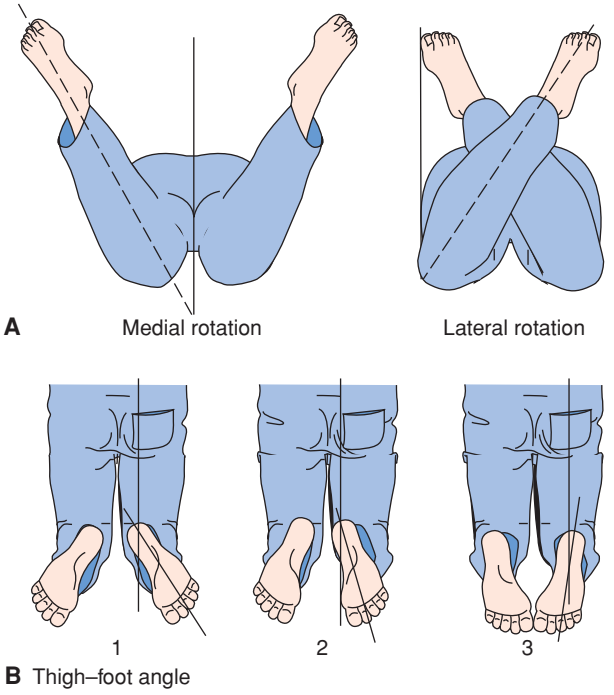


FIGURE 43-15. **(A)** Hip rotation is measured with the child prone and knees flexed at a 90-degree angle. On outward rotation the leg produces internal (medial) hip and femoral rotation; on inward rotation the leg produces external hip and femoral rotation. **(B)** Assessment for tibial torsion using thigh–foot angle. When the child is in the prone position with the knee flexed, with normal alignment there is slight external rotation (2); internal tibial torsion produces inward rotation (3); external tibial torsion produces outward rotation (1). (Adapted from Staheli L.T. [1986]. Torsional deformity. *Pediatric Clinics of North America* 33, 1378; and Kliegman R.M., Neider M.I., Super D.M. [Eds.]. [1996]. *Practical strategies in pediatric diagnosis and therapy.* Philadelphia: W.B. Saunders.)

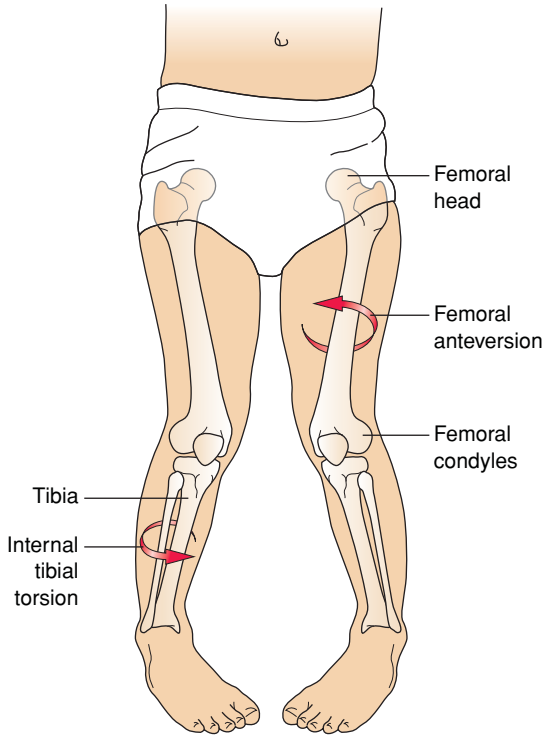


FIGURE 43-16. Femoral anteversion and internal tibial rotation. Femoral anteversion normally decreases from about 40 degrees at birth to 15 degrees at maturity, and internal tibial rotation from 5 degrees at birth to 15 degrees at maturity.

hip such that it does not provide the stable pressure needed to correct the anteversion that is present at birth. Children are most comfortable sitting in the "W" position, with their hips between their knees. It is believed that this position allows the lower leg to act as a lever, producing torsional changes in the femur. When the child stands, the knees turn in and the feet appear to point straight ahead, and when the child walks, the knees and toes point in (Fig. 43-16). Children with this problem are encouraged to sit cross-legged or in the so-called *tailor position* (with the knees touching and the legs folded under). If left untreated, the tibiae compensate by becoming externally rotated so that by 8 to 12 years of age, the knees may turn in but the feet no longer do so. This can result in patellofemoral malalignment with patellar subluxation or dislocation and pain.[48] A derotational osteotomy may be done in severe cases or if there is functional disability.

External femoral torsion is an uncommon disorder characterized by excessive external rotation of the hip. Bilateral external torsion is usually a benign condition, and treatment is observational. When the disorder is unilateral, slipped capital femoral epiphysis should be excluded (to be discussed).[45]

Tibial Torsion. Tibial rotation is determined by measuring the thigh–foot angle, which is done with the ankle and knee positioned at 90 degrees (see Fig. 43-15B). The angle is formed between the longitudinal axis of the femur and the longitudinal axis of the foot. Inward rotation, which is assigned a negative value, indicates internal tibial torsion, and outward rotation, which is given a positive value, represents external tibial rotation. Infants normally have a mean angle of –5 degrees as a consequence of normal in utero position.[45] In midchildhood through adult life the mean angle increases to about 10 degrees.

Internal or medial tibial torsion (i.e., bowing of the tibia) is a rotation of the tibia that makes the feet appear to turn inward. It is the most common cause of intoeing in children younger than 2 years of age.[45] It is present at birth and may fail to correct itself if children sleep on their knees with the feet turned in, or sit on in-turned feet. It is thought to be caused by genetic factors and intrauterine compression, such as an unstretched uterus during a first pregnancy or intrauterine crowding with twins or multiple fetuses. Tibial torsion improves naturally with growth, but this may take several years.[46]

External or *lateral tibial torsion* is a much less common disorder. It is usually seen between 4 and 7 years of age, and is often unilateral.[46] The natural growth rotates the tibia externally, and hence external tibial rotation can become worse with time.[45,46] Clinically, the patella faces outward when the foot is straight. There may be associated patellofemoral instability with knee pain. Although some correction may occur with growth, extremely symptomatic children may require surgical correction, which is usually done after 10 years of age.

Genu Varum and Genu Valgum

Genu varum and genu valgus are common pediatric deformities of the knee. As children grow, lower limb alignment usually follows a predicable pattern (Fig. 43-17). *Genu varum,* or *bowlegs,* is an outward bowing of the knees greater than 1 inch when the medial malleoli of the ankles are touching. Most infants and toddlers have some bowing of their legs up to 18 months of age. If there is a large separation between the knees (>15 degrees) after 2 years of age, the child may require bracing. The child also should be evaluated for diseases such as rickets or tibia vara (i.e., Blount disease, to be discussed).[48]

Genu valgum, or *knock-knees,* is a deformity in which there is decreased space between the knees.[52,53] The medial malleoli in the ankles cannot be brought in contact with each other when the knees are touching. Valgus gradually develops after age 24 months and is most apparent between 3 and 4 years of age (see Fig. 43-17). By 7 years of age, the lower limb is in slight valgus and changes very little thereafter. Genu valgum can be ignored up to 7 years of age, unless it is more than 15 degrees, unilateral, or associated with short stature. It usually resolves spontaneously and rarely requires treatment. Genu varum can cause gait awkwardness and increased risk for sprains and fractures. Uncorrected genu valgum may cause subluxation and recurrent dislocation of the patella, with a predisposition to chondromalacia and joint pain and fatigue. If genu varum or genu valgum persists and is uncorrected, osteoarthritis

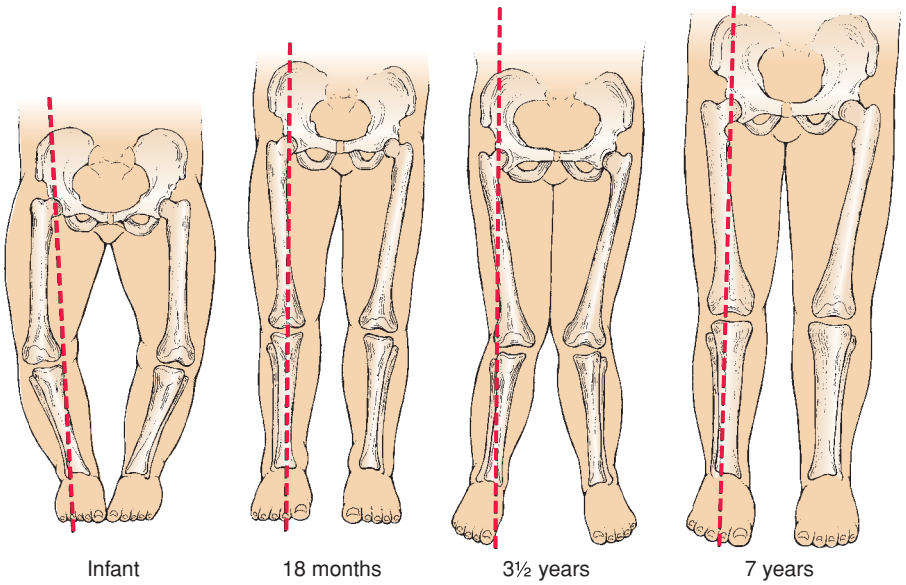


FIGURE 43-17. Lower limb alignment follows a predictable pattern. Infants typically have a gentle varus bow throughout the femur and tibia. By 18 to 24 months, the lower leg is nearly straight, with a neutral mechanical axis. Valgus gradually develops and is most apparent between 3 and 4 years of age. By 7 years of age, the lower limb is in slight valgus and changes very little thereafter. Varus should not recur, nor should valgus increase. (From Schoeneker P.L., Rich M.M. [2006]. The lower extremity. In Morissy R.T., Weinstein S.L. [Eds.], *Lovell & Winter's pediatric orthopaedics* [6th ed., pp. 1158–1213]. Philadelphia: Lippincott Williams & Wilkins.)

may develop in adulthood as a result of abnormal intra-articular stress.

Idiopathic tibia vara, or *Blount disease,* is an abnormal pathologic, developmental bowing that results from altered growth of the upper medial epiphysis[45,48,52] (Fig. 43-18). Although the cause of tibia vara remains unknown, it may occur secondary to growth suppression from increased compression forces across the medial aspect of the knee. Blount disease is more common in obese children who are early walkers. It is also more common in black children. It may be unilateral, in contrast to physiologic bowing, which is almost always bilateral. It has been classified into three types, dependent on the age of onset: infantile (1 to 3 years of age), juvenile (4 to 10 years of age), and adolescent (11 years or older). The juvenile and adolescent forms are commonly combined as late-onset tibia vara.

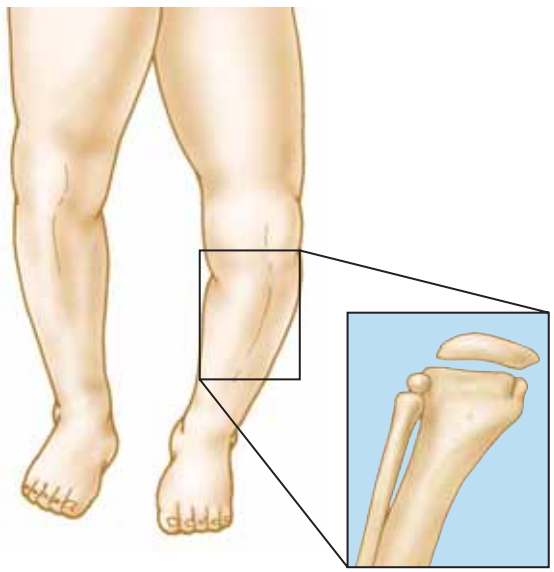


FIGURE 43-18. Rotational deformity of the proximal tibia, especially when unilateral, suggests tibia vera (Blount disease).

The infantile form of tibia vara, which is commonly bilateral, is the most common. Untreated infantile tibia vara is almost always progressive, with evidence of outward angulation, flexion, internal rotation, and abnormal lateral knee laxity. There is radiographic evidence of progressive depression of the medial metaphysis, the growth plate, and the epiphysis. Fusion of the metaphysis to the epiphysis may occur in severe cases. Night-brace treatment is used for mild early-onset disease. Valgus rotational osteotomy of the tibia is usually indicated if angulation persists beyond 3 years of age. Persistent tibia vara leads to early degenerative changes of the knee.

Late-onset Blount disease is more common in obese boys, who are of normal or greater-than-normal height. The condition may be bilateral or unilateral and is often characterized by pain rather than deformity as the primary initial complaint.[44] Radiography shows medial femoral and tibial bowing. Bracing is not practical in obese adolescents. Treatment includes osteotomy to realign the limb or lateral growth plate closure to allow growth to "catch up" medially.[48]

Hereditary and Congenital Disorders

Congenital skeletal deformities can be caused by many factors, including hereditary influences, external agents that injure the fetus (e.g., radiation, alcohol, drugs, viruses), and intrauterine environmental factors. They range in severity from mild limb deformities, which are relatively common, to major limb malformations, which are relatively rare. The most common anomaly of the toes or fingers is *polydactyly,* or the presence of an extra digit on the hand or foot. There may also be a simple webbing of the fingers or toes (syndactyly) or the absence of a bone such as the phalanx, rib, or clavicle. Joint contractures and dislocations produce more severe deformity, as does the absence of entire bones, joints, or limbs.

Osteogenesis Imperfecta

Osteogenesis imperfecta, or brittle bone disease, is a hereditary disorder caused by deficiencies in the synthesis of type I collagen.[15,16,54] It is one of the most common hereditary bone diseases, with an occurrence rate of approximately 1 case in 20,000 births.[54] Although it is usually transmitted as an autosomal trait, a distinctive form of the disorder with multiple lethal defects is thought to be transmitted as an autosomal recessive trait.[16,54] In some cases, the disorder is caused by a spontaneous mutation.

The clinical manifestations of osteogenesis imperfecta include a spectrum of disorders marked by extreme skeletal fragility. Four major subtypes of the disorder have been identified[16] (Table 43-2). The disorder is characterized by thin and poorly developed bones that are prone to multiple fractures. These children have short limbs and a soft, thin cranium with bifrontal prominences that give a triangular appearance to the face. Other problems associated with defective connective tissue synthesis include thin skin, blue or gray sclera, abnormal tooth development, hypotonic muscles, loose-jointedness, scoliosis, and a tendency toward hernia formation. Hearing loss due to otosclerosis of the tiny bones in the middle ear is common in affected adults.

The most serious defects occur when the disorder is inherited as a recessive trait (type II). Severely affected fetuses have multiple intrauterine fractures and bowing and shortening of the extremities. Many of these infants are stillborn or die during infancy. Less severe forms occur when the disorder is inherited as a dominant trait. The skeletal system is not as weakened, and fractures often do not appear until the child becomes active and starts to walk, or even later in childhood. These fractures heal rapidly, although with a poor-quality callus. In some cases, parents may be suspected of child abuse when the child is admitted to the health care facility with multiple fractures. There also is an increased incidence of complications such as hernias and congenital heart abnormalities.

There is no definitive treatment for correction of the defective collagen synthesis that is characteristic of osteogenesis imperfecta. However, a short course of treatment with bisphosphonates has been shown to produce an increase in cortical bone width and cancellous bone volume, as well as increased bone strength and mineral content. In children treated with intravenous pamidronate, this has led to a decrease in fractures, improvements in mobility, and less pain.[54,55] Prevention and treatment of fractures is important. Precise alignment is necessary to prevent deformities. Nonunion is common, especially with repeated fractures. Surgical intervention often is needed to stabilize fractures and correct deformities (e.g., internal fixation of long bones may be done with an intramedullary rod that "grows" with the child).

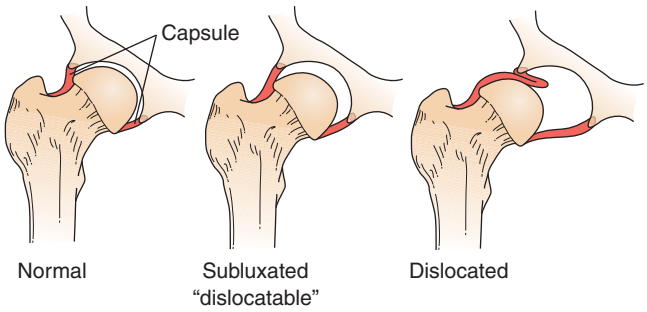


FIGURE 43-19. Normal **(left)** and abnormal relationships of hip joint structure in subluxation **(middle)** and dislocation **(right)**.

Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH), formerly known as *congenital dislocation of the hip*, is an abnormality in hip development that leads to a wide spectrum of hip problems in infants and children, including hips that are unstable, malformed, subluxated, or dislocated.[48,56,57] In less severe cases, the hip joint may be unstable, with excessive laxity of the joint capsule, or subluxated, so that the joint surfaces are separated and there is a partial dislocation (Fig. 43-19). With dislocated hips, the head of the femur is located outside of the acetabulum.

TABLE 43-2 Types of Osteogenesis Imperfecta

Type	Subtype	Inheritance	Major Features
I	Postnatal fractures, blue sclera	Autosomal dominant	Normal stature, skeletal fragility, hearing impairment, joint laxity, blue sclera
II	Perinatal, lethal	Autosomal recessive	Death in utero, or in days after birth Skeletal deformity with excessive fragility, multiple fractures, blue sclera
III	Progressive deformity	Autosomal dominant (75%) Autosomal recessive (25%)	Growth retardation, multiple fractures, progressive kyphoscoliosis, hearing impairment, blue sclera at birth
IV	Postnatal fractures, normal sclera	Autosomal dominant	Moderate skeletal fragility, short stature

Developed from Kumar V., Abbas A. K., Fausto N., Aster V. C. (2010). *Robbins pathologic basis of disease* (8th ed., p. 1212). Philadelphia: Elsevier Saunders.

The results of newborn screening programs have shown that up to 1 of 250 infants have some evidence of hip instability, whereas actual dislocation of the hip is less common, being found in 1 to 1.5 of every 1000 live births.[56] The left hip is involved more frequently than the right hip because of the left occipital intrauterine positioning of most infants. The disorder occurs most frequently in first-born children and is six times more common in female than in male infants.[48] The cause of DDH is multifactorial, with heredity, environmental, and mechanical factors playing a role. A positive family history and generalized laxity of the ligaments are related. The increased frequency in girls is thought to result from their susceptibility to maternal estrogens and other hormones associated with pelvic relaxation. Dislocation also may result from environmental factors such as fetal position, a tight uterus that prevents fetal movement, and breech delivery. The presence of other congenital abnormalities is associated with an increased incidence of DDH. Thus, the hips of children presenting with congenital abnormalities should be examined carefully.

Early diagnosis of DDH is important because treatment is easiest and most effective if begun during the first 6 months of life. Also, repeated dislocations cause damage to the femoral head and the acetabulum. In infants, signs of DDH include asymmetry of the hip or gluteal folds, shortening of the thigh so that one knee (on the affected side) is higher than the other hip, and limited abduction of the affected hip[56,57] (Fig. 43-20). The asymmetry of gluteal folds is not definitive but indicates the need for further evaluation. Physical examination remains the key to the diagnosis of DDH. However, the U.S. Preventive Services Task Force (USPSTF) recently concluded that evidence was insufficient to recommend routine screening of asymptomatic infants as a means of preventing adverse outcomes.[58] This recommendation applies only to infants who do not have obvious hip dislocation or other abnormalities evident without screening.

Several examination techniques can be used to screen for a dislocatable hip. Two provocative dynamic tests for assessing hip stability in the newborn are the Ortolani maneuver (for reducible dislocation) and the Barlow maneuver (for the dislocatable hip)[8,56,57] (Fig. 43-21). The Galeazzi test is a measurement of the length of the femurs that is done by comparing the height at the knees while they are flexed at 90 degrees. An inequality in the height of the knees is a positive Galeazzi sign and is usually caused by hip dislocation or congenital femoral shortening. This test is not useful in detecting bilateral DDH because both leg lengths will be equal. In an older child, instability of the hip may produce a delay in standing or walking and eventually cause a characteristic waddling gait. When the thumbs are placed over the anterior iliac crest and the hands are placed over the lateral pelvis in examination, the levels of the thumbs are not even; the child is unable to elevate the opposite side of the pelvis (positive Trendelenburg test).

Diagnosis of DDH is confirmed by ultrasonography or radiography. Ultrasonography is used in infants with high-risk factors (e.g., female infants born in the breech position) or an abnormal result on examination.[48,56,57] Radiographs of newborns with suspected DDH are of limited value because the femoral heads do not ossify until 4 to 6 months of age. After 6 months of age, the

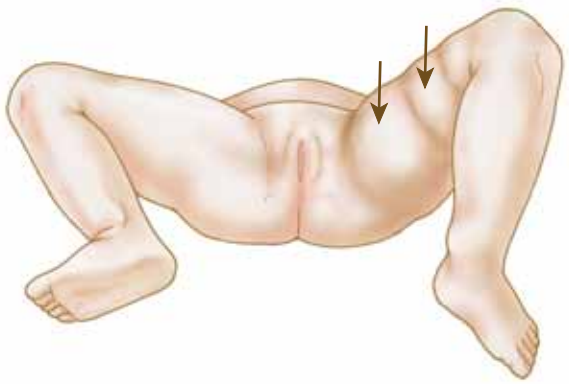


FIGURE 43-20. Congenital dysplasia of the left hip with shortening of the femur, as indicated by legs in abduction and asymmetric gluteal and thigh folds (*arrows*).

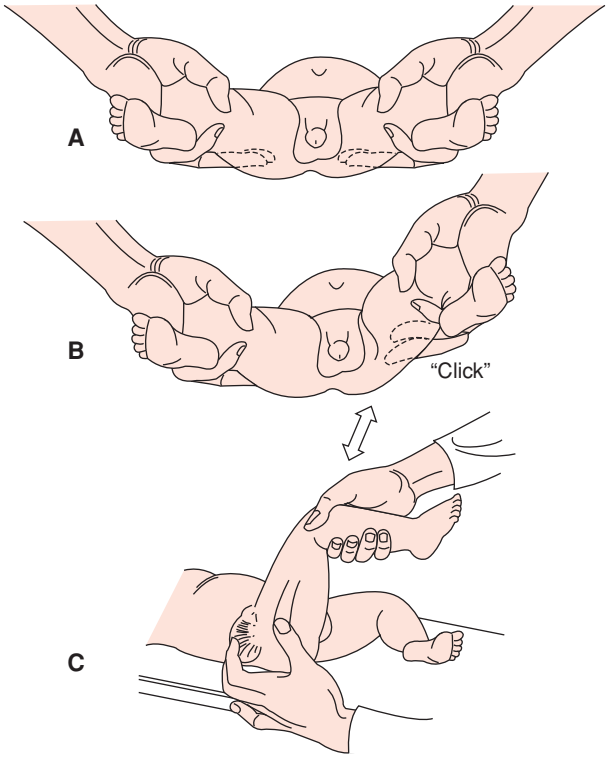


FIGURE 43-21. Examination for developmental dysplasia of the hip. **(A)** In the newborn, both hips can be equally flexed, abducted, and externally rotated without producing a "click." **(B)** A diagnosis of congenital dislocation of the hip may be confirmed by the Ortolani "click" test. The involved hip cannot be abducted as far as the opposite one, and there is a "click" as the hip reduces. **(C)** Telescoping of the femur to aid in the diagnosis of a congenitally dislocated hip. (From Hoppenfeld S. [1976]. *Physical examination of the spine and extremities.* New York: Appleton-Century-Crofts.)

increasing ossification of the femur renders ultrasonography less reliable, and radiographs are preferred.

Treatment of DDH should be individualized and depends on whether the hip is subluxated or dislocated. Subluxation of the hip at birth often resolves without treatment and should be observed for 2 weeks. When subluxation persists beyond this time, treatment may be indicated and referral is recommended. The best results are obtained if the treatment is begun before changes in the hip structure (e.g., 2 to 3 months) prevent it from being reduced by gentle manipulation or abduction devices. The Pavlik harness is used on newborns (up to 6 months) to maintain the femoral head in the acetabulum.[8,48,56,57] The principal goals for treatment of children 6 months to 2 years of age are to obtain and maintain reduction of the hip without damaging the femoral head. Closed reduction is often performed under general anesthesia, followed by several months of immobilization in a hip spica cast, plaster splints, or an abduction splint. Surgical treatment may be required for children who fail to maintain a stable hip with closed reduction methods. The most serious complication of any treatment is avascular necrosis of the femoral head as a result of the forced abduction.[56] This most often occurs as a complication of a closed or open reduction in an older child. In addition, hyperflexion has the potential to cause femoral nerve palsies.

Congenital Clubfoot

Clubfoot, or talipes, is one of the most common pediatric orthopedic conditions. The clubfoot deformity may be positional, congenital, or associated with a variety of other underlying congenital conditions. The positional clubfoot is a normal foot that has been held in a deformed position in utero and is found to be flexible on examination in the nursery. The congenital clubfoot involves a spectrum of severity, while the clubfoot associated with other congenital conditions is typically rigid and difficult to treat.

Congenital clubfoot has an incidence of approximately 1 to 2 cases per 1000 live births, is bilateral in about 50% of cases, and affects boys more often than girls.[50–52] Like congenital dislocation of the hip, its occurrence follows a multifactorial inheritance pattern. Clubfoot may be associated with chromosomal abnormalities or congenital syndromes that are transmitted by mendelian inheritance patterns. However, it is most commonly idiopathic and found in normal infants in whom no genetic or chromosomal abnormality or other extrinsic cause can be found.

In forefoot adduction, which accounts for approximately 95% of idiopathic cases, the foot is plantar flexed and inverted or twisted toward the midline of the leg. This is the so-called *equinovarus type* of clubfoot (Fig. 43-22). The other 5% of cases are of the equinovalgus type, or reverse clubfoot, in which the foot is dorsiflexed and everted. The reverse clubfoot can occur as an isolated condition or in association with multiple congenital defects. At birth, the feet of many infants assume one of these two positions, but they can be passively

FIGURE 43-22. Newborn with clubbing of the left foot. (From the Centers for Disease Control and Prevention Public Health Images Library. ID#: 2632. [Online] Available: http://phil.cdc.gov/phil/detail.asp.)

overcorrected or brought back into the opposite position. If the foot cannot be overcorrected, some type of correction may be necessary.

Treatment of clubfoot is begun as soon as the diagnosis is made. When treatment is initiated during the first few weeks of life, a nonoperative procedure may be effective. Serial manipulations and casting are used gently to correct each component of the deformity. One method, called the *Ponseti method*, involves weekly gentle stretching and manipulation of the misaligned bones followed by application of a well-molded long leg plaster cast with the knee held at a right angle.[59] The cast maintains the correction and allows for further relaxation of tight structures in anticipation of the next week's casting. Correction of the deformity is usually obtained within 6 to 8 weeks. Frequently, a percutaneous Achilles tendon lengthening is performed using a topical anesthetic cream before application of the final cast to allow for complete correction of the equinus deformity. The correction is maintained by full-time wear of a Denis Browne splint for 3 months and part-time wear during napping and at night for approximately 2 to 3 years.[59] Surgery may be required for severe deformities or when nonoperative treatment methods are unsuccessful. It is performed most commonly between 6 and 12 months of age.[48,50]

Juvenile Osteochondroses

The term *juvenile osteochondroses* is used to describe a group of children's diseases in which one or more growth ossification centers undergo a period of degeneration, necrosis, or inactivity that is followed by regeneration and usually deformity. The osteochondroses are separated

into two groups according to their causes. The first group consists of the true osteonecrotic osteochondroses, so called because the diseases are caused by localized osteonecrosis of an apophyseal or epiphyseal center (e.g., Legg-Calvé-Perthes disease, Freiberg infraction, Panner disease, Kienböck disease). The second group of juvenile osteochondroses is caused by abnormalities in ossification of cartilaginous tissue resulting from a genetically determined normal variation or from trauma (e.g., Osgood-Schlatter disease, Blount disease, Sever disease, Scheuermann disease). The discussion in this section focuses on Legg-Calvé-Perthes disease from the first group and Osgood-Schlatter disease from the second group. Slipped capital femoral epiphysis is a disorder of the growth plate.

Legg-Calvé-Perthes Disease

Legg-Calvé-Perthes disease is an idiopathic osteonecrotic disease of the proximal (capital) femoral epiphysis with later reabsorption.[48,56,60,61] The disorder usually, but not exclusively, affects children between the ages of 4 and 8 years. Boys are affected four to five times as often as girls and 10% to 5% of all cases are bilateral. Although no definite genetic pattern has been established, it occasionally affects more than one family member.

The cause of Legg-Calvé-Perthes disease is unknown. The disorder usually is insidious in onset and occurs in otherwise healthy children. It may, however, be associated with acute trauma. Affected children usually have a shorter stature. Recent evidence indicates that some cases may be caused by a subclinical hypercoagulable state such as deficiency in antithrombotic factors S or C or a decrease in fibrinolysis.[48,56] When girls are affected, they usually have a poorer prognosis than boys because they are skeletally more mature and have a shorter period for growth and remodeling than boys of the same age.

The primary pathologic feature of Legg-Calvé-Perthes disease is an avascular necrosis of the bone and marrow involving the epiphyseal growth center in the femoral head. The disorder may be confined to part of the epiphysis, or it may involve the entire epiphysis. In severe cases, there is a disturbance in the growth pattern that leads to a broad, short femoral neck. The necrosis is followed by slow absorption of the dead bone over 2 to 3 years. Although the necrotic trabeculae eventually are replaced by healthy new bone, the epiphysis rarely regains its normal shape.

The main symptoms of Legg-Calvé-Perthes disease are pain in the groin, thigh, or knee and difficulty in walking. The child may have a painless limp with limited abduction and internal rotation and a flexion contracture of the affected hip. The age of onset is important because young children have a greater capability for remodeling of the femoral head and acetabulum, and thus less flattening of the femoral head occurs. Early diagnosis is important and is based on correlating physical symptoms with radiographic findings that are related to the stage of the disease.

The goal of treatment is to reduce deformity and preserve the integrity of the femoral head. Conservative and surgical interventions are used in the treatment of Legg-Calvé-Perthes disease. Children younger than 4 years of age with little or no involvement of the femoral head may require only periodic observation. In all other children, some intervention is needed to relieve the force of weight bearing, muscular tension, and subluxation of the femoral head. It is important to maintain the femur in a well-seated position in the concave acetabulum to prevent deformity. This is done by keeping the hip in abduction and mild internal rotation. Treatment involves periods of rest, use of assistive devices for walking, non–weight bearing, and abduction braces to keep the legs separated in abduction with mild internal rotation. The Atlanta Scottish Rite brace, which does not extend below the knee, is the most widely used orthosis because it provides containment while allowing free knee motion and ambulation without crutches or external support[48,56] (Fig. 43-23). Surgery may be done to contain the femoral head in the acetabulum. This treatment usually is reserved for children older than 6 years of age who at the time of diagnosis have more serious involvement of the femoral head. The best surgical results are obtained when surgery is done early, before the epiphysis becomes necrotic.

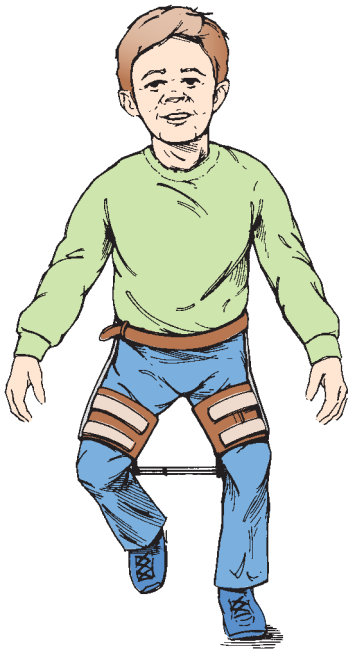


FIGURE 43-23. Scottish Rite brace for Legg-Calvé-Perthes disease produces containment for abduction and allows free knee motion. (From Crocetti M., Barone M.A. [2004]. *Oski's essential pediatrics* [2nd ed., p. 679]. Philadelphia: Lippincott Williams & Wilkins.)

Osgood-Schlatter Disease

Osgood-Schlatter disease involves microfractures in the area where the patellar tendon inserts into the tibial tubercle.[48,53] This area, which is an extension of the proximal tibial epiphysis, is particularly vulnerable to injury caused by sudden or continued strain from the patellar tendon during periods of growth. It occurs most

frequently in boys between the ages of 10 and 15 years and in girls about 2 years before that in boys.[53]

The disorder is characterized by pain in the front of the knee that is associated with inflammation and thickening of the patellar tendon. The pain usually is associated with specific activities such as kneeling, running, bicycle riding, or stair climbing. There is swelling, tenderness, and increased prominence of the tibial tubercle. The symptoms usually are self-limiting. They may recur during growth periods, but usually resolve after closure of the tibial growth plate.

Treatment consists of rest, restriction of activities, and occasionally a knee immobilizer. Complete resolution of symptoms through healing (physical closure) of the tibial tubercle usually requires 12 to 24 months.[53] Occasionally, minor symptoms or an increased prominence of the tibial tubercle may continue into adulthood.

Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis, or coxa vara, is a disorder of the growth plate that occurs near the age of skeletal maturity.[48,56] It involves a three-dimensional displacement of the epiphysis (posteriorly, medially, inferiorly), meaning that the femur is rotated externally from under the epiphysis. It is considered the most common hip disorder of adolescence with an increased prevalence among males, most often between 12 and 15 years of age.[56]

The cause of slipped capital femoral epiphysis is obscure, but it may be related to the child's susceptibility to stress on the femoral neck as a result of genetics or structural abnormalities. Affected children often are overweight with poorly developed secondary sex characteristics, or, in some instances, are extremely tall and thin. In many cases, there is a history of rapid skeletal growth preceding displacement of the epiphysis. The condition also may be affected by nutritional deficiencies or endocrine disorders such as hypothyroidism, hypopituitarism, and hypogonadism. Rapid growth after administration of growth hormone has been associated with displacement of the epiphysis.

Children with the condition often complain of referred knee pain accompanied by difficulty in walking, fatigue, and stiffness. The diagnosis is confirmed by radiographic studies in which the degree of slipping is determined and graded according to severity (mild, <33%; moderate, 33% to 50%; and severe, >50%).[48] Early treatment is imperative to prevent further slippage and permanent deformity. Avoidance of weight bearing on the femur and bed rest are essential parts of the treatment. Traction or gentle manipulation under anesthesia is used to reduce the slip. Surgical insertion of pins to keep the femoral neck and head of the femur aligned is a common method of treatment for children with moderate or severe slips. Crutches are used for several months after surgical correction to prevent full weight bearing until the growth plate closes.

Children with the disorder must be followed closely until the epiphyseal plate closes. Long-term prognosis depends on the amount of displacement that occurs. Complications include avascular necrosis, leg shortening, malunion, and problems with internal fixation. Degenerative arthritis may develop, requiring joint replacement later in life.

Scoliosis

Scoliosis is a lateral curvature of the spine in the upright position. Scoliosis is classified as postural or structural. With postural scoliosis, there is a small curve that corrects with bending. It can be corrected with passive and active exercises. Structural scoliosis does not correct with bending. It is a fixed deformity classified according to the cause: congenital, neuromuscular, or idiopathic. The majority of scoliotic deformities are idiopathic. Others can be congenital, associated with neuromuscular disorders or intraspinal deformities, or are caused by compensation for leg-length discrepancy.[62]

Congenital Scoliosis

Congenital scoliosis is caused by disturbances in vertebral development during the sixth to eighth weeks of embryologic development.[63,64] Congenital scoliosis may be divided into failures of formation and failures of segmentation. Failures of formation indicate the absence of a portion of the vertebra, such as hemivertebra (absence of a whole side of the vertebra) and wedge vertebra (missing only a portion of the vertebra). Failure of segmentation is the absence of the normal separation between the vertebrae. The child may have other anomalies and neurologic complications if the spine is involved. Early diagnosis and treatment of progressive curves are essential for children with congenital scoliosis. Surgical intervention is the treatment of choice for progressive congenital scoliosis.

Neuromuscular Scoliosis

Neuromuscular scoliosis develops from neuropathic or myopathic diseases. It is seen with cerebral palsy, myelodysplasia, and poliomyelitis. There is often a long, C-shaped curve from the cervical to the sacral region. In children with cerebral palsy, severe deformity may make treatment difficult. Myopathic neuromuscular scoliosis develops with Duchenne muscular dystrophy and usually is not severe.

Idiopathic Scoliosis

Idiopathic scoliosis is a structural spinal curvature for which no cause has been established. It occurs in healthy, neurologically normal children. Although the incidence is only slightly greater in girls than boys, it is more likely to progress and require treatment in girls.[8,62–64] The cause is most likely complex and multifactorial. It seems likely that heredity is involved because mother–daughter pairings are common, but identical twins are not uniformly affected. The magnitude of the curvature in an affected individual is not related to magnitude of curvature in relatives. A recent study of the melatonin receptor 1B (*MTNR1B*) gene in persons with adolescent idiopathic scoliosis suggests that the

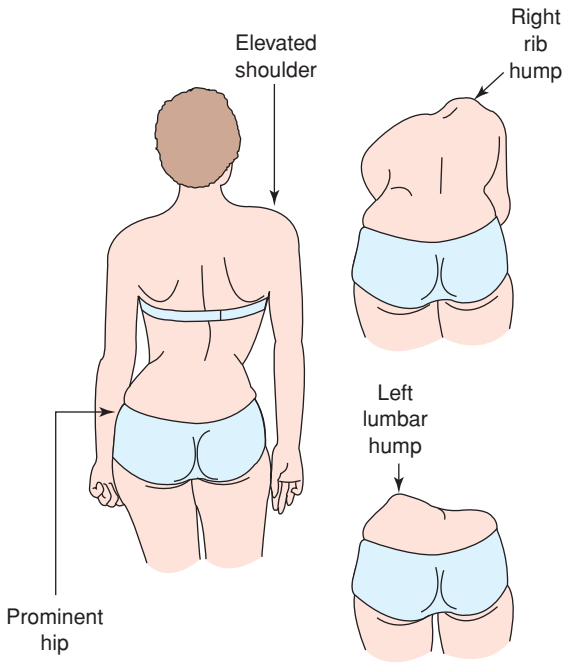


FIGURE 43-24. Scoliosis: abnormalities to be determined at initial screening examination. (From Gore D.R., Passehl R., Sepic S., et al. [1981]. Scoliosis screening: Results of a community project. *Pediatrics* 67, 196–200. Copyright © 1981 by the American Academy of Pediatrics.)

MTNR1B gene may serve as a susceptibility gene for adolescent idiopathic scoliosis.[65]

Idiopathic scoliosis usually appears clinically between the age of 10 and skeletal maturity, but may be seen at any age. By definition, the curve must be greater than 10 degrees. (This has been used historically because 10 degrees is the limit that can be detected by physical examination.)[8] Although a scoliotic curve may be present in any area of the spine, the most common curve is a right thoracic curve.

Manifestations. Scoliosis usually is first noticed because of the deformity it causes. A high shoulder, prominent hip, or projecting scapula may be noticed by a parent or in a school-based screening program (Fig. 43-24). In girls, difficulty in hemming or fitting a dress may call attention to the deformity. Idiopathic scoliosis usually is a painless process, although pain may be present in severe cases, usually in the lumbar region. The pain may be caused by pressure on the ribs or on the crest of the ilium. There may be shortness of breath as a result of diminished chest expansion and gastrointestinal disturbances from crowding of the abdominal organs. Adults with less severe deformity may experience mild backache. If scoliosis is left untreated, the curve may progress to an extent that compromises cardiopulmonary function and creates a risk for neurologic complications.

Diagnosis and Treatment. Early diagnosis of scoliosis can be important in the prevention of severe spinal deformity. The cardinal signs of scoliosis are uneven shoulders or iliac crest, prominent scapula on the convex side of the curve, malalignment of spinous processes, asymmetry of the flanks, asymmetry of the thoracic cage, and rib hump or paraspinal muscle prominence when bending forward (see Fig. 43-24). A complete physical examination is necessary for children with scoliosis because the defect may be indicative of other, underlying pathologic processes.

Diagnosis of scoliosis is made by physical examination and confirmed by radiography. A scoliometer should be used at the apex of the curvature to quantify a prominence; a scoliometer reading of greater than 10 degrees requires referral to a physician. The curve is measured by determining the amount of lateral deviation present on radiographs and is labeled "right" or "left" for the convex portion of the curve. Other radiographic procedures may be done, including CT scanning, MRI, and myelography.

Although school screening continues to be mandated in a number of states, the USPSTF recommends against the routine screening of asymptomatic adolescents for idiopathic scoliosis, indicating that the potential harms from screening include unnecessary follow-up visits and evaluations due to false-positive results, and adverse psychological effects, especially related to brace wear.[66] It is recommended, however, that health care professionals be prepared to evaluate idiopathic scoliosis when it is discovered incidentally or when an adolescent or parent expresses concern about scoliosis.

The treatment of scoliosis depends on the severity of the deformity and the likelihood of curve progression. The three determinants of progression are gender, the curve magnitude at the time of diagnosis, and skeletal growth potential.[62] In all cases, girls have a risk progression of 10 times greater than boys. Larger curves are more likely to progress. Age of presentation also is important. Curves that are detected before menarche are more likely to progress than those detected after menarche. For persons with lesser degrees of curvature (10 to 20 degrees), the trend has been away from aggressive treatment and toward a "wait and see" approach, taking advantage of the more sophisticated diagnostic methods that now are available. Treatment is considered for physically immature patients with curves between 20 and 30 degrees. Curves between 20 and 40 degrees usually are considered for bracing, and those greater than 40 to 45 degrees are considered for surgery.

A brace may be used to control the progression of the curvature during growth and can provide some correction. In an effort to improve compliance, a number of new bracing techniques have been developed. These orthoses consist of easily more concealed, prefabricated forms that are modified to suit the patient. The goals of surgery are to arrest progression of the deformity, improve appearance, and achieve a balanced spine, while limiting the number of vertebral segments that are stabilized. Instrumentation helps correct the curve and balance, and spinal fusion maintains the spine in the corrected position.[62–64] Several methods of instrumentation (i.e., rods that attach to the vertebral column and posterior fusion) are used. Combined anterior and posterior surgery is used for more severe curvatures. The newer systems provide better sagittal control and more stable fixation, which allow earlier mobility. Despite

great advances in spinal surgery, no one method seems to be the best for all cases. There is recent interest in growth modulation approaches using minimally invasive techniques, which will result in curve correction while preserving spinal motion and intervertebral disk viability.[67]

In summary, skeletal disorders can result from congenital or hereditary influences or from factors that occur during normal periods of skeletal growth and development. Newborn infants undergo normal changes in muscle tone and joint motion, causing torsional conditions of the femur or tibia. Many of these conditions are corrected as skeletal growth and development take place. Osteogenesis imperfecta is a rare autosomal hereditary disorder characterized by defective synthesis of connective tissue, including bone matrix. It results in poorly developed bones that fracture easily. Disorders such as developmental dysplasia of the hip and congenital clubfoot are present at birth. Both of these disorders are best treated during infancy. Regular examinations during the first year of life are recommended as a means of achieving early diagnosis of such disorders. Other childhood skeletal disorders, such as the osteochondroses, slipped capital femoral epiphysis, and scoliosis, are not corrected by the growth process. These disorders are progressive, can cause permanent disability, and require treatment.

Scoliosis is a lateral curvature of the spine. Scoliosis is classified as congenital, which results from defects in vertebral development; neuromuscular, which is caused by diseases such as cerebral palsy; and idiopathic, which is the most common form. Idiopathic scoliosis affects girls more often than boys and usually becomes evident between age 10 years and skeletal maturity. The treatment of scoliosis depends on the severity of the deformity and the likelihood of curve progression. Curves between 30 and 40 degrees usually are considered for bracing, and those greater than 40 to 45 degrees are considered for surgery.

REVIEW EXERCISES

1. A 34-year-old football player dislocates his hip during one of the season's games.

- **A.** Explain the need for immediate reduction of the dislocation based on the vascular anatomy of the hip.

2. A 39-year-old man is in intensive care after a motorcycle accident in which he skidded across the pavement on his right side. He has fractures of his right femur, pelvis, and several ribs on the right side. His right leg was crushed beneath the motorcycle, and he is beginning to lose movement in that leg.

- **A.** What are the priorities in treating his orthopedic injuries? What are the available options for stabilizing his leg?
- **B.** What risk factors for complications of fractures are present?
- **C.** What are the symptoms of compartment syndrome, and how is it treated?

3. A 73-year-old woman with a history of breast cancer sustained a comminuted fracture in the middiaphysis of her left humerus when her husband lifted her up in bed. She has multiple lucent lesions scattered throughout her proximal humerus, radius, and ulna. She was recently hospitalized for confusion and found to have diffuse bone metastases.

- **A.** What would you consider to be the most likely cause of her fracture?
- **B.** What are the most common sites for bone metastasis?
- **C.** Explain the treatment goals for persons with pathologic fractures.

4. A 14-year-old boy complains of recent pain and swelling of the knee, with some restriction in movement. Although he thinks he may have injured his knee playing football, his mother insists that he be seen by an orthopedic specialist and raises the possibility that the boy may have an osteosarcoma.

- **A.** Use the information that osteosarcoma originates in sites of maximal growth velocity to explain the site of this boy's possible tumor.
- **B.** What diagnostic tests could be used to establish a diagnosis of osteosarcoma?
- **C.** The boy and his family are concerned that the boy will require radical surgery with amputation of the leg. How would you go about explaining possible treatment options to him?

5. A newborn girl was found to have developmental dysplasia of the hip during a routine screening examination.

- **A.** Describe the anatomic abnormalities that are present in the disorder.
- **B.** Explain the need for early treatment of developmental dysplasia of the hip.

REFERENCES

1. National Centers for Disease Control and Prevention, Centers for Disease Control and Prevention. (2006). *CDC injury fact book*. Atlanta: Centers for Disease Control and Prevention.
2. Wilder R.P., Sethi S. (2004). Overuse injuries: Tendinopathies, stress fractures, compartment syndrome, and shin splints. *Clinics in Sports Medicine* 23, 55–81.
3. Patel D.R., Baker R.J. (2006). Musculoskeletal injuries in sports. *Primary Care Clinics in Office Practice* 32, 545–579.

4. Landry G.L., Logan K. (2007). Sports medicine. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2448–2369). Philadelphia: Saunders Elsevier.
5. Green W.B. (Ed.). (2005). *Essentials of musculoskeletal care* (3rd ed., pp. 62–72, 132–134, 144–233, 401–466, 511–512). Rosemont, IL: American Academy of Orthopedic Surgeons.
6. Weintraub W. (2003). *Tendons and ligament healing* (pp. 11–47). Brookline, MA: Paradigm Publications.
7. Liu S.H., Yang R-S., Al-Shaikh R., et al. (1995). Collagen in tendon, ligament, and bone healing. *Clinical Orthopedics and Related Research* 318, 265–278.
8. Mercier L.R. (2008). *Practical orthopedics* (6th ed., pp. 7–28, 55–87, 158–161, 193–213, 215–241). Philadelphia: Mosby Elsevier.
9. Quillen D.M., Wuchner M., Hatch R.L. (2004). Acute shoulder injuries. *American Family Physician* 70, 1949–1954.
10. Pimentel L. (2006). Orthopedic trauma: Management of major joint injury. *Medical Clinics of North America* 90, 355–382.
11. Englund M., Guermanzi A., Lohmander S.L. (2009). The role of the meniscus in knee osteoarthritis: A cause or consequence. *Radiology Clinics of North America* 47, 703–712.
12. Dixit S., Burton M., Mines B. (2007). Management of patellofemoral pain syndrome. *American Family Physician* 75, 194–204.
13. Brunner L., Eshilian-Oats L. (2003). Hip fractures in adults. *American Family Physician* 67, 537–542.
14. Zuckerman J.D. (1996). Hip fracture. *New England Journal of Medicine* 334, 1519–1525.
15. Hoch B.L., Klein M.J., Schiller A.L. (2008). Bones and joints. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1098–1106). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.
16. Rosenberg A.E. (2010). Bones, joints, and soft tissue tumors. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of medicine* (7th ed., pp. 1205–1256). Philadelphia: Saunders Elsevier.
17. Einhorn T.A. (1998). The cell and molecular biology of fracture healing. *Clinical Orthopaedics and Related Research* 355(Suppl), S7–S21.
18. Hayda R.A., Brighton C.T., Esterhai J.L. (1998). Pathophysiology of delayed healing. *Clinical Orthopedics and Related Research* 355(Suppl), S31–S36.
19. Hoover T.J., Siefert J.A. (2000). Soft tissue complications of orthopedic emergencies. *Emergency Medicine Clinics of North America* 18, 115–139.
20. Tull F., Borrelli J. Jr. (2003). Soft-tissue injury associated with closed fractures: Evaluation and management. *Journal of the American Academy of Orthopedic Surgeons* 11, 431–438.
21. Köstler W., Strom P.C., Sudkamp N.P. (2004). Acute compartment syndrome of the limb. *Injury* 35, 1221–1227.
22. Newton E.J. (2007). Acute complications of extremity trauma. *Emergency Clinics of North America* 25, 751–761.
23. McQueen M.M. (2006). Acute compartment syndrome. In Rockwood C.A., Green D.P, Bucholz R.W. (Eds.), *Rockwood & Green's fractures in adults* (6th ed., Vol. 1, pp. 426–443). Philadelphia: Lippincott Williams & Wilkins.
24. Parisi D.M., Koval K., Egot K. (2002). Fat embolism syndrome. *American Journal of Orthopedics* 31, 507–512.
25. Mellor A., Soni M. (2001). Fat embolism. *Anaesthesia* 56, 145–154.
26. Arai F., Kia T., Nakai T., et al. (2007). Histopathologic features of fat embolism in fulminant fat embolism syndrome. *Anesthesiology* 107, 509–511.
27. Gutierrez K. (2005). Bone and joint infections in children. *Pediatric Clinics of North America* 53, 779–764.
28. Lew D.P., Waldvogel F.A. (2004). Osteomyelitis. *Lancet* 364, 369–379.
29. Calhoun J.J., Manring M.M. (2005). Adult osteomyelitis. *Infectious Disease Clinics* 19, 765–786.
30. Ludwig B., Lazarus A.A. (2007). Musculoskeletal tuberculosis. *Disease of the Month* 53, 39–45.
31. Assouline-Dayan Y., Chang C., Greenspan A., et al. (2002). Pathogenesis and natural history of osteonecrosis. *Seminars in Arthritis and Rheumatism* 32, 94–124.
32. Childs S.G. (2005). Osteonecrosis: Death of bone cells. *Orthopedic Nursing* 24, 295–301.
33. Goytia R.N., Salama A., Khanuja H.S. (2009). Bisphosphonates and osteonecrosis: Potential treatment or serious complication? *Orthopedic Clinics of North America* 40, 223–234.
34. American Cancer Society. (2009). *What is bone cancer?* [Online] Available: http://www.cancer.org. Accessed October 18, 2009.
35. Arndt C.S. (2007). Neoplasms of bone. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 2146–2151). Philadelphia: Saunders Elsevier.
36. Turcotte R.E. (2006). Giant cell tumor of bone. *Orthopedic Clinics of North America* 37, 35–51.
37. Hayden J.B., Hoang B.H. (2006). Osteosarcoma: Basic science and clinical implications. *Orthopedic Clinics of North America* 37, 1–7.
38. Terek R.M. (2006). Recent advances in the basic science of chondrosarcomas. *Orthopedic Clinics of North America* 37, 9–14.
39. Carvajal R., Meyers P. (2005). Ewing's sarcoma and primitive neuroectodermal family of tumors. *Hematology/Oncology Clinics of North America* 19, 501–525.
40. Roodman G.D. (2004). Mechanisms of bone metastasis. *New England Journal of Medicine* 350, 1655–1664.
41. Juan J., Pollock C.B., Kelly K. (2005). Mechanisms of cancer metastasis to the bone. *Cell Research* 15, 57–62.
42. Hershey M.S. (2004). Toward new horizons: The future of bisphosphonate therapy. *The Oncologist* 9(Suppl 4), 38–47.
43. Dunne K.B., Clarren S.K. (1986). The origin of neonatal and postnatal deformities. *Pediatric Clinics of North America* 33(6), 1277–1297.
44. Schoeneker P.L., Rich M.M. (2006). The lower extremity. In Morissy R.T., Weinstein S.L. (Eds.), *Lovell & Winter's pediatric orthopaedics* (6th ed., pp. 1158–1213). Philadelphia: Lippincott Williams & Wilkins.
45. Hosalker H.S., Gholve P.A., Wells L. (2007). Torsional and angular deformities. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2784–2791). Philadelphia: Saunders Elsevier.
46. Sass P., Hassan G. (2003). Lower extremity abnormalities in children. *American Family Physician* 68, 461–468.
47. Maher A.B., Salmond S.B., Pellino T.A. (2002). *Orthopaedic nursing* (3rd ed., pp. 552–568, 601–603). Philadelphia: W.B. Saunders.
48. Crocetti M., Barone M.A. (2004). *Oski's essential pediatrics* (2nd ed., pp. 676–694). Philadelphia: Lippincott Williams & Wilkins.
49. Weinstein S.L. (2005). The pediatric foot. In Weinstein S.L., Buckwalter J.A. (Eds.), *Turek's orthopaedics: Principles and their application* (6th ed., pp. 633–670). Philadelphia: Lippincott Williams & Wilkins.
50. Hosalter H.S., Spiegel D., Davidson R.S. (2007). The foot and toes. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2777–2781). Philadelphia: Saunders Elsevier.
51. Gore A.I., Spencer J. (2004). The newborn foot. *American Family Physician* 69, 865–872.
52. Kim H.W., Park H.W. (2005). The pediatric leg and knee. In Weinstein S.L., Buckwalter J.A. (Eds.), *Turek's orthopaedics: Principles and their application* (6th ed., pp. 575–588). Philadelphia: Lippincott Williams & Wilkins.

53. Holsalter H.S., Wells L. (2007). The knee. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2796–2800). Philadelphia: Saunders Elsevier.
54. Marini J.C. (2007). Osteogenesis imperfecta. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (17th ed., pp. 2887–2890). Philadelphia: Saunders Elsevier.
55. Reid I.R. (2003). Bisphosphonates: New indications and methods of administration. *Current Opinion in Rheumatology* 15, 458–463.
56. Holsalter H.S., Horn D., Friedman J.E., et al. (2007). The hip. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2800–2810). Philadelphia: Saunders Elsevier.
57. Storer S., Skaggs D.L. (2006). Developmental dysplasia of the hip. *American Family Physician* 74, 1310–1316.
58. U.S. Preventive Services Task Force. (2006). Screening for developmental dysplasia of the hip: Recommendation statement. *Pediatrics* 117, 898–902.
59. Faulks S. (2005). Changing paradigm for treatment of clubfeet. *Orthopedic Nursing* 26(1), 25–30.
60. Kocher M.S., Tucker R. (2006). Pediatric athlete hip disorders. *Clinics in Sports Medicine* 25, 241–253.
61. Herring J.A. (2002). Legg-Calvé-Perthes disease. In Herring A.J. (Ed.), *Tachdjian's pediatric orthopaedics* (3rd ed., Vol. 1, pp. 655–709). Philadelphia: W.B. Saunders.
62. Reamy B.V., Slakey J.B. (2001). Adolescent scoliosis: Review and current comments. *American Family Physician* 64, 111–116.
63. Weinstein S. (2005). The thoracolumbar spine. In Weinstein S.L., Buckwalter J.A. (Eds.), *Turek's orthopaedics: Principles and their application* (6th ed., pp. 477–518). Philadelphia: Lippincott Williams & Wilkins.
64. Spiegel D.A., Hosalter H.S., Dormans J.P. (2007). The spine. In Behrman R.E., Kliegman R.M., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 2811–2815). Philadelphia: Saunders Elsevier.
65. Qiu X.S., Tang N.L., Yeung H.Y., et al. (2007). Melatonin receptor 1B (MTNR1B) gene polymorphism is associated with occurrence of adolescent idiopathic scoliosis. *Spine* 32, 1748–1753.
66. U.S. Preventive Services Task Force. (2006). Screening for idiopathic scoliosis in adolescents: Recommendation statement of U.S. Preventative Task Force. *American Family Physician* 71, 1975–1976.
67. Lonner B.S. (2007). Emerging minimally invasive technologies for management of scoliosis. *Orthopedic Clinics of North America* 38, 431–440.

Metabolic Bone Disease
- *Osteopenia*
- *Osteoporosis*
  - Etiology and Pathogenesis
  - Clinical Features
- *Osteomalacia and Rickets*
  - Osteomalacia
  - Rickets
- *Paget Disease*
  - Etiology and Pathogenesis
  - Clinical Features

Rheumatic Disorders
- *Systemic Autoimmune Rheumatic Diseases*
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
  - Systemic Sclerosis/Scleroderma
- *Seronegative Spondyloarthropathies*
  - Ankylosing Spondylitis
  - Reactive Arthritis
  - Psoriatic Arthritis
- *Osteoarthritis*
  - Etiology and Pathogenesis
  - Clinical Features
- *Crystal-Induced Arthropathies*
  - Gout

Rheumatic Diseases in Children and the Elderly
- *Rheumatic Diseases in Children*
  - Juvenile Idiopathic Arthritis
  - Juvenile Dermatomyositis
  - Juvenile Spondyloarthropathies
- *Rheumatic Diseases in the Elderly*
  - Osteoarthritis
  - Rheumatoid Arthritis
  - Crystal-Induced Arthropathies
  - Polymyalgia Rheumatica
  - Management of Rheumatic Diseases in the Elderly

Chapter 44

Disorders of the Skeletal System: Metabolic and Rheumatic Disorders

The skeletal system plays an essential role in mineral homeostasis and mobility. The bones of the skeletal system provide the basic framework that supports the body, protects its organs, and provides for movement. Joints hold the bones of the skeleton together, making movement possible. Bone is also one of the few tissues that normally undergo mineralization. It is a storehouse for 99% of the body's calcium and 85% of its phosphorus. This chapter focuses on two types of skeletal disorders: metabolic bone disorders, which produce a decrease in bone mass and mineralization, and joint disorders, which disrupt mobility.

Metabolic Bone Disease

Metabolic bone disease represents disorders of bone metabolism that result in structural effects on the skeleton, including decreased bone density and diminished bone strength. The strength of bone is determined by its composition and structure.[1] Bone must be both rigid and flexible. It must be rigid enough to support the body, yet flexible enough to absorb energy by deforming, to shorten and widen when compressed, and to lengthen and narrow under tension without cracking.

There are two types of bone: cortical and trabecular. Cortical or compact bone is composed of densely packed layers of mineralized collagen; it provides rigidity and is the major component of tubular bones (see Chapter 42, Fig. 42-1). Trabecular or cancellous bone is spongy on cross-section; it provides strength and elasticity, and constitutes the major part of axial skeletal structures such as the vertebrae. Disorders in which cortical bone is defective or reduced in mass lead to fractures of the long bones, whereas those of cancellous bone lead preferentially to vertebral fractures.

Metabolic Bone Disorders

- Metabolic bone disorders have their origin in the bone remodeling process that involves an orderly sequence of osteoclastic bone reabsorption, the formation of new bone by the osteoblasts, and mineralization of the newly formed osteoid tissue.
- Osteoporosis represents an increased loss of total bone mass due to an imbalance between bone absorption and bone formation, most often related to the aging process and decreased estrogen levels in postmenopausal women.
- Osteomalacia and rickets represent a softening of bone due to inadequate mineralization of the bone matrix caused by a deficiency of calcium or phosphate.
- Paget disease is a disorder involving excessive bone destruction and repair, resulting in structural deformities of the long bones, spine, pelvis, and cranium.

Osteopenia

Osteopenia is a condition that is common to all metabolic bone diseases. It is characterized by a reduction in bone mineral density greater than expected for age, race, or gender, and occurs because of a decrease in bone formation, inadequate bone mineralization, or excessive bone deossification.[2] *Osteopenia* is not a diagnosis but a term used to describe an apparent lack of bone density seen on x-ray studies. Approximately 60% of bone is mineral content, approximately 30% is organic matrix, and the remainder is living bone cells. Osteopenia can involve a decrease in bone matrix due to an imbalance between bone formation and destruction, or a decrease in mineralization. The major causes of osteopenia are osteoporosis, osteomalacia, malignancies such as multiple myeloma, and endocrine disorders such as hyperparathyroidism and hyperthyroidism.

Osteoporosis

Osteoporosis is a metabolic bone disease characterized by decreased bone density (i.e., increased porosity) and strength in which both the bone matrix and mineralization are decreased.[3–8] The World Health Organization has defined osteoporosis as a bone mineral density (BMD) value greater than 2.5 standard deviations below the mean for normal young white women.[7] The exact value is difficult to determine because bone loss varies in the different parts of the skeleton where bone mass is measured, and definitions of osteoporosis have not been developed for all subpopulations. Osteoporosis can occur as the result of a number of disorders, but is most often associated with the aging process. In the United States alone, osteoporosis affects approximately 10 million persons aged 50 years or older, and an additional 34 million have low bone mass (osteopenia) and are potentially at risk for development of osteoporosis and its complications.[8]

Etiology and Pathogenesis

The cause of osteoporosis remains largely unknown, but most data suggest an imbalance between bone resorption and formation such that bone resorption exceeds bone formation. Although both of these factors play a role in most cases of osteoporosis, their relative contribution to bone loss may vary depending on age, gender, genetic predisposition, activity level, and nutritional status.

Under normal conditions, bone mass increases steadily during childhood, reaching a peak in the young adult years. The peak bone mass, or BMD, is an important determinant of the subsequent risk for osteoporosis. It is determined in part by genetic factors, hormone (estrogen) levels, exercise, calcium intake and absorption, and environmental factors (Chart 44-1). Genetic factors are linked, in largest part, to the maximal amount of bone in a given person, referred to as *peak bone mass*. Race is a

CHART 44-1 Risk Factors Associated with Osteoporosis*

Personal Characteristics
Advanced age
Female
Gender Ethnicity (white or Asian)
Small bone structure/low body weight
Postmenopausal
Family history

Lifestyle
Sedentary
Calcium/Vitamin D deficiency
High-protein diet
Excessive alcohol intake
Excessive caffeine intake
Smoking

Drug and Disease Related
Aluminum-containing antacids
Anticonvulsants
Heparin
Corticosteroids or Cushing disease
Gastrectomy
Celiac disease
Diabetes mellitus
Anorexia nervosa/female athlete triad
Hyperthyroidism
Hyperparathyroidism
Rheumatoid arthritis

*Not exclusive

key determinant of BMD and the risk of fractures. Incidence rates obtained from studies among racial and ethnic groups demonstrate that although women have higher fracture rates compared with men overall, these differences vary by race and age. White and Asian women had higher rates for all age groups older than 50 years.[9] The highest BMD values and lowest fracture rates have been reported for black women.[9] Body size is another factor affecting the risk of osteoporosis and risk of fractures. Women with smaller body builds are at increased risk of hip fracture because of lower hip BMD.

Hormonal factors play a significant role in the development of osteoporosis, particularly in postmenopausal women.[10] Postmenopausal osteoporosis, which is caused by an estrogen deficiency, is manifested by a loss of cancellous bone and a predisposition to fractures of the vertebrae and distal radius. The loss of bone mass is greatest during early menopause, when estrogen levels are withdrawing. Several factors appear to influence the increased loss of bone mass associated with an estrogen deficiency, including an increased secretion of cytokines by monocytes and bone marrow cells. These cytokines stimulate osteoclast recruitment and activity by increasing the levels of RANK ligand (RANKL) while diminishing the expression of osteoprotegerin (OPG)[3] (see Chapter 42, Understanding Bone Remodeling). Compensatory osteoblastic activity and new bone formation occurs, but does not keep pace with the bone that is lost.

Male sex hormone deficiency may contribute to age-related bone loss in men, although the effect is not of the same magnitude as that caused by estrogen deficiency. Unlike women, men do not have a midlife loss of sex hormone production.[11] Another factor that provides relative protection for men is the fact that they achieve 8% to 10% more peak bone mass than women. Although androgens have long been assumed to be critical for growth and maintenance of the male skeleton, it has recently been suggested that estrogens obtained from peripheral conversion of testicular and adrenal hormone precursors may be even more important than androgens in the maintenance of bone mass in men.

Age-related changes in bone density occur in all individuals and contribute to the development of osteoporosis in both sexes. Age-related changes in bone cells and matrix have a strong impact on bone metabolism. Osteoblasts from elderly persons have reduced replicative and biosynthetic potential compared with those of younger persons. Growth factors that stimulate osteoblastic activity also lose their potential over time. The end result is a skeleton that has decreased ability to make bone. Reduced physical activity increases the rate of bone loss because mechanical forces are important stimuli for normal bone remodeling. Thus, the decreased physical activity that often accompanies aging may also contribute to the loss of bone mass in the elderly.

Secondary osteoporosis is associated with many conditions, including endocrine disorders, malabsorption disorders, malignancies, alcoholism, and certain medications.[12] Persons with endocrine disorders such as hyperthyroidism, hyperparathyroidism, Cushing syndrome, or diabetes mellitus are at high risk for development of osteoporosis. Hyperthyroidism causes an acceleration of bone turnover. Some malignancies (e.g., multiple myeloma) secrete osteoclast-activating factor, causing significant bone loss. Alcohol is a direct inhibitor of osteoblasts and may also inhibit calcium absorption. Corticosteroid use is the most common cause of drug-related osteoporosis, and long-term corticosteroid use in the treatment of disorders such as rheumatoid arthritis and chronic obstructive lung disease is associated with a high rate of fractures. The prolonged use of aluminum-containing antacids, which increase calcium excretion, and anticonvulsants, which impair vitamin D production, may also contribute to bone loss. Persons with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) who are being treated with antiretroviral therapy may develop a decrease in bone density and signs of osteopenia and osteoporosis.[13]

Several groups of children and adolescents are at particular risk for decreased bone mass, including premature infants and those with low birth weight who have lower-than-expected bone mass in the early weeks of life, children who require treatment with corticosteroid drugs (e.g., those with childhood inflammatory diseases and transplant recipients), children with cystic fibrosis, and those with hypogonadal states (e.g., anorexia nervosa and the female athlete triad). Children with cystic fibrosis often have impaired gastrointestinal function that reduces the absorption of calcium and other nutrients, and many also require the frequent use of corticosteroid drugs.

Premature osteoporosis is increasingly being seen in female athletes owing to an increased prevalence of eating disorders and amenorrhea.[14] It most frequently affects women engaged in endurance sports, such as running and swimming; in activities where appearance is important, such as figure skating, diving, and gymnastics; or in sports with weight categories, such as horse racing, martial arts, and rowing. The *female athlete triad* refers to a pattern of disordered eating that leads to amenorrhea and eventually osteoporosis. Poor nutrition, combined with intense training, can decrease the critical body fat–to–muscle ratio needed for normal menses and estrogen production by the ovary. The decreased levels of estrogen combined with the lack of calcium and vitamin D from dietary deficiencies result in a loss of bone density and increased risk for fractures. There is a concern that athletes with low BMD will be at increased risk for fractures during their competitive years. It is unclear whether osteoporosis induced by amenorrhea is reversible. Data are emerging that even having only one or two elements of the triad greatly increases the risk of these women for long-term morbidity.[14]

Clinical Features

Osteoporotic changes occur in the diaphysis and metaphysis of bone. There is loss of trabeculae from cancellous bone and thinning of the cortex to such an extent that minimal stress causes fractures. The changes that occur with osteoporosis have been explained by two distinct disease processes: postmenopausal and senile, or age-related, osteoporosis. In postmenopausal women, the

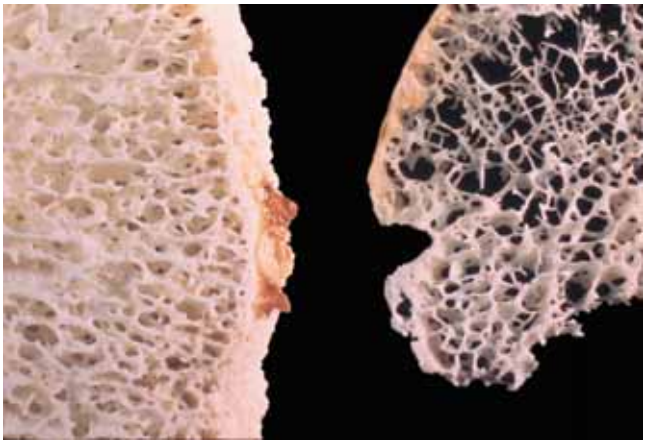


FIGURE 44-1. Osteoporosis. Femoral head of an 82-year-old woman with osteoporosis and femoral neck fracture **(right)**, compared with a normal control bone cut to the same thickness **(left)**. (From Hoch B.J., Klein M.J., Schiller A.L. [2008]. Bones and joints. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1109]. Philadelphia: Lippincott Williams & Wilkins.)

increase in osteoclastic activity affects mainly bones or portions of bone that have increased surface area, such as the cancellous compartment of the vertebral bodies. The osteoporotic trabeculae become thinned and lose their interconnections, leading to microfractures and eventual vertebral collapse. In senile osteoporosis, the osteoporotic cortex is thinned by subperiosteal and endosteal resorption and the haversian systems are widened. In severe cases, the haversian systems are so enlarged that the cortex resembles cancellous bone (Fig. 44-1). Hip fractures, which are seen later in life, are more commonly associated with senile osteoporosis.

Clinical Manifestations. Osteoporosis is usually a silent disorder. Often, the first manifestations of the disorder are those that accompany a skeletal fracture—a vertebral compression fracture or fracture of the hip, pelvis, humerus, or other bones (Fig. 44-2). Fractures are typically sudden in onset and may be caused by a fall, sudden movement, lifting, jumping, or even coughing. Hip fractures occur mainly in persons over age 65. Wedging and collapse of vertebrae cause a loss of height in the vertebral column and kyphosis, a condition commonly referred to as *dowager hump*. Usually, there is no generalized bone tenderness. When pain occurs, it usually is related to fractures. Systemic symptoms such as weakness and weight loss suggest that the osteoporosis may be caused by underlying disease.

Diagnosis and Treatment. An important advance in diagnostic methods used for the identification of osteoporosis has been the use of BMD assessment. The clinical method of choice for BMD studies is dual-energy x-ray absorptiometry (DEXA) of the spine and hip.[15,16] Measurement of serial heights in older adults is another simple way to screen for osteoporosis. A further advance in the diagnosis of osteoporosis is the refinement of risk

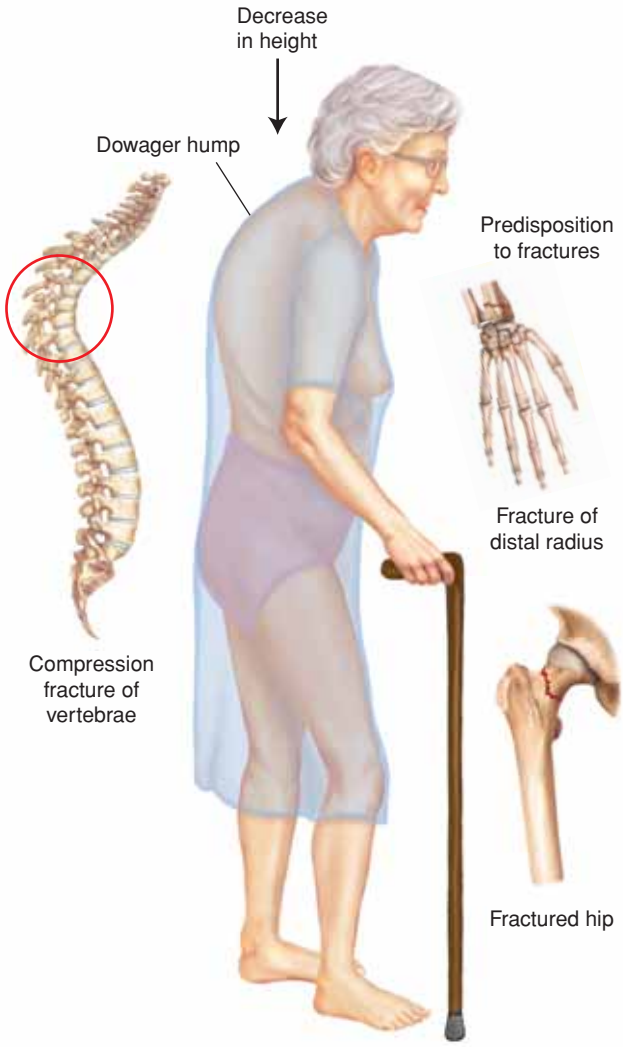


FIGURE 44-2. Clinical manifestations of osteoporosis.

factors, permitting better analysis of risk pertaining to particular persons. The U.S. Preventive Services Task Force (USPSTF) recommends a screening DEXA of all women 65 years of age and older, as well as women 60 to 64 years of age who have an increased fracture risk.[17] Although there are no USPSTF guidelines for BMD testing in men, the National Osteoporosis Foundation (NOF) recommends screening for all men 70 years of age and older and men 50 to 69 years of age with risk factors.[18]

Prevention and early detection of osteoporosis are essential to the prevention of associated deformities and fractures. It is important to identify persons in high-risk groups so that preventive measures can begin early (see Chart 44-1). Regular exercise and adequate calcium and vitamin D intake are important factors in preventing osteoporosis. Weight-bearing exercises such as walking, jogging, rowing, and weight lifting are important in the maintenance of bone mass. Studies have indicated that premenopausal women need more than 1000 mg/day of calcium, and postmenopausal women need at least 1200 mg of calcium daily.[15,18] Because most older American women do not consume a sufficient quantity of dairy

products to meet their calcium needs, calcium supplementation is recommended. A daily intake of 800 to 1000 IU of vitamin D is recommended for adults age 50 years and older. Many elderly persons are at high risk for vitamin D deficiency, especially those with chronic illness, malabsorption disorders (e.g., celiac disease), and limited exposure to sunlight. It is recommended that serum vitamin D levels be obtained for persons at risk of a deficiency and that supplemental vitamin D be prescribed for persons with low serum levels.[18]

There are four main types of drugs used in the treatment of osteoporosis: bisphosphonates, selective estrogen receptor modulators, calcitonin, and recombinant parathyroid hormone. Bisphosphonates are effective inhibitors of bone resorption and the most effective agents for prevention and treatment of osteoporosis.[15,18] The bisphosphonates (e.g., alendronate, risedronate, ibandronate) are analogs of endogenous inorganic pyrophosphate that the body cannot break down. In bone, they bind to hydroxyapatite and prevent bone resorption by inhibiting osteoclast activity. The most dramatic impact has been in the reduction of multiple spine fractures, showing that treatment can decrease progression of the disease.

Raloxifene, a selective estrogen receptor modulator (SERM) that acts only on specific estrogen receptors, has been approved by the U.S. Food and Drug Administration (FDA) for prevention and treatment of osteoporosis in postmenopausal women. Although hormone therapy (i.e., estrogen with or without progesterone) has been shown to slightly reduce the risk of hip and vertebral fractures in postmenopausal women, the use of hormone therapy has come under scrutiny after the recent release of data from the Women's Health Initiative, which linked hormone replacement therapy to an increased risk of stroke, venous thromboembolism, coronary heart disease, and breast cancer.[19]

Calcitonin is an endogenous peptide that partially inhibits osteoclastic activity. Nasal calcitonin has been approved for the treatment of postmenopausal osteoporosis. It has been shown to decrease the occurrence of vertebral fractures, but not nonvertebral or hip fractures. Because more effective drugs are available, it is not usually considered first-line treatment for osteoporosis. Teriparatide, a recombinant human parathyroid hormone, was recently approved by the FDA for the treatment of osteoporosis.[15] Unlike the antiresorptive drugs, parathyroid hormone is a potent anabolic agent that stimulates bone remodeling by increasing osteoblast-mediated bone formation.

Persons with osteoporosis have many special needs. Walking and swimming are encouraged. Unsafe conditions that predispose persons to falls and fractures should be corrected or avoided. In treating fractures, it is important to minimize immobility. Surgical interventions are used to provide stable fixation of lower extremity fractures and allow for early weight bearing and restoration of mobility and function. Vertebral fractures are treated symptomatically. Conservative treatment with bracing is most often seen, especially in fractures of the thoracic vertebra. Vertebroplasty and kyphoplasty are minimally invasive spinal procedures that use bone cement to restore vertebral height and relieve pain.[20] Bone cement is instilled directly into the fractured vertebral body to restore height and shape. Kyphoplasty involves the use of a balloon as a tamp to create a void for the cement, and seems to be associated with less cement extravasation and better restoration of vertebral height than vertebroplasty.[20]

Osteomalacia and Rickets

In contrast to osteoporosis, which causes a loss of total bone mass and results in brittle bones, osteomalacia and rickets produce a softening of the bones resulting from an inadequate mineralization of newly formed bone matrix.[4] The term *rickets* refers to the disorder in children in which changes in bone growth produce characteristic skeletal abnormalities, and *osteomalacia* is used in adults because the bone that forms during the remodeling process is undermineralized.[4]

Osteomalacia

Osteomalacia is a generalized bone condition in which there is inadequate mineralization of bone. There are two main causes of osteomalacia: (1) insufficient calcium absorption from the intestine because of a lack of dietary calcium or a deficiency of or resistance to the action of vitamin D and (2) phosphate deficiency caused by increased renal losses or decreased intestinal absorption. Vitamin D is ingested in the diet and synthesized in the skin from 7-dehydrocholesterol under the influence of ultraviolet B (UVB) sunlight. The vitamin is first hydroxylated in the liver to form its major metabolite, 25-hydroxyvitamin D. It is then hydroxylated in the kidney to produce the active hormone $1,25(OH)_2D$ (see Chapter 42). There are many causes of vitamin D deficiency including reduced skin synthesis, inadequate dietary intake, diminished intestinal absorption, and heritable and acquired disorders of vitamin D metabolism and responsiveness.[21,22]

The incidence of osteomalacia is high among the elderly because of diets deficient in calcium and vitamin D, a problem often compounded by the intestinal malabsorption that accompanies aging. Melanin is extremely efficient in absorbing UVB radiation; thus, decreased skin pigmentation markedly reduces vitamin D synthesis, as does the use of sunscreens. Osteomalacia also may occur in persons on long-term treatment with medications such as anticonvulsants (e.g., phenytoin, carbamazepine, valproate) that decrease the activation of vitamin D in the liver. There also is a greater incidence of osteomalacia in the colder regions of the world, particularly during the winter months, probably because of lessened exposure to sunlight.

A form of osteomalacia called *renal rickets* occurs in persons with chronic renal failure. It is caused by the inability of the kidney to activate vitamin D and excrete phosphate and is accompanied by hyperparathyroidism, increased bone turnover, and increased bone resorption (see Chapter 26). Another form of osteomalacia results

from renal tubular defects that cause excessive phosphate losses. This form of osteomalacia is commonly referred to as *vitamin D–resistant rickets,* and often is a familial disorder.[4] It is inherited as an X-linked dominant gene passed by mothers to one half of their children and by fathers to their daughters only. This form of osteomalacia affects boys more severely than girls. Long-standing primary hyperparathyroidism causes increased calcium resorption from bone and hypophosphatemia, which can lead to rickets in children and osteomalacia in adults.

The clinical manifestations of osteomalacia are bone pain, tenderness, and fractures as the disease progresses. In severe cases, muscle weakness often is an early sign. Osteomalacia predisposes a person to pathologic fractures in the weakened bones, especially those in the distal radius and the proximal femur. In contrast to osteoporosis, it is not a significant cause of hip fractures. There may be delayed healing and poor retention of internal fixation devices. Osteomalacia usually is accompanied by a compensatory or secondary hyperparathyroidism stimulated by low serum calcium levels. Parathyroid hormone reduces renal absorption of phosphate and removes calcium from the bone. Serum calcium levels are only slightly reduced in osteomalacia.

Diagnostic measures are directed toward identifying osteomalacia and establishing its cause. Diagnostic methods include x-ray studies, laboratory tests, bone scan, and bone biopsy. X-ray findings typical of osteomalacia are the development of transverse lines or pseudofractures called *Looser zones*. These apparently are caused by stress fractures that are inadequately healed or by the mechanical inadequacy of penetrating nutrient vessels.[4] A bone biopsy may be done to confirm the diagnosis of osteomalacia in a person with nonspecific osteopenia who shows no improvement after treatment with exercise, vitamin D, and calcium.

The treatment of osteomalacia is directed at the underlying cause. If the problem is nutritional, restoring adequate amounts of calcium and vitamin D to the diet may be sufficient. The elderly and persons with an inadequate dietary intake or sunlight exposure may require supplemental vitamin D. Supplemental vitamin D is specific for vitamin D–resistant rickets, but large doses usually are needed to overcome the resistance to calcium absorption action and to prevent renal loss of phosphate. The biologically active forms of vitamin D, 25-OH vitamin D (calciferol) or 1,25-$(OH)_2$ vitamin D (calcitriol), are available for use in the treatment of osteomalacia resistant to vitamin D (i.e., osteomalacia resulting from chronic liver disease and kidney failure). If osteomalacia is caused by malabsorption, the treatment is directed toward correcting the primary disease. For example, adequate replacement of pancreatic enzymes is of paramount importance in pancreatic insufficiency. In renal tubular disorders, the treatment is directed at the altered renal physiology.

Rickets

Rickets is a metabolic bone disorder characterized by a failure or delay in calcification of the cartilaginous growth plate in children whose epiphyses have not yet fused.[23–25] It is also manifested by widening and deformation of the metaphyseal regions of long bones and a delay in the mineralization of trabecular, endosteal, and periosteal bone surfaces. There are several forms of rickets, including nutritional rickets, vitamin D–dependent rickets, and vitamin D–resistant rickets. As with osteomalacia in the adult, rickets can result from kidney failure; malabsorptive syndromes such as celiac disease and cystic fibrosis; and medications such as anticonvulsants, which impair the activation of vitamin D in the liver, and aluminum-containing antacids, which bind phosphorus and prevent its absorption.

Nutritional rickets results from inadequate sunlight exposure or inadequate intake of vitamin D, calcium, or phosphate. Although uncommon in developed countries of the world, rickets still can occur, particularly when an infant is solely breast fed, is dark skinned, or has limited exposure to sunlight. Modern conditions of dress, lifestyle, and recommendations regarding sun avoidance to reduce skin cancer risk may prevent a large proportion of the population from producing adequate amounts of vitamin D. Because rickets is not a reportable disease, the only current prevalence estimates have been obtained mainly from case reports and hospital records. According to reported and published cases in the United States, nutritional rickets increased from 65 cases between 1975 and 1985 to 166 cases between 1986 and 2003.[25] Since then, 3 reports added another 62 cases to the American literature. In 2003, the American Academy of Pediatrics recommended a vitamin D supplement for breast-fed infants who do not consume at least 500 mL of vitamin D–fortified formula/beverages and non–breast-fed infants who do not consume greater than 500 mL of vitamin D—fortified beverages.[25] The supplementation should start during the first 2 months of life and continue throughout childhood and adolescence.

Vitamin D–dependent rickets can result from abnormalities in the gene coding for the enzyme that converts inactive vitamin D to the active form of vitamin D, or from an autosomal disorder caused by mutations in the vitamin D receptor.[24] Vitamin D–resistant rickets involves hypophosphatemia or a decrease in serum phosphate levels, the most common form being caused by mutations of the phosphate-regulating gene on the X chromosome.[24] The gene mutation causes renal wasting of phosphate at the proximal tubular level of the kidney.

Clinical Features. Rickets is characterized by changes in the growing bones of children with overgrowth of the epiphyseal cartilage due to inadequate provisional calcification and failure of the cartilage cells to disintegrate. Bones become deformed; ossification at the epiphyseal plates is delayed and disordered, resulting in widening of the epiphyseal cartilage plate. Any new bone that does grow is unmineralized. The conformation of the gross skeletal changes depends on the severity and duration of the rachitic process, and in particular on the stresses to which the individual bones are subjected. During the nonmobile stage of infancy, the head and chest undergo

FIGURE 44-3. A child suffering from nutritional rickets. Note the bowed legs, protruding abdomen, and enlarged left wrist. (From Centers for Disease Control and Prevention Public Health Images Library.)

the greatest stresses. The skull is enlarged and soft, and closure of the fontanels is delayed. Teeth are slow to develop, and the child may have difficulty standing. When an ambulating child develops rickets, deformities are likely to affect the spine, pelvis, and long bones (i.e., tibia), causing, most notably, lumbar lordosis and bowing of the legs (Fig. 44-3). The ends of long bones and ribs are enlarged. The thorax may be abnormally shaped, with prominent rib cartilage (i.e., rachitic rosary). The child usually has stunted growth, with a height sometimes far below the normal range. Weight often is not affected so that the children, many of whom present with a protruding abdomen (i.e., rachitic potbelly), have been described as presenting a Buddha-like appearance when sitting.

Nutritional rickets is treated with a balanced diet sufficient in calcium, phosphorus, and vitamin D. Exposure to sunlight also is important, especially for premature infants and those on artificial milk feedings. Supplemental vitamin D in excess of normal requirements is given for several months. Children with vitamin D–dependent rickets caused by lack of the enzyme needed to convert vitamin D to its active form are treated with calcitriol, the active form of vitamin D.[24] Vitamin D–resistant forms of rickets are treated with oral phosphorus or oral phosphorus and calcitriol. Maintenance of good posture, positioning, and bracing in older children are used to prevent deformities. After the disease is controlled, deformities may have to be surgically corrected as the child grows.

Paget Disease

Paget disease (i.e., osteitis deformans) is the second most common bone disease after osteoporosis.[3,4,26–28] The disease, which has been described as a "collage of matrix madness," is characterized by focal areas of excessive osteoclast-mediated bone reabsorption preceding disorganized osteoblast-mediated bone repair. Paget disease usually begins during midadulthood and becomes progressively more common with increasing age. It is more common in people of Northern European heritage. Men are about twice as likely as women to have the disease.[28]

Etiology and Pathogenesis

Although the pathogenesis of Paget disease remains unclear, there is evidence of both genetic and environmental influences. It has been reported that 15% to 40% of persons with the disease have a first-degree relative with Paget disease, and numerous studies have described extended family members with the disease.[28] There is increasing evidence that Paget disease and some related diseases are caused by mutations in genes encoding proteins in the RANK signaling pathways.[3,4] Other evidence presents a probable association with a virus, possibly a paramyxovirus, suggesting that a viral infection may serve as a trigger for development of Paget disease in genetically predisposed individuals.[4,28]

Paget disease is a focal process with considerable variation in its stage of development in separate skeletal sites. At the onset, the disease is marked by regions of furious osteoclastic bone resorption, followed by a period of hectic bone formation with increased numbers of osteoblasts rapidly depositing bone in a chaotic fashion such that the newly formed bone is of poor quality and is disorganized rather than lamellar. The poor quality of bone accounts for the bowing and fractures that occur in bones affected by the disease. The bone marrow adjacent to the bone-forming surface is replaced by loose connective tissue that contains osteoprogenitor cells and numerous blood vessels, which transport blood to and from these metabolically active sites. The lesions of Paget disease may be solitary or may occur in multiple sites. They tend to localize to the bones of the axial skeleton, including the skull, spine, and pelvis. The proximal femur and tibia may be involved in more widespread forms of the disease. Histologically, Paget lesions show increased vascularity and bone marrow fibrosis with intense cellular activity. The bone has a somewhat mosaic-like pattern caused by areas of density outlined by heavy blue lines, called *cement lines* (Fig. 44-4).

Clinical Features

The clinical manifestations of Paget disease are extremely variable and depend on the extent and site of the disease (see Fig. 44-4). The disease is usually asymptomatic and discovered as an incidental radiograph finding.[27] Skeletal expansion and distortion may be obvious if the disease

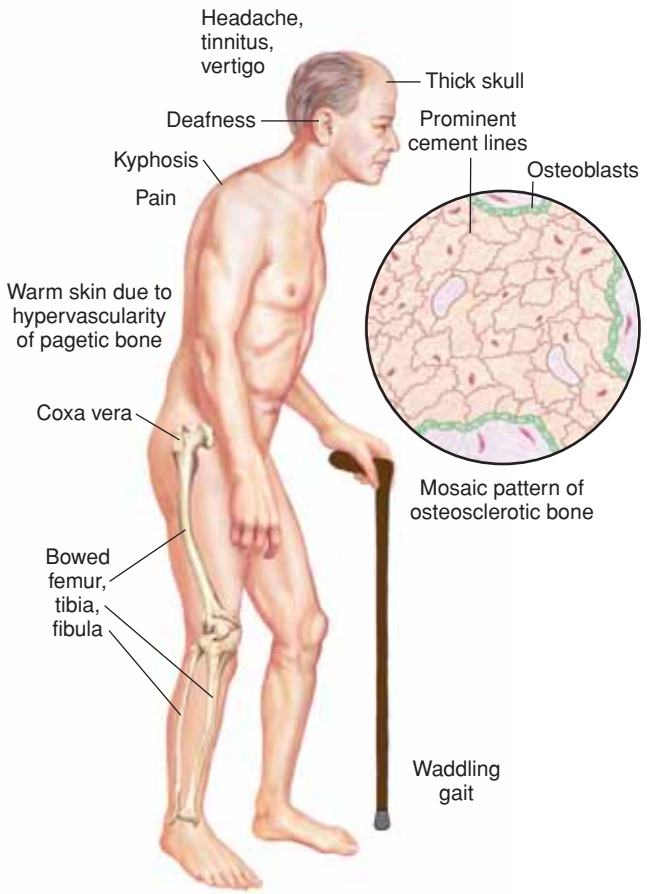


FIGURE 44-4. Clinical manifestations of Paget disease.

affects the skull, jaw, clavicle, or long bones of the leg. Involvement of the skull causes headaches, intermittent tinnitus, vertigo, and eventual hearing loss. The vertebrae of the spine may enlarge, weaken, and collapse, causing kyphosis of the thoracic spine and nerve compression. Weight bearing may cause anterior bowings of the femur and tibia. Softening of the femoral neck can cause coxa vara (i.e., reduced angle of the femoral neck), which in combination with involvement of the pelvis can cause a waddling gait and secondary osteoarthritis. Mild to moderate deep, aching pain characteristically begins late in the course of the disease, persists throughout the day and at rest, and becomes worse at night. In some persons, the early hypervascularity of the pagetic bone produces warmth of the overlying skin and subcutaneous tissue. In persons with extensive disease, blood flow to the bones and subcutaneous tissue can increase remarkably, leading to high-output heart failure or exacerbation of underlying cardiac disease.[3]

A variety of tumor and tumorlike conditions develop in pagetic bone, the most dreaded of which is sarcoma. Osteogenic sarcomas occur in 5% to 10% of persons with extensive disease.[3] The bones most often affected, in order of frequency, are the femur, pelvis, and humerus.[4]

Diagnosis and Treatment. Diagnosis of Paget disease is based on characteristic bone deformities and x-ray changes. Elevated levels of serum alkaline phosphatase and urinary hydroxyproline support the diagnosis, and continued surveillance of these levels may be used to monitor the effectiveness of treatment. Bone scans are used to detect the rapid bone turnover indicative of active disease and to monitor the response to treatment. The scan cannot identify bone activity resulting from malignant lesions. Bone biopsy may be done to differentiate the lesion from osteomyelitis or a primary or metastatic bone tumor.

The treatment of Paget disease is based on the degree of pain and the extent of the disease. Pain can be reduced with nonsteroidal or other anti-inflammatory agents. Suppressive agents such as the bisphosphonates and calcitonin are used to manage pain and prevent further spread of the disease and neurologic defects. Persons with Paget disease should receive adequate doses of calcium and vitamin D.

In summary, metabolic bone disease represents disorders of the skeletal system that result from an imbalance between bone formation and destruction or a decrease in mineralization. Osteopenia is a condition that is common to all metabolic bone diseases. It is characterized by a reduction in bone mineral density greater than expected for age, race, or gender, and it occurs because of a decrease in bone formation, inadequate bone mineralization, or excessive bone deossification.

Osteoporosis, the most common of the metabolic bone diseases, is a disorder of bone remodeling that is characterized by increased bone porosity (decreased bone mass density) and diminished bone strength. It is associated with an increase in bone fragility and susceptibility to fractures. The cause of osteoporosis remains largely unknown, but most data suggest an imbalance between bone resorption and formation such that bone resorption exceeds bone formation. Although the disease can occur as the result of a number of disorders, the most common causes are age-related changes in bone metabolism and a relative absence of estrogen in postmenopausal women.

Osteomalacia and rickets are caused by inadequate mineralization of bone matrix, primarily because of a deficiency of vitamin D. In contrast to osteoporosis, which causes bones to become brittle, osteomalacia and rickets produce bone softening. Osteomalacia is a disorder of adults and is caused by insufficient calcium absorption from the intestine because of lack of dietary vitamin D, resistance to the action of the vitamin, or a phosphate deficiency. Rickets, which affects children, is characterized by failure or delay in calcification of the cartilaginous growth plate, widening and deformation of the metaphyseal regions in long bones, and a delay in mineralization of trabecular, endosteal, and periosteal bone surfaces. Rickets is beginning to reemerge as a problem in developed countries due to a number of factors including modern

conditions of dress, diet, lifestyle, and avoidance of sun exposure to prevent skin cancer.

Paget disease results from excessive osteoclastic activity and is characterized by focal areas of excessive osteoclast-mediated bone resorption, disorganized osteoblast bone formation, and increased blood flow due to hypervascularity in the bone marrow adjacent to the lesions. The disease is often asymptomatic and discovered as an incidental radiographic finding. Symptomatic disease may be manifest as skeletal changes and symptoms related to expansion of the skull, jaw, clavicle, spine, and long bones of the leg. Involvement of the skull may cause headache, intermittent tinnitus, vertigo, and hearing loss; involvement of the spine may cause the vertebrae to collapse, leading to kyphosis of the thoracic spine and nerve compression. Hypervascularity may produce warmth of the overlying pagetic bone and, in extensive disease, high-output heart failure or exacerbation of underlying heart disease.

Systemic Autoimmune Rheumatic Disorders

- Systemic autoimmune rheumatic disorders are immune-mediated inflammatory connective tissue disorders that have similar clinical features and may affect many of the same organs.
- Rheumatoid arthritis is an autoimmune disorder that affects many tissues but principally attacks joints by producing a proliferative synovitis that progresses to produce a disabling form of arthritis by destroying the articular joint cartilage and underlying bone.
- Systemic lupus erythematosus is an autoimmune disorder that can affect almost any organ system, including the joints of the musculoskeletal system, skin, kidneys, lungs, nervous system, and heart.
- Systemic sclerosis is another autoimmune disorder that produces progressive disability by producing extensive fibrosis of many body organs and systems, including structures of the musculoskeletal system.

Rheumatic Disorders

Arthritis is a descriptive term applied to more than 100 rheumatic disorders, ranging from localized, self-limiting conditions to those that are systemic immune-mediated processes. The term, which is used to describe any disorder that affects the joints, oversimplifies the nature of the varied disease processes, the difficulty in differentiating one form of arthritis from another, and the complexity of treatment of these usually chronic conditions. These diverse rheumatic conditions share inflammation of the joint as a prominent or accompanying symptom. In the systemic rheumatic diseases, such as rheumatoid arthritis, the inflammation is primary, resulting from an immune response, probably autoimmune in origin. In rheumatic conditions limited to a single or few diarthrodial joints, such as osteoarthritis, the inflammation is secondary, resulting from the degenerative process and joint irregularities.

Systemic Autoimmune Rheumatic Diseases

Systemic autoimmune rheumatic diseases are a group of chronic disorders characterized by diffuse inflammatory vascular lesions and degenerative changes in connective tissue that share clinical features and may affect many of the same tissues and organs. They include rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, all of which share an immune-mediated pathogenesis.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disease that affects all ethnic groups throughout the world, with women affected 2.5 times more frequently than men.[29] The onset of the disease can occur at any age, but its peak incidence is between 40 and 50 years of age. Although the cause of RA remains uncertain, evidence points to a genetic predisposition and the development of joint inflammation that is immunologically mediated.[3,4] It has been suggested that the disease is initiated in a genetically predisposed individual by the activation of a T-cell–mediated response to an immunologic trigger, such as a microbial agent (Fig. 44-5). The importance of genetic factors in the pathogenesis of RA is supported by the increased frequency of the disease among first-degree relatives and monozygotic twins.[4] In addition, specific major histocompatibility complex (MHC) alleles or human leukocyte antigen (HLA) types have been associated with RA (see Chapter 15). An increased prevalence of RA has been associated with specific HLA DR alleles that share a sequence of amino acids located in the antigen-binding site of the DR molecule. This location is presumably the specific binding site of the immunologic trigger.[3]

The pathogenesis of RA can be viewed as an aberrant immune response that leads to synovial inflammation and destruction of the joint architecture. It has been suggested that the disease is initiated by the activation of $CD4^+$ helper T cells, the local release of inflammatory mediators and cytokines (e.g., tumor necrosis factor [TNF], interleukin [IL]-1) that destroy the joint, and formation of antibodies directed against joint-specific and systemic autoantigens. Approximately 70% to 80% of persons with the disease have a substance called the *rheumatoid factor* (RF), which is an antibody that reacts with a fragment of immunoglobulin G (IgG) to form immune complexes.[3,30] Although persons with RA may

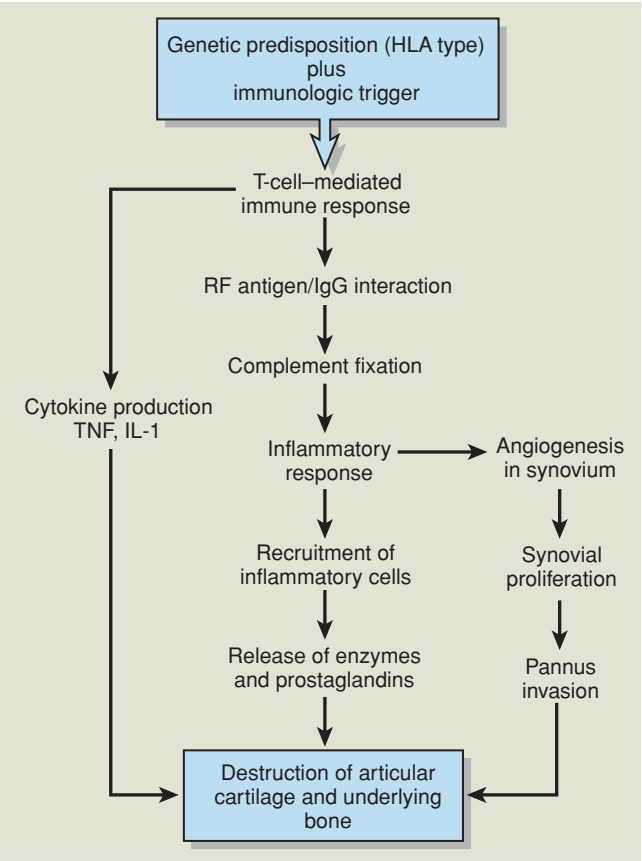


FIGURE 44-5. Disease process in rheumatoid arthritis. IL, interleukin; TNF, tumor necrosis factor.

be seronegative (not have Ig RF in their serum), the presence of a high RF titer is frequently associated with severe and unremitting disease, mainly systemic complications. Anticyclic citrullinated peptide (anti-CCP) antibodies are another key antibody system in RA.[29] Citrulline is a nonnaturally occurring amino acid that is generated by the enzymatic digestion of arginine on proteins. Recent research suggests that citrulline-containing proteins may serve as specific targets for the IgG antibody response in RA.

The role of the autoimmune process in the joint destruction of RA remains obscure. At the cellular level, neutrophils, macrophages, and lymphocytes are attracted to the area. The neutrophils and macrophages phagocytize the immune complexes and, in the process, release lysosomal enzymes capable of causing destructive changes in the joint cartilage (see Fig. 44-5). The inflammatory response that follows attracts additional inflammatory cells, setting into motion a chain of events that perpetuates the process. As the inflammatory process progresses, synovial cells and subsynovial tissues undergo reactive hyperplasia. The joint swelling that occurs is the result increased blood flow and capillary permeability that accompanies the inflammatory process.

Characteristic of RA is the development of an extensive network of new blood vessels in the synovial membrane that contributes to the advancement of the rheumatoid synovitis. This destructive vascular granulation tissue, which is called *pannus,* extends from the synovium to involve the "bare area," a region of unprotected bone at the junction between cartilage and subchondral bone (Fig. 44-6B). Pannus is a feature of RA that differentiates it from other forms of inflammatory arthritis.[3,4] The inflammatory cells found in the pannus have a destructive effect on the adjacent cartilage and bone. Eventually, pannus develops between the joint margins, leading to reduced joint motion and the possibility of eventual ankylosis (joint fusion). With progression of the disease, joint inflammation and the resulting structural changes lead to joint instability, muscle atrophy from disuse, stretching of the ligaments, and involvement of the tendons and muscles. The effect of the pathologic changes on joint structure and function is related to the degree of disease activity, which can change at any time. Unfortunately, the destructive changes are irreversible.

Rheumatoid arthritis often is associated with articular as well as extra-articular (i.e., systemic) manifestations (see Fig. 44-6). It usually has an insidious onset marked by systemic manifestations such as fatigue, weakness, and generalized aching and stiffness.[29,31] The disease, which is characterized by exacerbations and remissions, may involve only a few joints for brief durations, or it may become relentlessly progressive and debilitating.

Articular Manifestations. Joint involvement usually is symmetric and polyarticular. Any diarthrodial joint can be involved. The person may complain of joint pain and stiffness that lasts for 30 minutes and frequently for several hours. The limitation of joint motion that occurs early in the disease usually is because of pain; later, it is because of fibrosis. In early disease, the wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints of the fingers, interphalangeal joints of the thumb, and metatarsophalangeal (MTP) joints are most commonly affected. Pain in the ball of the foot upon arising from bed and widening of the forefoot necessitating an increase in shoe size are frequently reported due to inflammation of the metatarsophalangeal joints.[29] Pain with turning door knobs, opening jars, and buttoning shirts is commonly reported due to swelling of the wrists and small joints of the hand. As the disease progresses, larger joints such as the ankles, knees, elbows, and shoulders become affected. Spinal involvement usually is limited to the cervical region.

Progressive joint destruction may lead to subluxation (i.e., dislocation of the joint resulting in misalignment of the bone ends) and instability of the joint and limitation of movement. Swelling and thickening of the synovium can result in stretching of the joint capsule and ligaments. When this occurs, muscle and tendon imbalances develop, and mechanical forces applied to the joints through daily activities produce joint deformities. In the MCP joints, the extensor tendons can slip to the ulnar side of the metacarpal head, causing ulnar deviation of the fingers (see Fig. 44-6A). Hyperextension of the PIP joint and partial flexion of the distal interphalangeal (DIP) joint is called a *swan neck deformity.* After this

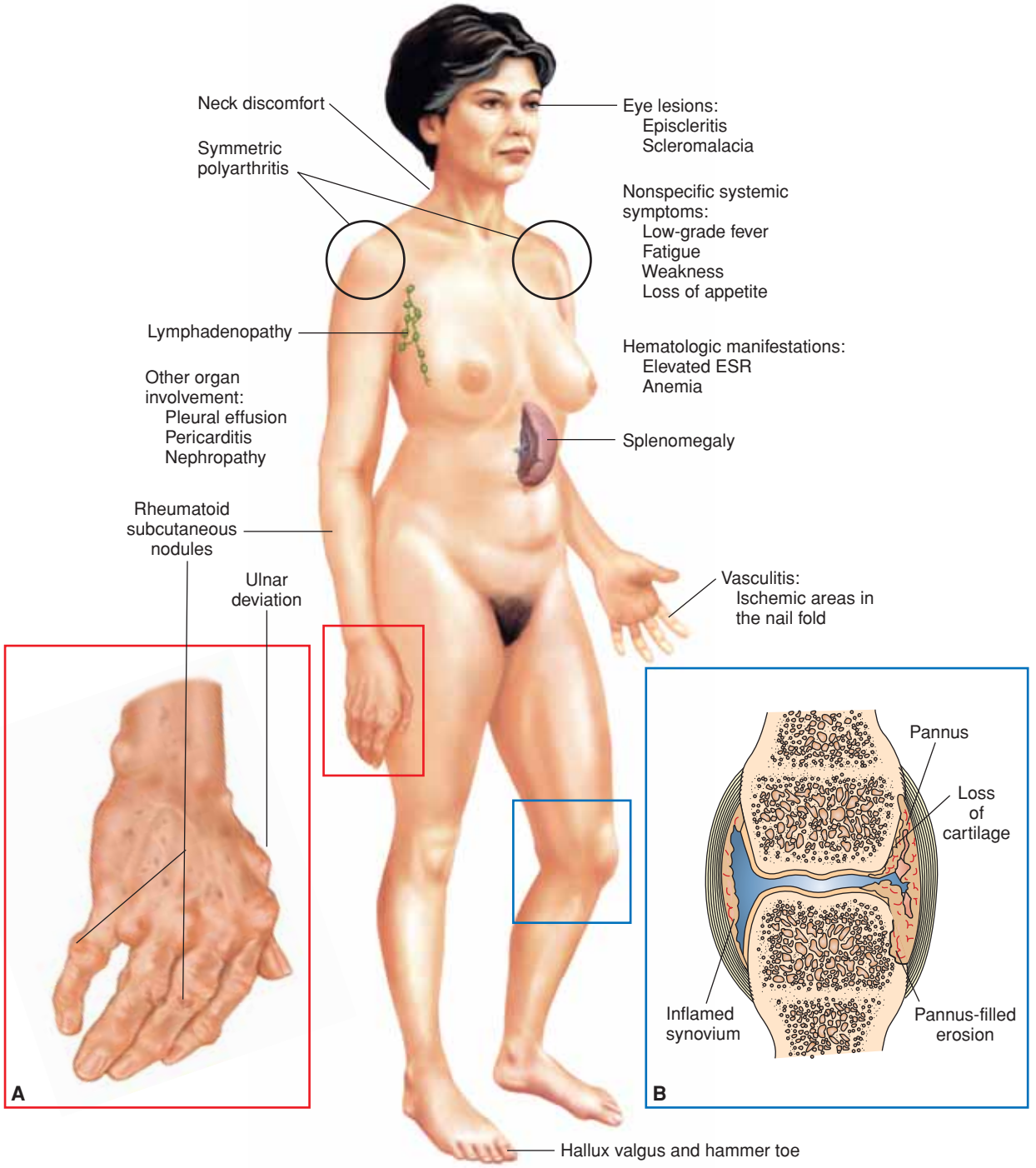


FIGURE 44-6. Clinical manifestations of rheumatoid arthritis featuring **(A)** hand and finger manifestations and **(B)** destructive joint changes. ESR, erythrocyte sedimentation rate.

condition becomes fixed, severe loss of function occurs because the person can no longer make a fist.

The knee is one of the most commonly affected joints and is responsible for much of the disability associated with the disease. Active synovitis may be apparent as visible swelling that obliterates the normal contour over the medial and lateral aspects of the patella. Joint contractures, instability, and genu valgus (knock-knee) deformity are other possible manifestations. Severe quadriceps atrophy can contribute to the disability. A *Baker cyst* may develop in the popliteal area behind the knee. This is caused by enlargement of the bursa but does not usually cause symptoms unless the cyst ruptures, in which case symptoms mimicking thrombophlebitis appear. Ankle involvement can limit flexion and extension, which can create difficulty in walking. Involvement of

the metatarsophalangeal joints can cause subluxation, hallux valgus, and hammertoe deformities. Neck pain and stiffness occur later in the disease.

Extra-Articular Manifestations. In addition to articular manifestations, persons with early RA frequently have constitutional symptoms such as fatigue, weakness, anorexia, and weight loss that are due to systemic inflammation.[29,31,32] The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which commonly are elevated during inflammatory processes, have been found to correlate with the amount of disease activity. A moderate hypochromic anemia is common.

Extra-articular involvement tends to occur in long-standing disease and includes rheumatic nodules (Fig. 44-6A). Rheumatoid nodules are granulomatous lesions that have a central core of fibrinoid necrosis that is made up of a mixture of fibrin and other proteins such as degraded collagen.[4] The nodules may be tender or nontender, movable or immovable, and small or large. Typically, they are found over pressure points such as the extensor surfaces of the ulna. The nodules may remain unless surgically removed, or they may resolve spontaneously.

Vasculitis, or inflammation of small and medium-sized arteries, is an uncommon manifestation of RA in persons with a long history of active arthritis and high titers of RF (see Chapter 18). Manifestations include ischemic areas in the nail fold and digital pulp that appear as brown spots. Ulcerations may occur in the lower extremities, particularly around the malleolar areas. In some cases, neuropathy may be the only symptom of vasculitis. The visceral organs, such as the heart, lungs, and gastrointestinal tract, also may be affected.

Dryness of the eyes, mouth, and other mucous membranes may occur, especially in advanced disease. Ocular manifestations include episcleritis, scleritis, and scleromalacia, which is due to scleral nodules. Additional extra-articular manifestations of RA include pulmonary fibrosis and pericarditis. A small number of persons have splenomegaly and lymph node enlargement.

Diagnosis and Treatment. The diagnosis of RA is based on findings of the history, physical examination, and laboratory tests. The criteria for RA developed by the American Rheumatism Association are useful in establishing the diagnosis[32] (Chart 44-2). At least four of the criteria must be present to make a diagnosis of RA. Although these criteria were developed for classification purposes and for use in epidemiologic studies, they can be used as guidelines for diagnosing the illness in individual patients.

Because changes in joint structure usually are not visible early in the disease, diagnosis is often difficult. On physical examination, the affected joints show signs of inflammation, swelling, tenderness, and possibly warmth and reduced motion. The joints have a soft, spongy feeling because of the synovial thickening and inflammation. Body movements may be guarded to prevent pain.

The combined presence of the RF and anti-CCP antibodies in laboratory tests are findings that are sensitive and fairly specific for RA.[3,4,29] The presence of anti-CCP antibodies, which have been detected very early in RA, appear to be a good prognostic marker for the disease and discriminate between erosive and nonerosive forms of the disease. Disease severity and activity tend to correlate with RF levels; patients with high RF levels tend to have a significantly higher frequency of extra-articular involvement (e.g., rheumatoid nodules, vasculitis, neuropathy). Synovial fluid analysis can be helpful in the diagnostic process. The synovial fluid has a cloudy appearance, the white blood cell count is elevated as a result of inflammation, and the complement components are decreased. Radiologic findings provide the most specific evidence of joint changes in RA, but are often normal during the early stages of the disorder.

The treatment goals for a person with RA are to reduce pain, minimize stiffness and swelling, maintain mobility, and become an informed health care consumer. The treatment plan includes education about the disease and its treatment, physical rest, therapeutic exercises, and medications. Because of the chronicity of the disease and the need for continuous, long-term adherence to the prescribed treatment modalities, it is important that the treatment be integrated with the person's lifestyle.

Both physical rest and therapeutic exercises are important aspects of care.[32] Physical rest reduces joint stress. Rest of specific joints is recommended to relieve pain. For example, sitting reduces the weight on an inflamed knee, and the use of lightweight splints reduces undue movement of the hand or wrist. Although rest is essential, therapeutic exercises also are important in maintaining joint motion and muscle strength.[33] Proper posture, positioning, body mechanics, and the use of supportive shoes can provide further comfort. There often is a need for information about the principles of joint protection and work simplification. Some persons need assistive devices to reduce pain and improve their ability to perform activities

CHART 44-2 Criteria for Classification of Rheumatoid Arthritis

Four or more of the following conditions must be present to establish a diagnosis of rheumatoid arthritis:

1. Morning stiffness for at least 1 hour and present for at least 6 weeks
2. Simultaneous swelling of three or more joints for at least 6 weeks
3. Swelling of wrist, metacarpophalangeal, or proximal interphalangeal joints for 6 or more weeks
4. Symmetric joint swelling for 6 or more weeks
5. Rheumatoid nodules
6. Serum rheumatoid factor identified by a method that is positive in less than 5% of normal subjects
7. Radiographic changes typical of rheumatoid arthritis on hand or wrist radiographs.

Adapted from Arnett F.C., Edworthy S.M., Block D.L., et al. (1988). The American Rheumatism Association 1987 revised criteria for the clarification of rheumatoid arthritis. *Arthritis and Rheumatism* 31, 315–324.

of daily living. Instruction in the safe use of heat and cold modalities to relieve discomfort and in the use of relaxation techniques also is important.

The classes of drugs used in the treatment of RA include salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective cyclooxygenase (COX)-2 inhibitors; disease-modifying antirheumatic drugs (DMARDs); corticosteroids; and biologic agents.[34]

The NSAIDs, including salicylates, inhibit COX-mediated synthesis of prostaglandins, which have a damaging effect on joint structures (see Chapter 3, Fig. 3-4). There are two COX isomers—COX-1 and COX-2. COX-1 is continuously expressed in many cells and is responsible for the general effects of prostaglandins, including protection of the gastric mucosa, whereas COX-2 is induced by cytokines and mainly expressed in inflammatory tissues. The selective COX-2 inhibitors (e.g., celecoxib) were developed with the goal of decreasing the gastrointestinal adverse effects seen with the traditional NSAIDs.

The DMARDs are a diverse group of therapeutic drugs that reduce the signs and symptoms of RA as well as retard radiographic progression of the disease. The DMARDs include gold salts, hydroxychloroquine, sulfasalazine, methotrexate, and azathioprine. Methotrexate has become the drug of choice because of its potency, and it is relatively fast acting (i.e., improvement is seen in 1 month) compared with the slower-acting DMARDs, which can take 3 to 4 months to work. Methotrexate is thought to interfere with purine metabolism, leading to the release of adenosine, a potent anti-inflammatory compound. All of the DMARDs can be toxic and require close monitoring for adverse effects, especially those related to bone marrow suppression.

Corticosteroid drugs interrupt the inflammatory and immune cascade at several levels, such as interfering with inflammatory cell adhesion and migration, impairing prostaglandin synthesis, and inhibiting neutrophil superoxide production. To avoid long-term side effects, they are used only in specific situations for short-term therapy at a low dose level. The corticosteroids do not modify the disease and are unable to prevent joint destruction. Intra-articular corticosteroid injections can provide rapid relief of acute or subacute inflammatory synovitis (after infection is excluded) in a few joints. They should not be repeated more than a few times each year.

The biologic agents are structurally engineered versions of natural molecules (e.g., monoclonal antibodies) designed to target specific pathogenic mediators of joint inflammation and damage. Leflunomide is a pyrimidine synthesis inhibitor that blocks the proliferation of T cells. Etanercept, infliximab, and adalimumab are biologic response–modifying agents that block TNF-α, one of the key proinflammatory cytokines in RA. Abatacept and rituximab are among the most recent biologic agents available for treatment of moderate to severe RA. Abatacept is a recombinant protein that prevents the costimulatory signal that results in full T-cell activation. Rituximab is a chimeric antibody that causes B-cell depletion.

Surgery also may be a part of the treatment of RA.[32] Synovectomy may be indicated to reduce pain and joint damage when synovitis does not respond to medical treatment. The most common soft tissue surgery is tenosynovectomy (i.e., repair of damaged tendons) of the hand to release nerve entrapments. Total joint replacements (i.e., arthroplasty) may be indicated to reduce pain and increase motion. Arthrodesis (i.e., joint fusion) is indicated only in extreme cases when there is so much soft tissue damage and scarring or infection that a replacement is impossible.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect virtually any organ system, including the musculoskeletal system. It is a major rheumatic disease, with a prevalence of approximately 1 case per 2000 persons. SLE is primarily a disease of young women, with a peak incidence between the ages of 15 and 40 years.[35] It is more common in African Americans, Hispanics, and Asians than whites, and the incidence in some families is higher than in others.

Etiology and Pathogenesis. The cause of SLE is unknown. It is characterized by the formation of autoantibodies and immune complexes (type III hypersensitivity; see Chapter 16). Persons with SLE appear to have defective elimination of self-reactive B cells with a resultant increase in production of antibodies that can directly damage tissues or combine with corresponding antigens to form tissue-damaging immune complexes. Autoantibodies have been identified against an array of self-molecules found in the nucleus, in the cytoplasm, or on the surface of cells. Among the autoantibodies found in the serum of persons with SLE, those directed against components of the cell nucleus (antinuclear antibodies [ANAs]) are the most characteristic. These antibodies bind deoxyribonucleic acid (DNA), ribonucleic acid (RNA), nuclear proteins, and protein nuclear complexes. Antibodies to double-stranded DNA and a nuclear antigen called *Sm* are essentially found in all persons with SLE and are included as a serologic classification of the disease. In addition to ANAs, persons with lupus have a host of other self-autoantibodies including those directed against elements of the blood (red cells, platelets, lymphocytes) and plasma proteins (clotting and complement factors).

The development of autoantibodies can result from a combination of factors, including genetic, hormonal, and environmental factors.[36,37] Genetic predisposition is evidenced by the occurrence of familial cases of SLE, especially among identical twins. The increased incidence among African Americans compared with whites also suggests genetic factors. As many as four genes may be involved in the expression of SLE in humans. Genes linked to the HLA-DQ loci in the MHC class II molecules provide strong support for a genetic link in the development of SLE.[37] Studies also suggest that an imbalance in sex hormone levels may play a role in the development of the disease, especially because the disease is so prevalent among women.

Possible environmental triggers include ultraviolet (UV) light, chemicals (e.g., drugs, hair dyes), some foods,

and infectious agents.[36,37] UV light, specifically UVB associated with exposure to the sun or unshielded fluorescent bulbs, may trigger exacerbations. Photosensitivity occurs in approximately one third of patients with SLE. Certain drugs may also provoke a lupus-like disorder in susceptible persons, particularly in the elderly. The most common of these drugs are hydralazine and procainamide.[37,38] Other drugs, such as quinidine, chlorpromazine, methyldopa, isoniazid, minocycline, and phenytoin, also have been known to produce this syndrome. The disorder usually recedes when the drug is discontinued.

Clinical Manifestations. Systemic lupus erythematosus can manifest in a variety of ways. The disease has been called the *great imitator* because it has the capacity for affecting many different body systems, including the musculoskeletal system, the skin, the cardiovascular system, the lungs, the kidneys, the central nervous system (CNS), and the red blood cells and platelets[36,38] (Fig. 44-7). The onset may be acute or insidious, and the course of the disease is characterized by exacerbations and remissions. Rare cases result in death within weeks or months.

Arthralgias and arthritis are among the most commonly occurring early symptoms of SLE; approximately 90% of all persons with the disease complain of joint pain at some point during the course of their disease.[36] The polyarthritis of SLE initially can be confused with other forms of arthritis, especially RA. However, articular destruction rarely is found on radiologic examination. Although arthritis can affect any joint, it is most often symmetric with involvement of the small joints of the hands, wrists, and knees, but sparing the spine. Ligaments, tendons, and the joint capsule may be involved, causing varied deformities. Flexion contractures, hyperextension of the interphalangeal joints, and subluxation of the carpometacarpal joints contribute to the deformity and subsequent loss of function in the hands. Other musculoskeletal manifestations of SLE include tenosynovitis, rupture of the intrapatellar and Achilles tendons, and avascular necrosis, frequently of the femoral head.

Skin manifestations can vary greatly and may be classified as acute, subacute, or chronic. The acute skin lesions include the classic malar or "butterfly" rash on the nose and cheeks (see Fig. 44-7). This rash is seen in SLE but may be associated with other skin lesions, such as hives or livedo reticularis (i.e., reticular cyanotic discoloration of the skin, often precipitated by cold), and fingertip lesions, such as periungual erythema, nail fold infarcts, and splinter hemorrhages. Hair loss is common. Mucous membrane lesions tend to occur during periods of exacerbation. Sun sensitivity may occur in SLE even after mild sun exposure.

Renal involvement occurs in approximately one half to two thirds of persons with SLE.[38] Several forms of glomerulonephritis may occur, including mesangial, focal proliferative, diffuse proliferative, and membranous (see Chapter 25). Interstitial nephritis also may occur. Nephrotic syndrome causes proteinuria with resultant edema in the legs and abdomen, and around the eyes. Renal failure may or may not be preceded by the nephrotic syndrome. Kidney biopsy is the best determinant of renal damage and the extent of treatment needed.

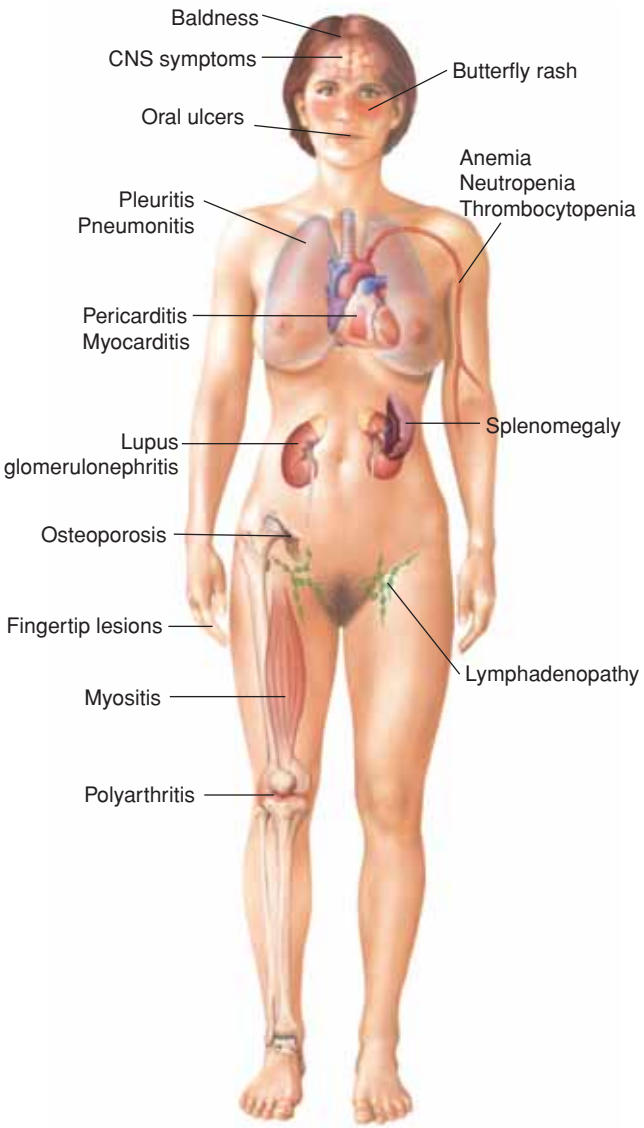


FIGURE 44-7. Clinical manifestations of systemic lupus erythematosus.

Pulmonary involvement occurs in 30% of persons with SLE and is manifested primarily by pleural effusions or pleuritis.[38] Less frequently occurring pulmonary problems include acute pneumonitis, pulmonary hemorrhage, chronic interstitial lung disease, and pulmonary embolism. Pericarditis is the most common of the cardiac manifestations, occurring in up to 45% of persons with SLE and often accompanied by pleural effusions.[38] Myocarditis affects as many as 25% of those with SLE. Congenital heart block can occur in infants of mothers with SLE who have a specific type of ANA (anti-Ro) in their serum. Secondary heart disease also is a problem in those with SLE. Hypertension may be associated with lupus nephritis and long-term corticosteroid use. Ischemic heart disease can occur in older persons with longer-duration SLE. Infective endocarditis is rare but

can occur with valvular lesions.[36] Hematologic disorders may manifest as hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia.

The CNS is involved in approximately two thirds of persons with SLE.[38] The pathologic basis for the CNS symptoms is not well understood, probably because of the inaccessibility of the tissue involved. It has been ascribed to an acute vasculitis that impedes blood flow, causing strokes or hemorrhage; an immune response involving antineuronal antibodies that attack nerve cells; or production of antiphospholipid antibodies that damage blood vessels and cause blood clots in the brain. Seizures can occur and are more frequent when renal failure is present. Psychotic symptoms, including depression and unnatural euphoria, as well as decreased cognitive functioning, confusion, and altered levels of consciousness, may develop.

Chronic discoid cutaneous lupus is a disease in which the skin manifestations may mimic SLE, but systemic manifestations are rare. It is characterized by plaquelike lesions on the head, scalp, and neck. These lesions first appear as red, swollen patches of skin, and later there can be scarring, depigmentation, and plugging of hair follicles. The disease is usually confined to the skin, but 5% to 10% of persons with the disorder may go on to develop multisystem manifestations after many years.

Subacute cutaneous lupus erythematosus is a less severe form of lupus that presents with predominant skin involvement that may resemble psoriasis. These lesions are found in sun-exposed areas such as the face, chest, upper back, and arms. Most persons have mild systemic manifestations of SLE, which usually are limited to joint and muscle pains. There is also a low incidence of lupus nephritis.

Diagnosis and Treatment. The diagnosis of SLE is based on a complete history, physical examination, and analysis of blood work. The most common laboratory test performed is the immunofluorescence test for ANA. Ninety-five percent of persons with untreated SLE have high ANA levels. The ANA test is not specific for SLE, and positive ANA results may be found in healthy persons or may be associated with other disorders. Antibodies to double-stranded DNA are more specific, but are not as sensitive since they present in only about 60% of persons with SLE.[39,40] Other serum tests may reveal moderate to severe anemia, thrombocytopenia, and leukocytosis or leukopenia. Additional immunologic tests may be done to give support to the diagnosis or to differentiate SLE from other connective tissue diseases.

Treatment of SLE focuses on managing the acute and chronic symptoms of the disease. The goals of treatment include preventing progressive loss of organ function, reducing the possibility of exacerbations, minimizing disability from the disease process, and preventing complications from medication therapy. Persons with photosensitivity should be cautioned against sun exposure and should apply a protective lotion when out of doors. Skin lesions often respond to local application of corticosteroids and minor joint symptoms are usually relieved by rest and NSAIDs.

An antimalarial drug (e.g., hydroxychloroquine) may be helpful in treating lupus rashes or musculoskeletal manifestations not relieved by NSAIDs. Corticosteroids are used to treat more significant symptoms of SLE, such as renal and CNS disorders. High-dose corticosteroid treatment is used for acute symptoms, and the drug is tapered to the lowest therapeutic dose as soon as possible to minimize the adverse effects. Immunosuppressive drugs, such as cyclophosphamide, may be used in cases resistant to corticosteroids.

Systemic Sclerosis/Scleroderma

Systemic sclerosis, commonly called *scleroderma,* is an autoimmune disease of connective tissues that causes extensive fibrosis throughout the body.[37,41,42] The disease affects women four times as frequently as men, with a peak incidence in the 35- to 50-year-old age group.[42]

The cause of systemic sclerosis is poorly understood, although there is evidence of both humoral and cellular immune system abnormalities. Fibroblast activation with excessive fibrosis is a hallmark of the disease. Skin involvement is the usual presenting symptom, but it is the involvement of organs such as the lungs, gastrointestinal tract, heart, lungs, and kidneys that produce the major morbidity and mortality. Microvascular disease is also consistently present early in the disease, with repeated cycles of endothelial damage followed by platelet activation and release of platelet factors that lead to fibrosis and narrowing of the microvasculature and tissue ischemia.

Clinical Manifestations. Scleroderma presents as two distinct clinical subsets: limited and diffuse scleroderma. The most common subset, which accounts for approximately 60% of cases, is limited cutaneous scleroderma in which the skin changes are limited to the fingers, forearms, and face.[42] Some persons with limited involvement also develop a condition called the *CREST* syndrome, characterized by a combination of *c*alcinosis (i.e., calcium deposits in the subcutaneous tissue that erupt through the skin), *R*aynaud phenomenon (a vascular disorder characterized by reversible vasospasm of the arteries supplying the fingers [see Chapter 18]), *e*sophageal dysmotility, *s*clerodactyly (localized scleroderma of the fingers), and *t*elangiectasia (dilated skin capillaries).[42]

Diffuse scleroderma, which accounts for approximately 35% of persons with scleroderma, is characterized by severe widespread and progressive skin involvement and early onset of organ involvement.[42] The typical person has a "stone facies" due to tightening of the facial skin with restricted motion of the mouth. Other cutaneous manifestations include hair loss on the involved skin and telangiectasis on the face, buccal mucosa, chest, and hands. Almost all persons with diffuse scleroderma develop Raynaud phenomenon. Musculoskeletal involvement is common in early systemic sclerosis and often prompts persons to seek medical attention. Puffy hands with arthralgia and myalgia may lead to difficulty forming a fist. There are palpable or audible friction rubs over the extensor and flexor tendons

of the hands, knees, and ankles. Involvement of the esophagus that leads to difficulty swallowing is common in persons with early systemic sclerosis. Malabsorption may develop if the disease affects the intestine. Pulmonary involvement leads to dyspnea and eventually respiratory failure. Vascular involvement of the kidneys is responsible for malignant hypertension and progressive renal insufficiency. Cardiac problems include pericarditis, heart block, and myocardial fibrosis.

Treatment. Treatment of systemic sclerosis is largely symptomatic and supportive.[42,43] Advances in treatment, primarily the use of angiotensin-converting enzyme (ACE) inhibitors in renal involvement, have led to a substantial decrease in the mortality from hypertensive renal disease. Cardiopulmonary manifestations of scleroderma, specifically pulmonary hypertension, can be treated with prostanoids (or endothelial receptor antagonists [bosentan]).

Seronegative Spondyloarthropathies

The *spondyloarthropathies* are an interrelated group of multisystem inflammatory disorders that primarily affect the axial skeleton, particularly the spine.[3,4,44] Sacroiliitis is a pathologic hallmark of the disorders. Typically, the inflammation begins at sites, called *entheses*, where tendon and ligament insert into bone rather than in the synovium. There may also be inflammation and involvement of the peripheral joints, in which case the signs and symptoms overlap with other inflammatory types of arthritis. Because there is an absence of the RF, these disorders often are referred to as *seronegative spondyloarthropathies*.

The seronegative spondyloarthropathies include ankylosing spondylitis, reactive arthritis, and psoriatic arthritis. Although they differ in terms of factors such as age and type of onset and extent of joint involvement, there is clinical evidence of overlap between the various disorders.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic, systemic inflammatory disease of the joints of the axial skeleton manifested by pain and progressive stiffening of the spine.[44] The disease usually begins in late adolescence or early adulthood. The incidence is greater in men than in women, and symptoms are generally more prominent in men.

Although the pathogenesis of ankylosing spondylitis has not been established, the presence of mononuclear cells in the acutely involved tissue suggests an immune response. Epidemiologic findings indicate that genetic and environmental factors play a role in the pathogenesis of the disease. The HLA-B27 antigen remains one of the best-known examples of an association between a disease and a hereditary marker. Although approximately 90% of those with ankylosing spondylitis possess the HLA-B27 antigen, the HLA-B27 antigen also is present in approximately 5% to 15% of the normal population.[45] Several theories have been advanced to account for the association between the HLA-B27 antigen and ankylosing spondylitis. One possibility is that the gene that determines the HLA-B27 antigen may be linked to other genes that determine the pathologic autoimmune phenomena or lead to increased susceptibility to infections or environmental agents that trigger the response.

Clinical Manifestations. The typical musculoskeletal lesion associated with ankylosing spondylitis is inflammation, or *enthesitis*, at sites where tendons and ligaments attach to bones. Typically, the disease process begins with bilateral involvement of the sacroiliac joints and then moves to the smaller joints of the posterior elements of the spine (Fig. 44-8). The result is ultimate destruction of these joints with ankylosis or posterior fusion of the spine. The vertebrae take on a squared appearance and bone bridges fuse one vertebral body to the next across the intervertebral disks. Progressive spinal changes usually follow an ascending pattern beginning with the sacroiliac area and then moving up the spine to involve the costovertebral joints and cervical spine. Occasionally, large synovial joints (i.e., hips, knees, and shoulders) may be involved. The small peripheral joints usually are not affected. The disease spectrum ranges from an asymptomatic sacroiliitis to a progressive disease that can affect many body systems.

The usual presenting symptom is back pain that may be persistent or intermittent.[44,46] The pain, which becomes worse when resting, particularly when lying in bed, initially may be blamed on muscle strain or spasm from physical activity. Lumbosacral pain also may be present, with discomfort in the buttocks and hip areas. Sometimes, pain can radiate to the thigh in a manner similar to that of sciatic pain. Prolonged stiffness is present in the morning and after periods of rest. Mild physical activity or a hot shower helps reduce pain and stiffness. Sleep patterns frequently are interrupted because of these manifestations. Walking or exercise may be needed to provide the comfort needed to return to sleep.[46] The most common extraskeletal involvement is acute anterior uveitis (iritis), which occurs in approximately 30% of persons sometime in the course of their disease.[44] Systemic features of weight loss, fever, and fatigue may be apparent. Sometimes, the fatigue is a greater problem than pain or stiffness. Osteoporosis

Seronegative Spondyloarthropathies

- The seronegative spondyloarthropathies represent a group of related multisystem disorders that lack the RF.
- The inflammatory process associated with the disorders commonly affects the axial skeleton, involving areas where ligaments and tendons attach to bone.
- Although the cause of the disorders is unknown, there is a striking association between the HLA-B27 antigen and development of the spondyloarthropathies.

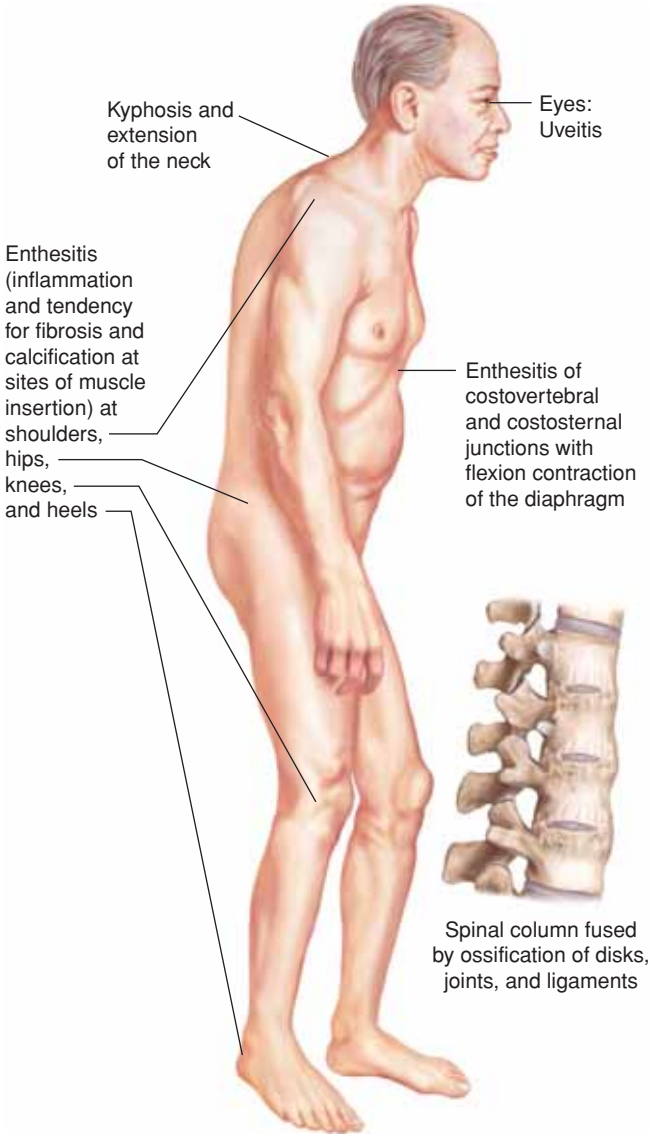


FIGURE 44-8. Clinical manifestations of ankylosing spondylitis.

may occur, especially in the spine, which contributes to the risk of spinal fracture. Loss of motion in the spinal column is characteristic of the disease (see Fig. 44-8). The severity and duration of disease activity influence the degree of mobility. Loss of lumbar lordosis occurs as the disease progresses, and this is followed by kyphosis of the thoracic spine and extension of the neck. A spine fused in the flexed position is the end result in severe ankylosing spondylitis. A kyphotic spine makes it difficult for the patient to look ahead and to maintain balance while walking. The image is one of a person bent over looking at the floor and unable to straighten up. X-ray films show a rigid, bamboolike spine. The heart and lungs are constricted in the chest cavity. Abnormal weight bearing can lead to degeneration and destruction of the hips, necessitating joint replacement procedures. Peripheral arthritis is more common in the hips and shoulders.

Diagnosis and Treatment. The diagnosis of ankylosing spondylitis is based on history, physical examination, and x-ray examination. The history and physical examination should include measures of physical function, pain, spinal mobility, duration of morning stiffness, involvement of peripheral joints and entheses, and fatigue. Laboratory findings frequently include an elevated ESR. The person also may have a mild normocytic normochromic anemia. HLA typing is not diagnostic of the disease and should not be used as a routine screening procedure. Radiologic evaluations help differentiate ankylosing spondylitis from sacroiliitis due to other diseases. However, x-ray images may be negative in early disease.

Treatment of ankylosing spondylitis is directed at controlling pain and maintaining mobility by suppressing inflammation. Proper posture and positioning are important. This includes sleeping in a supine position on a firm mattress and using one small pillow or no pillow. A bed board may be used to supply additional firmness. Therapeutic exercises are important to assist in maintaining motion in peripheral joints and in the spine. Muscle-strengthening exercises for extensor muscle groups also are prescribed. Heat applications or a shower or bath may be beneficial before exercise to improve ease of movement. Swimming is an excellent general conditioning exercise that avoids joint stress and enhances muscle tone. Immobilizing joints is not recommended. Maintaining ideal weight reduces the stress on weight-bearing joints. Deep breathing exercises and avoidance or discontinuation of smoking should be emphasized. Pharmacologic treatment includes the use of NSAIDs to reduce inflammation, relieve pain, and reduce muscle spasm. DMARDs are potential second-line therapies, but their efficacy in ankylosing spondylitis is unproven. Sulfasalazine and methotrexate have not shown benefit for spondylitis-associated back pain, but have shown efficacy for the peripheral joint involvement. Anti–TNF-α therapies, including etanercept, infliximab, and adalimumab, have demonstrated rapid effectiveness in reducing both the axial and peripheral symptoms of ankylosing spondylitis, as well as improving quality-of-life measures.[47]

The disease process in ankylosing spondylitis varies considerably among individuals. Exacerbations and remissions are common; almost all persons have persistent symptoms over decades. Fortunately, most of those affected are able to lead productive lives. Progression during the first decade of the disease tends to predict the prognosis.

Reactive Arthritis

Reactive arthritis is an inflammatory joint disorder that arises after certain inciting gastrointestinal or genitourinary tract infections and manifests as a sterile oligoarthritis, typically of the lower extremities.[48] Most cases of reactive arthritis develop after either a gastrointestinal infection (*Salmonella, Shigella, Campyobacter,* or *Yersinia*) or sexually transmitted infection (*Chlamydia trachomatis*). The infecting agents cannot be cultured and are not viable once having reached the joints. A clinically

indistinguishable syndrome can occur without antecedent infection, suggesting that subclinical infection or some other unrecognized agent can precipitate reactive arthritis. *Reiter syndrome* is a form of reactive arthritis defined by a triad of arthritis, nongonococcal urethritis or cervicitis, and conjunctivitis.[3] *Enteropathic arthritis* is a reactive arthritis that is associated with inflammatory bowel disease (i.e., Crohn disease and ulcerative colitis) or triggered by enterogenic bacteria.

Clinical Manifestations. Reactive arthritis is most commonly asymmetric and frequently involves the lower extremities. Symptoms typically start within 1 to 4 weeks of the initial infection. Hip disease is uncommon and involvement of the upper extremities is rare. The joints are typically warm, swollen, and tender. Systemic manifestations including fever and weight loss are common at the onset. Enthesitis is a common feature of reactive arthritis. The Achilles tendon and plantar fascia are the most common sites of involvement, but pain in the iliac crests, ischial tuberosities, and back may occur. This aspect of the disease can be disabling, with marked restriction in weight bearing and ambulation. Extra-articular lesions are common and include circinate balanitis (shallow ulcers on the glans or shaft of the penis), stomatitis (e.g., painless oral ulcers on the hard palate or tongue), and keratoderma blennorrhagicum (a papulosquamous rash most commonly affecting the palms of the hands and soles of the feet [Fig. 44-9]). While most of the signs and symptoms disappear within days or weeks, the arthritis may persist for several months, and in a small number of cases, it may follow a continuous and unremitting course.

Treatment. The treatment is largely symptomatic. NSAIDs are used in treating the arthritic symptoms. Vigorous treatment of possible triggering infections is thought to prevent relapses of reactive arthritis, but in many cases the triggering infection passes unnoticed or is mild, and the person seeks medical care only with the onset of definite arthritis. Short antibiotic courses at this time are not effective.

FIGURE 44-9. Keratoderma blennorrhagia of soles due to reactive arthritis (Reiter syndrome). (Courtesy Susan Lindsley, Centers for Disease Control and Prevention Public Health Images Library.)

Psoriatic Arthritis

Psoriatic arthritis is a seronegative inflammatory arthropathy that occurs in 6% to 11% of people with psoriasis.[49,50] It is a disease with various and similar features of the spondyloarthropathies in some persons, of RA in others, and of both coexisting in yet others. Although the arthritis can antedate a detectable skin rash, the definitive diagnosis of psoriatic arthritis cannot be made without evidence of skin or nail changes typical of psoriasis (see Chapter 46).

The etiology of psoriasis and psoriatic arthritis is unknown. Genetic, environmental, and immunologic factors appear to affect susceptibility and play a role in expression of the psoriatic skin disease and the arthritis. Environmental factors that may play a role in the pathogenesis of the disorder include infectious agents and physical trauma. T-cell–mediated immune responses seem to play an important role in the skin and joint manifestations of the disease, as indicated by the observation that there is improvement in disease status after treatment with immunosuppressant agents such as cyclosporine.

Psoriatic arthritis falls into five subgroups: (1) an oligoarticular form affecting four or fewer joints; (2) a spondylitis form in which sacroiliitis and spinal involvement predominate; (3) a polyarticular, or symmetric, form that resembles RA; (4) a form in which the distal interphalangeal joints are primarily affected; and (5) arthritis mutilans, a very destructive form of arthritis.[49,50] The joint involvement of peripheral psoriatic arthritis is inflammatory in nature, presenting with swelling and stiffness of the affected joints. Early in the disease, the arthritis tends to be oligoarticular, but may become polyarticular over time. The affected joints of persons with psoriatic arthritis are often less tender than those of persons with RA. Thus, persons with psoriatic arthritis may present with deformity and joint damage, not having perceived any pain during the inflammatory phase of the disease.[49] Sacroiliac involvement, when it occurs, tends to be asymmetric, involving only one sacroiliac joint and sparing the other or with different degrees of radiologic involvement. Likewise, spinal involvement tends to be asymmetric, with skip lesions. *Dactylitis*, or *sausage digit*, is a typical feature of distal interphalangeal joint disease and reflects inflammation of the entire digit.[49]

Basic management is similar to the treatment of RA. Suppression of the skin disease may be important in helping control the arthritis. Often, affected joints are surprisingly functional and only minimally symptomatic. The biologic response modifiers, specifically the TNF inhibitors (e.g., etanercept, infliximab, and adalimumab), have been found to be beneficial in controlling the arthritis as well as the psoriasis in patients with psoriatic arthritis.[50]

Osteoarthritis

Osteoarthritis (OA), also called *degenerative joint disease*, is the most prevalent type of joint disease and is one

Osteoarthritis

- Often referred to as "wear-and-tear" arthritis, osteoarthritis, often is a slowly destructive disorder of the articular cartilage.
- It can present as a primary disease of unknown etiology or as a secondary disorder related to congenital or acquired defects that affect the distribution of joint stress.
- The pathogenesis of osteoarthritis includes the progressive disruption of the smooth surface of the articular cartilage with development of surface cracks that deepen to involve the subchondral bone, followed by complete erosion of the articular cartilage with exposure of ivory-like polished subchondral bone, dislodgment of fragments of free-floating osteocartilaginous bodies, development of bone cysts, and formation of abnormal bony spurs at the joint margins.

of the 10 most disabling conditions in developing nations.[3,4] The disorder, which is characterized by degenerative changes of the articular cartilage, can affect any one of 200 or so synovial joints in the body, and can occur as a primary idiopathic disorder or as a secondary disorder. In most instances, OA appears insidiously, without an apparent initiating cause, as an aging phenomenon (idiopathic or primary OA).[3,4] In these cases the disorder is usually oligoarticular, but may be generalized. Secondary OA has a known underlying cause such as congenital or acquired defects of joint structures, trauma, metabolic disorders, or inflammatory diseases.

Joint changes associated with OA include a gradual loss of articular cartilage, combined with thickening of the subchondral bone, bony outgrowths (osteophytes) at joint margins, and mild synovial inflammation.[51] These changes are accompanied by joint pain, stiffness, and limitation of motion, and in some cases by joint instability and deformity.

Etiology and Pathogenesis

Osteoarthritis is a multifactorial disease that has genetic and environmental risk factors. Studies of families and twins suggest that the risk of OA is related to the net impact of multiple genes, each with a small effect.[3] Age, gender, and race interact to influence the time of onset and the pattern of joint involvement in OA.[52] Age is one of the strongest risk factors for OA of all joints. The increase in incidence and prevalence with age probably is the consequence of cumulative exposure to the various risk factors and biologic changes that occur with aging. Women are more likely to have OA than men, and they tend to have more severe OA as well. The prevalence of OA and pattern of joint involvement varies among racial and ethnic groups. Hand OA is more likely to affect white women, whereas knee OA is more common in black women. The incidence of hip OA is lower among the Chinese than Europeans, perhaps representing the influence of other factors such as occupation, obesity, or heredity. Bone mass may also influence the risk of developing OA. In theory, thinner subchondral bone mass may provide a greater shock-absorbing function than denser bone, allowing less direct trauma to the cartilage. Obesity is a particular risk factor for OA of the knee in women and a contributory biomechanical factor in the pathogenesis of the disease.[53] Excess fat may have a direct metabolic effect on cartilage beyond the effects of excess joint stress. Weight loss reduces the risk of developing symptomatic arthritis of the knee.

The pathogenesis of OA resides in the homeostatic mechanisms that maintain the articular cartilage.[3,4] Articular cartilage plays two essential mechanical roles in joint physiology. First, the articular cartilage serves as a remarkably smooth weight-bearing surface. In combination with synovial fluid, the articular cartilage provides extremely low friction during movement of the joint. Second, the cartilage transmits the load down to the bone, dissipating the mechanical stress.[3] Thus, the subchondral bone protects the overlying articular cartilage, providing it with a pliable bed and absorbing the energy of the force (Fig. 44-10). Articular cartilage has two major components: an extracellular matrix, which is rich in proteoglycan and collagen fibers, and a limited number of chondrocytes, which produce the matrix.

Popularly known as *wear-and-tear* arthritis, OA is characterized by significant changes in both the composition and mechanical properties of cartilage.[3,4,51,54] The articular cartilage injury that occurs in OA is thought to result from chondrocyte injury and release of cytokines such as IL-1 and TNF (Fig. 44-11). These chemical messengers stimulate the production and release of proteases (enzymes) that are destructive to joint structures. The resulting damage predisposes the chondrocytes to additional injury and impairs their ability to maintain cartilage synthesis and repair the damage. The combined

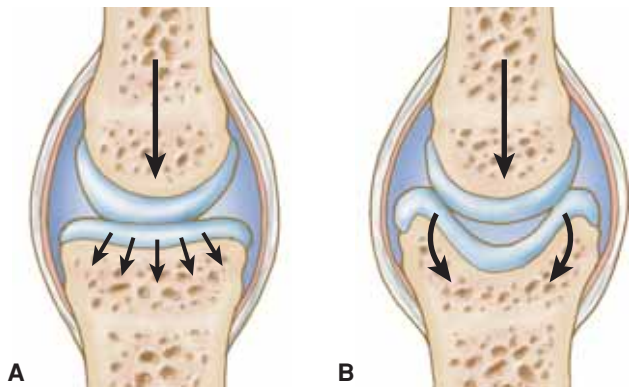


FIGURE 44-10. **(A)** A joint normally undergoes deformation of the articular cartilage and the subchondral bone when carrying a load. This maximizes the contact area and spreads the force of the load. **(B)** If the joint does not deform with a load, the stresses are concentrated and the joint breaks down.

effects of inadequate repair mechanisms and imbalances between the proteases and their inhibitors contribute further to disease progression.

The earliest structural changes in OA include enlargement and reorganization of the chondrocytes in the superficial part of the articular cartilage.[3,4] This is accompanied by edematous changes in the cartilaginous matrix, principally the intermediate layer. The cartilage loses its smooth aspect and surface cracks or microfractures occur, allowing synovial fluid to enter and widen the crack. As the crack deepens, vertical clefts form and eventually extend through the full thickness of the articular surface and into the subchondral bone. Portions of the articular cartilage eventually become completely eroded and the exposed surface of the subchondral bone becomes thickened and polished to an ivory-like consistency (eburnation). Fragments of cartilage and bone often become dislodged, creating free-floating osteocartilaginous bodies ("joint mice") that enter the joint cavity. Synovial fluid may leak though the defects in the residual cartilage to form cysts within the bone (Fig. 44-12). As the disease progresses, the underlying subchondral bone becomes sclerotic and thickened in response to increased pressure on the surface of the joint, rendering it less effective as a shock absorber. Sclerosis, or formation of new bone and cysts, usually occurs at the joint margins, forming abnormal bony outgrowths called *osteophytes,* or *spurs* (Fig. 44-12). As the joint begins to lose its integrity, there is trauma to the synovial membrane, which results in nonspecific inflammation. Compared with RA, however, the inflammatory changes in the synovium that occur in OA are not as pronounced, nor do they occur as early (Fig. 44-12).

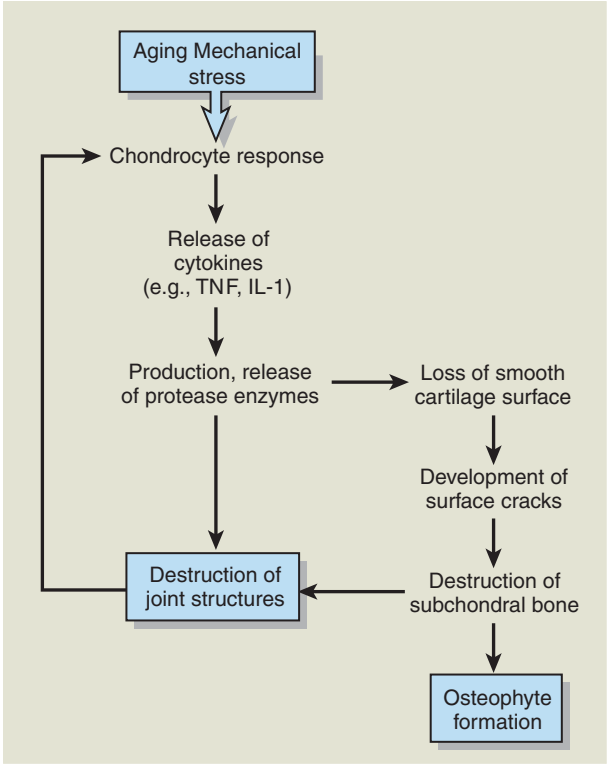


FIGURE 44-11. Disease process in osteoarthritis.

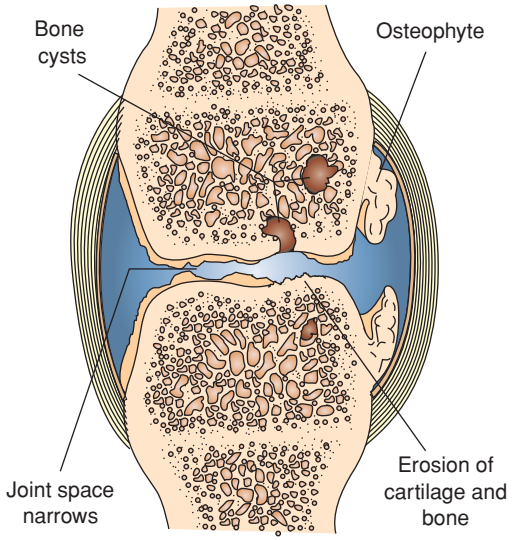


FIGURE 44-12. Joint changes in osteoarthritis. The left side denotes early changes and joint space narrowing with cartilage breakdown. The right side shows more severe disease progression with lost cartilage and osteophyte formation.

In secondary forms of OA, repetitive impact loading contributes to joint failure, accounting for the high prevalence of OA specific to vocational or avocational sites, such as the shoulders and elbows of baseball pitchers, ankles of ballet dancers, and knees of basketball players. Immobilization also can produce degenerative changes in articular cartilage. Cartilage degeneration due to immobility may result from loss of the pumping action of lubrication that occurs with joint movement. These changes are more marked and appear earlier in areas of contact but occur also in areas not subject to mechanical compression. Although cartilage atrophy is rapidly reversible with activity after a period of immobilization, impact exercise during the period of remobilization can prevent reversal of the atrophy. Therefore, slow and gradual remobilization may be important in preventing cartilage injury. Clinically, this has implications for instructions concerning the recommended level of physical activity after removal of a cast.

Clinical Features

Clinical Manifestations. Typically, OA presents with joint pain.[51,55] Initially, pain may be described as aching and may be somewhat difficult to localize. It usually worsens with use or activity and is relieved by rest. A common phenomenon, often referred to as "gelling," involves difficulty initiating joint movement after inactivity, epitomized by the problems older people with OA have in "getting started" after sitting down for a while. In later stages of disease activity, night pain may be experienced during rest. Cracking of joints (audible crepitus) and joint locking may occur when the joint is moved. As the disease advances, even minimal activity may cause pain.

TABLE 44-1 Clinical Features of Osteoarthritis

Joint	Clinical Features
Cervical spine	Localized stiffness; radicular or nonradicular pain; posterior osteophyte formation may cause vascular compression
Lumbar spine	Low back pain and stiffness; muscle spasm; decreased back motion; nerve root compression causing radicular pain; spinal stenosis
Hip	Most common in older men; characterized by insidious onset of pain, localized to groin region or inner aspect of the thigh; may be referred to buttocks, sciatic region, or knee; reduced hip motion; leg may be held in external rotation with hip flexed and adducted; limp or shuffling gait; difficulty getting in and out of chairs
Knee	Localized discomfort with pain on motion; limitation of motion; crepitus; quadriceps atrophy due to lack of use; joint instability; genu varus or valgus; joint effusion
First carpometacarpal joint	Tenderness at base of thumb; squared appearance to joint
Proximal interphalangeal joint—Bouchard nodes	Same as for distal interphalangeal joint disease
Distal interphalangeal joint—Heberden nodes	Occurs more frequently in women; usually involves multiple DIPs, lateral flexor deviation of joint, spur formation at joint margins, pain and discomfort after joint use
First metatarsophalangeal joint	Insidious onset; irregular joint contour; pain and swelling aggravated by tight shoes

The most frequently affected joints are the hips, knees, lumbar and cervical vertebrae, proximal and distal joints of the hands, the first carpometacarpal joint, and the first metatarsophalangeal joints of the feet. Table 44-1 identifies the joints that commonly are affected by OA and the common clinical features correlated with the disease activity of each particular joint. A single joint or several may be affected. Although a single weight-bearing joint may be involved initially, other joints often become affected because of the additional stress placed on them while trying to protect the initial joint. It is not unusual for a person having a knee replacement to discover soon after the surgery is done that the second knee also needs to be replaced. Other clinical features are limitations of joint motion and joint instability. Joint enlargement usually results from new bone formation; the joint feels hard, in contrast to the soft, spongy feeling characteristic of the joint in RA. Sometimes, mild synovitis or increased synovial fluid can cause joint enlargement.

Diagnosis and Treatment. The diagnosis of OA usually is determined by history and physical examination, x-ray studies, and laboratory findings that exclude other diseases. Although OA often is contrasted with RA for diagnostic purposes, the differences are not always readily apparent. Other rheumatic diseases may be superimposed on OA. Psychological factors, severity of joint disease, and educational level affect the expression of symptoms.

Because there is no cure, the treatment of OA is symptomatic and includes physical rehabilitative, pharmacologic, and surgical measures. Physical measures are aimed at improving the supporting structures of the joint and strengthening opposing muscle groups involved in cushioning weight-bearing forces.[55,56] This includes a balance of rest and exercise, use of splints to protect and rest the joint, use of heat and cold to relieve pain and muscle spasm, and adjusting the activities of daily living. Weight reduction is helpful when the knee is involved. The involved joint should not be further abused, and steps should be taken to protect and rest it. These include weight reduction (when weight-bearing surfaces are involved) and the use of a cane or walker if the hips and knees are involved. Muscle-strengthening exercises may help protect the joint and decrease pain.

Several nutritional products are available and advertised as beneficial for OA, but few have undergone rigorous testing. Among these, glucosamine and chondroitin sulfate have been evaluated in clinical trials, some of which demonstrated greater pain relief with treatment with either compound than with placebo, and others finding little or no difference.[56] A recent multicenter trial funded by the National Institutes of Health found that glucosamine and chondroitin (alone or in combination) were no better than placebo in reducing pain in the total group of persons with knee pain, but that the combination may be effective in those with moderate to severe pain.[57]

Oral medications are aimed at reducing inflammation or providing analgesia. Popular medications used in the treatment of OA are the NSAIDs, many of which are available without a prescription. For many persons, acetaminophen may be as effective and less toxic than NSAIDs. The American College of Rheumatology (ACR) recommends the use of acetaminophen as the initial systemic treatment for OA.[58]

Intra-articular corticosteroid injections may be used when other treatment measures have been unsuccessful in adequately relieving symptoms. They are especially helpful in persons who have an effusion of the joint. Injections usually are limited to no more than three times a year in the same joint because their use is thought to accelerate joint destruction.[56] Viscosupplementation is a newer concept in treatment and is based on the hypothesis that joint lubrication is abnormal in OA. Hyaluronate is injected into the joint weekly for 3 to 5 weeks. Topical capsaicin may have some pain-relieving effect in osteoarthritic knees and hands.[59]

Surgery is considered when the person is having severe pain and joint function is severely reduced.[56] Procedures include arthroscopic lavage and débridement, bunion resections, osteotomies to change alignment of the knee and hip joints, and decompression of the spinal roots in osteoarthritic vertebral stenosis. Total hip replacements have provided effective relief of symptoms and improved range of motion for many persons, as have total knee replacements, although the latter procedure has produced less consistent results. Joint replacement is available for the first carpometacarpal joint. Arthrodesis (surgical stiffening of a joint) is used in advanced disease to reduce pain; however, this results in loss of motion.

Crystal-Induced Arthropathies

Musculoskeletal disorders result from biochemical and metabolic disorders that affect the joints. Metabolic and endocrine diseases associated with joint symptoms include amyloidosis, osteogenesis imperfecta, diabetes mellitus, hyperparathyroidism, thyroid disease, AIDS, and hypermobility syndromes. The discussion in this chapter is limited to the crystal-induced arthropathy caused by monosodium urate deposition, or gout.

Crystal deposition in joints produces arthritis. In gout, monosodium urate or uric acid crystals are found in the joint cavity. Another condition in which calcium pyrophosphate dihydrate crystals are found in the joints sometimes is referred to as *pseudogout* or *chondrocalcinosis*. A brief discussion of pseudogout is found in the section on rheumatic diseases in the elderly.

Gout

Gout is actually a group of diseases known as the *gout syndrome*.[60,61] It includes acute gouty arthritis with recurrent attacks of severe articular and periarticular inflammation; tophi or the accumulation of crystalline deposits in articular surfaces, bones, soft tissue, and cartilage; gouty nephropathy or renal impairment; and uric acid kidney stones.

The term *primary gout* is used to designate cases in which the cause of the disorder is unknown or an inborn error in metabolism and is characterized primarily by hyperuricemia and gout. Primary gout is predominantly a disease of men, with a peak incidence in the fourth to sixth decade. In secondary gout, the cause of the hyperuricemia is known but the gout is not the main disorder. Asymptomatic hyperuricemia is a laboratory finding and not a disease. Most persons with hyperuricemia do not develop gout.

Pathogenesis. The pathogenesis of gout resides in an elevation of serum uric acid levels. Uric acid is the end product of purine (adenine and guanine from DNA and RNA) metabolism.[3,4] The elevation of uric acid and the subsequent development of gout can result from overproduction of purines, decreased salvage of free purine bases, augmented breakdown of nucleic acids as a result of increased cell turnover, or decreased urinary excretion of uric acid. Primary gout, which constitutes 90% of cases,[3] may be a consequence of enzyme defects that result in an overproduction of uric acid; inadequate elimination of uric acid by the kidney; or a combination of the two. In most cases, the reason is unknown. In secondary gout, the hyperuricemia may be caused by the increased breakdown of nucleic acids, as occurs with rapid tumor cell lysis during treatment for lymphoma or leukemia. Other cases of secondary gout result from chronic kidney disease. Some of the diuretics, including the thiazides, can interfere with the excretion of uric acid.

An attack of gout occurs when monosodium urate crystals precipitate in the joint and initiate an inflammatory response. Synovial fluid is a poorer solvent for uric acid than plasma, and uric acid crystals are even less soluble at temperatures below 37°C. Crystal deposition usually occurs in peripheral areas of the body, such as the great toe, where the temperatures are cooler than other parts of the body. With prolonged hyperuricemia, crystals and microtophi (i.e., small, hard nodules with irregular surfaces that contain crystalline deposits of monosodium urate) accumulate in the synovial lining cells and in the joint cartilage. The released crystals are chemotactic to leukocytes and also activate complement. Phagocytosis of urate crystals by polymorphonuclear leukocytes occurs and leads to polymorphonuclear cell death with the release of lysosomal enzymes. As this process continues, the inflammation causes destruction of the cartilage and subchondral bone.

Repeated attacks of acute arthritis eventually lead to chronic arthritis and the formation of the large, hard nodules called *tophi*[3,4] (Fig. 44-13). They are found most commonly in the synovium, olecranon bursa, Achilles tendon, subchondral bone, and extensor surface of the forearm and may be mistaken for rheumatoid nodules. Tophi usually do not appear until 10 years or more after the first gout attack. This stage of gout, called *chronic tophaceous gout,* is characterized by more frequent and prolonged attacks, which often are polyarticular.[61]

Clinical Manifestations. The typical acute attack of gout is monoarticular and usually affects the first metatarsophalangeal joint.[61] The tarsal joints, insteps, ankles, heels, knees, wrists, fingers, and elbows also may be initial sites of involvement. Acute gout often begins at night and may be precipitated by excessive exercise, certain medications or foods, alcohol, or dieting. The onset of pain typically is abrupt, and redness and swelling are observed. The attack may last for days or weeks. Pain may be severe enough to be aggravated even by the weight of a bed sheet covering the affected area.

In the early stages of gout after the initial attack has subsided, the person is asymptomatic, and joint abnormalities are not evident. This is referred to as *intercritical gout*. After the first attack, it may be months or years before another attack. As attacks recur with increased frequency, joint changes occur and become permanent.

Diagnosis and Treatment. Although hyperuricemia is the biochemical hallmark of gout, the presence of hyperuricemia cannot be equated with gout because many persons with this condition never develop gout. A definitive

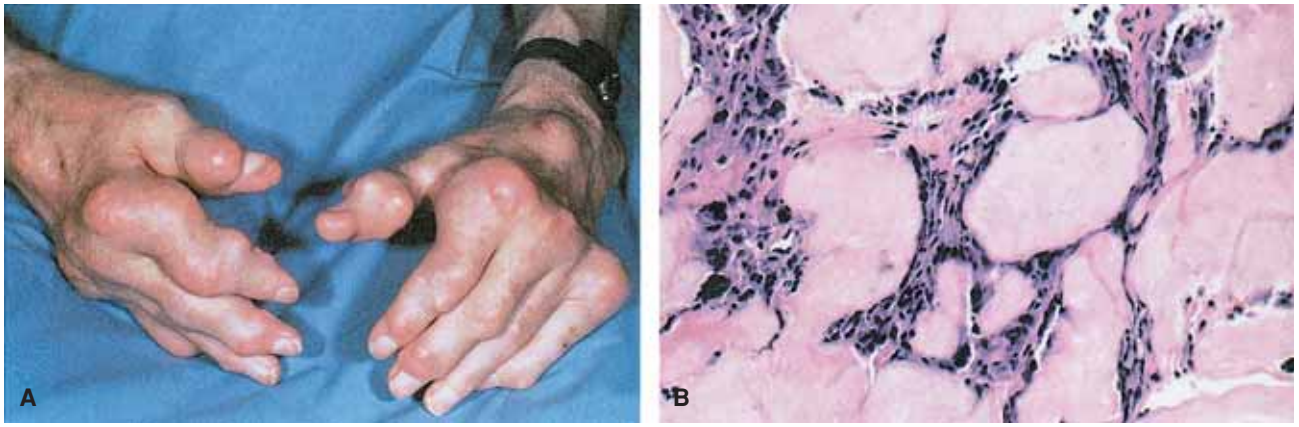


FIGURE 44-13. Gout. **(A)** Gouty tophi project from the fingers as rubbery nodules. **(B)** A section from a tophus shows extracellular masses of urate crystals with accompanying foreign body giant cells. (From Rubin E., Farber J.L. [Eds.]. [1999]. *Pathology* [3rd ed., p. 1404]. Philadelphia: Lippincott Williams & Wilkins.)

diagnosis of gout can be made only when monosodium urate crystals are present in the synovial fluid or in tissue sections of tophaceous deposits.[61] Synovial fluid analysis is useful in excluding other conditions, such as septic arthritis, pseudogout, and RA. Diagnostic methods also include measures to determine if the disorder is related to overproduction or to underexcretion of uric acid. This is done through measurement of serum uric acid levels and collection of a 24-hour urine sample for determination of urate excretion in the urine.

The objectives for treatment of gout include the termination and prevention of the acute attacks of gouty arthritis and the correction of hyperuricemia, with consequent inhibition of further precipitation of sodium urate and absorption of urate crystal deposits already in the tissues.

Pharmacologic management of acute gout is directed toward reducing joint inflammation. Hyperuricemia and related problems of tophi, joint destruction, and renal problems are treated after the acute inflammatory process has subsided. NSAIDs, particularly indomethacin and ibuprofen, are used for treating acute gouty arthritis.[61] Alternative therapies include colchicine and intra-articular deposition of corticosteroids. Colchicine produces its anti-inflammatory effects by inhibition of leukocyte migration and phagocytosis. Although the drug usually is given orally, a more rapid response is obtained when colchicine is given intravenously. The acute symptoms of gout usually subside within 48 hours after treatment with oral colchicine has been instituted and within 12 hours after intravenous administration of the drug. The corticosteroid drugs have not been systemically studied, but can be useful in the treatment of acute gout limited to a single joint or bursa.

Between acute attacks nonpharmacologic and pharmacologic measures are used to normalize uric acid levels as a means of reducing or preventing the frequency and severity of recurrence. Nonpharmacologic methods include maintenance of ideal weight, moderation in alcohol consumption, and avoidance of purine-rich foods (e.g., liver, kidney, sardines, anchovies, and sweetbreads). Avoidance of medications that inhibit renal excretion of uric acid (e.g., loop and thiazide diuretics, low-dose aspirin, and niacin) is also needed. Two classes of drugs may be used to lower the serum uric acid—allopurinol and the uricosuric agents.[61] Allopurinol inhibits xanthine oxidase, an enzyme needed for the conversion of hypoxanthine to xanthine and xanthine to uric acid. The uricosuric drugs (e.g., probenecid) prevent the tubular reabsorption of urate and increase its excretion in the urine. The serum urate concentrations are monitored to determine efficacy and dosage. Prophylactic colchicine or NSAIDs may be used between gout attacks.

In summary, the systemic autoimmune rheumatic disorders are a group of chronic disorders with overlapping symptoms that are characterized by diffuse inflammatory lesions and progressive changes in connective tissue. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder affecting multiple joints. Joint involvement, which is symmetric, begins with inflammatory changes of the synovium and formation of a destructive granulation tissue called *pannus* that leads to joint instability and eventual deformity. Systemic lupus erythematosus is a chronic autoimmune disorder that affects multiple body systems, including the musculoskeletal system, skin, kidneys, cardiovascular system, hematologic system, and CNS. There is an exaggerated production of autoantibodies, which interact with antigens to produce an immune complex. These immune complexes produce an inflammatory response in affected tissues. Systemic sclerosis, often prefixed by the term *progressive,* is sometimes called *scleroderma.* In this disorder, the skin is thickened through fibrosis with an accompanying fixation to the subdermal structures, including the sheaths or fascia covering tendons and muscles.

The spondyloarthropathies affect the axial skeleton, particularly the spine. Inflammation develops at sites where ligaments insert into bone. Because they lack the rheumatoid factor (RF), they are referred to as *seronegative spondyloarthropathies*. They include ankylosing spondylitis, reactive arthropathies, and psoriatic arthritis. Ankylosing spondylitis, which is characterized by bilateral sacroiliitis and loss of motion in the spinal column, is considered a prototype of this classification category. The cause remains unknown; however, a strong association between the HLA-B27 antigen and ankylosing spondylitis has been identified.

Osteoarthritis (OA), the most common form of arthritis, is a localized condition affecting primarily the weight-bearing joints. It can occur as a primary idiopathic disorder or as a secondary disorder due to congenital or acquired defects in joint structures. Risk factors for OA progression include older age, multiple joint involvement, neuropathy, and, for knees, obesity. The joint changes associated with OA, which include progressive loss of articular cartilage and subchondral bone, result from inflammatory changes that occur when cartilage tries to repair itself.

Gout is a crystal-induced arthropathy caused by the presence of monosodium urate crystals in the joint cavity. It includes acute gouty arthritis with recurrent attacks of auricular and periauricular inflammation, and tophi or the accumulation of crystalline deposits in articular surfaces, bones, and soft tissue surrounding joints. The disorder is accompanied by hyperuricemia, which results from overproduction of uric acid or from the reduced ability of the kidney to rid the body of excess uric acid.

Rheumatic Diseases in Children and the Elderly

Rheumatic Diseases in Children

Children can be affected with almost all of the rheumatic diseases that occur in adults. In addition to disease-specific differences, these conditions affect not only the child but also the family. Growth and development require special attention. Rheumatic disorders of children include juvenile RA, juvenile dermatomyositis, and juvenile spondyloarthropathies.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis and one of the most common chronic childhood illnesses.[62] It is characterized by synovitis and can influence epiphyseal growth by stimulating growth of the affected side. Generalized stunted growth also may occur. The initial symptoms of JIA may be subtle or acute, and often include morning stiffness and gelling; easy fatigability, particularly after school; and joint swelling. The involved joints are often warm, resist full range of motion, and are painful on motion, but not erythematous.[63] JIA can be regarded not as a single disease, but as a category of diseases with three principal types of onset: (1) oligoarticular or pauciarticular arthritis (affecting four or fewer joints), (2) polyarthritis (affecting five or more joints), and (3) systemic-onset disease.[62,63]

Oligoarthritis (pauciarticular disease), which is the most common type of JIA, predominantly affects joints of the lower extremities, usually the knees or ankle. Involvement of upper extremity large joints and the hip is rarely a presenting sign. Often a single joint is affected at onset. The severity of joint symptoms is usually mild and it is not uncommon for children to present with normal or near-normal overall function. Children with this form of JIA are usually younger (1 to 5 years at onset), more likely to be girls (girls outnumber boys by 4 to 1), often RF positive, and at greater risk for developing chronic eye inflammation.[62] The inflammation primarily involves the anterior chamber of the eye and is associated with minimal, if any, symptoms in about 80% of cases. Because severe eye changes can occur, these children should be screened at regular intervals and treated by an experienced eye specialist.

Polyarthritis (polyarticular disease) is generally characterized by involvement of both large and small joints. This form of JIA may develop at any age up to 16 years of age, with girls outnumbering boys by 3 to 1.[62] This form of arthritis more closely resembles the adult form of the disease than the other two subgroups. RF sometimes is present and may indicate a more active disease process. Clinical manifestations are highly variable and include fatigue, low-grade fever, weight loss, malaise, anemia, stunted growth, slight organomegaly (e.g., hepatosplenomegaly), and lymphadenopathy.

Systemic-onset disease, which affects approximately 2% to 17% of children with JIA, is characterized by arthritis and prominent visceral involvement that include hepatosplenomegaly, lymphadenopathy, and serositis, such as pericardial effusion.[62] The symptoms of systemic JIA include a daily intermittent high fever, which usually is accompanied by a characteristic faint erythematous, macular rash. The salmon-colored lesions of the rash may be linear or circular, from 2 to 5 mm in size, and appear in groups with a linear distribution on the trunk and proximal extremities. The rash is not pruritic. The most prominent diagnostic feature is its transient nature, with a group of lesions lasting less than an hour. Systemic symptoms usually subside in 6 to 12 months.

The prognosis for most children with JIA is good. NSAIDs are the first-line drugs used in treating JIA. Most children with polyarticular or systemic JIA, however, need additional anti-inflammatory therapy.[63] Glucocorticoids are recommended only for overwhelming inflammation of systemic disease. Careful attention to growth and development and nutritional issues are additional aspects of treatment of children with JIA. Children are encouraged to lead as normal a life as possible.

Juvenile Dermatomyositis

Juvenile dermatomyositis (JDMS) is an inflammatory myopathy primarily involving skin and muscle and associated with a characteristic rash. JDMS can affect children

of all ages, with an average age at onset of 7 years.[64] There is an increased incidence among girls. The cause is unknown, but there is a history of infection in the 3 months before disease onset in most affected children. Symmetric proximal muscle weakness, elevated muscle enzymes, evidence of vasculitis, and electromyographic changes confirming an inflammatory myopathy are diagnostic for JDMS. Generalized vasculitis is not seen in the adult form of the disease. The rash may precede or follow the onset of proximal muscle weakness. Periorbital edema, erythema, and eyelid telangiectasia are common.

Calcifications can occur in 30% to 50% of children with JDMS and are by far the most debilitating symptom. The calcifications appear at pressure points or sites of previous trauma. JDMS is treated primarily with corticosteroids to reduce inflammation. Occasionally, immunosuppressives are used in cases of refractory disease. All children with JDMS should avoid exposure to sun and also use a sunscreen with a sun protection factor (SPF) greater than 36, a calcium-sufficient diet, and vitamin D therapy.[64]

Juvenile Spondyloarthropathies

Ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and spondyloarthropathies associated with ulcerative colitis and regional enteritis can affect children as well as adults. Psoriatic arthritis is particularly common in young girls. The arthropathies of inflammatory bowel disease and reactive arthritis are much less common in childhood. They can affect children of any age.[65]

In children, spondyloarthropathy manifests in peripheral joints first, mimicking pauciarticular JIA, with no evidence of sacroiliac or spine involvement for months to years after onset. The spondyloarthropathies are more common in boys and commonly occur in children who have a positive family history. HLA-B27 typing is helpful in diagnosing children because of the unusual presentation of the disease.

Management of the disease involves physical therapy, education, and attention to growth and developmental issues. Medication includes the use of salicylates or other NSAIDs. In children who are not responsive to these medications, methotrexate may be considered. Exercises to maintain range of motion of the back, thorax, and affected joints should be instituted early in the disease. Custom-fitted shoes are particularly useful in managing painful entheses of the feet.[65]

Rheumatic Diseases in the Elderly

Rheumatic disorders are common causes for complaint among elderly persons.[66] The pain, stiffness, and muscle weakness affect daily life, often threatening independence and quality of life. Symptoms of the rheumatic diseases can also have an indirect effect on and even threaten the duration of life for the elderly. The weakness and gait disturbance that often accompany the rheumatic diseases can contribute to the likelihood of falls and fracture, causing suffering, increased health care costs, further loss of independence, and the potential for a decreased life span.

Arthritic complaints in the elderly are most frequently associated with degenerative forms of arthritis, such as osteoarthritis, but forms of inflammatory arthritis such as RA and gouty arthritis are also seen. One form of rheumatic disease that has a predilection for the elderly is polymyalgia rheumatica.

Osteoarthritis

Osteoarthritis is by far the most common form of arthritis among the elderly.[56,66] It is the greatest cause of disability and limitation of activity in older populations. Knee OA, which affects 13% of adults over age 55, can be particularly disabling.[56] It has been suggested that OA begins at a very young age, expressing itself in the elderly only after a long period of latency. Management of OA in older persons focuses on education about both the disease process and its management, pain control, improving function and preventing disability, and altering the disease and its consequences. Because of their side effects, pharmacologic therapy is used only when conservative efforts fail to improve function and surgical interventions are usually used as a last resort.[56] Nonpharmacologic approaches include weight loss in persons who are obese, exercise, physical therapy, and use of braces and walking aids. Attention to environmental hazards to prevent falls is essential. For persons with knee OA, bracing and orthotics provide a shift in the medial knee compartment and, in so doing, may provide considerable relief of pain and improvement in function.[66] A cane reduces the loading force on a joint, and persons with hip or knee OA should consider using a cane in the hand contralateral to the painful joint. All persons with knee and hip OA should also receive appropriate advice concerning footwear.

Rheumatoid Arthritis

The prevalence of RA increases with advancing age, at least until 75 years of age.[66] Seropositive patients are more likely to have an acute onset with systemic features and higher disease activity. Patients with seronegative, elderly-onset RA have a disease that usually follows a mild course. The close resemblance of the manifestations of seronegative RA in the elderly to those of polymyalgia rheumatica has led to speculation concerning the relationship of these syndromes. It may be that RA in the elderly is a broad disorder that includes a number of distinct subsets with characteristic manifestations, courses, and outcomes.

Crystal-Induced Arthropathies

The two best-recognized forms of crystal-induced joint disease are caused by the deposition of monosodium urate (gout) and calcium pyrophosphate (pseudogout).[67] Gout typically has its onset in middle-aged adults, whereas, pseudogout has an increasing prevalence in older adults and is often associated with unique and atypical features.

Gout. The incidence of clinical gout increases with advancing age, in part because of the increased involvement of joints after years of continued hyperuricemia. High serum urate levels rarely occur in women before menopause; initial attacks of clinical gout occur around the age of 70 years, or 20 years after menopause. The treatment of gout is often more difficult in the elderly. Although colchicine may be effective in controlling the symptoms of chronic gout, it may cause diarrhea in some patients, limiting its effectiveness in maintenance therapy.

Pseudogout. As part of the tissue aging process, OA develops with associated cartilage degeneration and the shedding of calcium pyrophosphate crystals into the joint cavity. These crystals may produce a low-grade chronic inflammation—the chronic pseudogout syndrome. The accumulation of calcium pyrophosphate and related crystalline deposits in articular cartilage is common in the elderly. There are no medications that can remove the crystals from the joints. Although it may be asymptomatic, presence of the crystals may contribute to more rapid cartilage deterioration. This condition may coexist with severe OA. Calcium pyrophosphate deposition disease may also present with proximal muscle pain mimicking polymyalgia rheumatica.

Polymyalgia Rheumatica

Polymyalgia rheumatica is an inflammatory condition of unknown origin characterized by aching and morning stiffness in the cervical regions and shoulder and pelvic girdle areas.[68,69] Of the forms of arthritis affecting the elderly, it is one of the more difficult to diagnose and one of the most important to identify. Elderly women are especially at risk. Polymyalgia rheumatica is a common syndrome of older patients, rarely occurring before 50 years and usually after 60 years of age. The onset can be abrupt, with the patient going to bed feeling well and awakening with pain and stiffness in the neck, shoulders, and hips.

Diagnosis is based on the pain and stiffness persisting for at least 1 month and an elevated ESR. The diagnosis is confirmed when the symptoms respond dramatically to a small dose of prednisone, a corticosteroid. Biopsies have shown that the muscles are normal, despite the name, but that a nonspecific inflammation affecting the synovial tissue is present. It is possible that a number of patients are erroneously diagnosed as having RA or OA. For patients with an elevated ESR, the diagnosis usually is based on a 3-day trial of prednisone treatment.[69] Patients with polymyalgia rheumatica typically exhibit striking clinical improvement on approximately the second day. Patients with RA also show improvement, although usually days later.

Treatment with NSAIDs provides relief for some patients, but most require continuing therapy with prednisone, with gradual reduction of the dose over the course of 1.5 to 2 years, using the person's symptoms as the primary guide. Patients need close monitoring during the maintenance phase with prednisone therapy. Because their symptoms are relieved, they often quit taking the prednisone and their symptoms recur, or doses are missed and the decreased dosage leads to an increase in symptoms. Unless careful assessment reveals the frequency of missed doses, the physician may be misled into increasing the dosage when it is not needed. Because of the side effects of the corticosteroids, the goal is to use the lowest dose of the drug necessary to control the symptoms. Weaning patients off low-dose prednisone therapy after this length of time can be a difficult and extended process.

A certain percentage of patients with polymyalgia rheumatica also develop *giant cell arteritis* (i.e., temporal arteritis) with involvement of the ophthalmic arteries. The two conditions are considered to represent different manifestations of the same disease. Giant cell arteritis, a form of systemic vasculitis, is a systemic inflammatory disease of large and medium-sized arteries. The inflammatory response seems to be a T-cell response to an antigen.

Clinical manifestations of giant cell arteritis usually begin insidiously and may exist for some time before being recognized.[68] It is potentially dangerous if missed or mistreated, especially if the temporal artery or other vessels supplying the eye are involved, in which case blindness can ensue quickly without treatment. The condition is responsive to appropriate therapy. For those patients at risk, adherence to the medication program is critical, with preservation of sight being the goal. Because this complication can occur so quickly and is relatively asymptomatic, it is vital that the patient understand the importance of taking the correct dose regularly as prescribed. Initial treatment consists of large doses of prednisone. This dosage is continued for 4 to 6 weeks and then decreased gradually.

Management of Rheumatic Diseases in the Elderly

In addition to diagnosis-specific treatment, the elderly require special considerations. Management techniques that rely on modalities other than drugs are particularly important for the elderly. These include splints, walking aids, muscle-building exercise, and local heat. Muscle-strengthening and stretching exercises are particularly effective in the elderly person with age-related losses in muscle function and should be instituted early. Rest, the cornerstone of conservative therapy, is hazardous in the elderly, who can rapidly lose muscle strength.

In terms of medications, the selection of drugs used in the treatment of arthritic disorders and their dosages may need to be considered when prescribing for the elderly. For example, the NSAIDs may be less well tolerated by the elderly, and their side effects are more likely to be serious. In addition to bleeding from the gastrointestinal tract and renal insufficiency, there may be cognitive dysfunction manifested by forgetfulness, inability to concentrate, sleeplessness, paranoid ideation, and depression.

Joint arthroplasty can also be used for pain relief and increased function. Chronologic age is not a contraindication to surgical treatment of arthritis. In appropriately selected elderly candidates, survival and functional

outcome after surgery are equivalent to those in younger age groups. The more sedentary activity level of the elderly makes them even better candidates for joint replacement because they put less stress and demand on the new joint.

In summary, rheumatic diseases that affect children include juvenile idiopathic arthritis, juvenile dermatomyositis, and juvenile-onset spondyloarthropathies. Although the childhood form of the arthritis may be similar to that seen in the adult, there are manifestations and treatment issues that are unique to the younger population. Managing rheumatic diseases in children requires a team approach to address issues related to the family, school, growth and development, and coping strategies, with development of a comprehensive disease management program.

Arthritis is the most common complaint of the elderly population. There is a difference in the manifestations, diagnosis, and treatment of some of the rheumatic diseases in the elderly compared with those in the younger population. OA is the most common form of arthritis among the elderly. The prevalence of RA and gout increases with advancing age. One form of rheumatic disease that has a predilection for the elderly is polymyalgia rheumatica. A certain percentage of patients with polymyalgia rheumatica also develop giant cell arteritis, a condition that can potentially cause blindness if not recognized and treated.

REVIEW EXERCISES

1. A 60-year-old postmenopausal woman presents with a compression fracture of the vertebrae. She has also noticed increased backache and loss of height over the last few years.

- **A.** Explain how the lack of estrogen and aging contribute to the development of osteoporosis.
- **B.** What other factors should be considered when assessing the risk for developing osteoporosis?
- **C.** What is the best way to measure bone density?
- **D.** Name the two most important factors in preventing osteoporosis.
- **E.** What medications might be used to treat this woman's condition?

2. A 30-year-old woman, recently diagnosed with rheumatoid arthritis (RA), complains of general fatigue and weight loss along with symmetric joint swelling, stiffness, and pain. The stiffness is more prominent in the morning and subsides during the day. Laboratory measures reveal an RF of 120 IU/mL (nonreactive, 0 to 39 IU/mL; weakly reactive, 40 to 79 IU/mL; reactive, >80 IU/mL).

- **A.** Describe the immunopathogenesis of the joint changes that occur with RA.
- **B.** How do these changes relate to this woman's symptoms?
- **C.** What is the significance of her RF test results?
- **D.** How do her complaints of general fatigue and weight loss relate to the RA disease process?

3. A 65-year-old obese woman with a diagnosis of Osteoarthritis (OA) has been having increased pain in her right knee that is made worse with movement and weight bearing and is relieved by rest. Physical examination reveals an enlarged joint with a varus deformity; coarse crepitus is felt over the joint on passive movement.

- **A.** Compare the pathogenesis and articular structures involved in OA with those of RA.
- **B.** What is the origin of the enlargement of the affected joint, the varus deformity, and the crepitus that is felt on movement of the affected knee?
- **C.** Explain the predilection for involvement of the knee in persons such as this woman.
- **D.** What types of treatment are available for this woman?

4. A 75-year-old woman is seen by a health care provider because of complaints of fever, malaise, and weight loss. She is having trouble combing her hair, putting on a coat, and getting out of a chair because of the stiffness and pain in her shoulders, hip, and lower back. Because of her age and symptoms, the health care provider suspects the woman has polymyalgia rheumatica.

- **A.** What laboratory test can be used to substantiate the diagnosis?
- **B.** What other diagnostic strategies are used to confirm the diagnosis?
- **C.** How is the disease treated?

REFERENCES

1. Seeman E., Delmas P.D. (2006). Bone quality—The material and structural basis of bone strength and fragility. *New England Journal of Medicine* 354(21), 2250–2261.
2. Khosia S., Melton L.J. (2007). Osteopenia. *New England Journal of Medicine* 356(22), 2293–2300.
3. Rosenberg A.E. (2010). Bones, joints, and soft tissue tumors. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of medicine* (8th ed., pp. 1205–1219, 1235–1246). Philadelphia: Elsevier Saunders.
4. Hoch B.J., Klein M.J., Schiller A.L. (2008). Bones and Joints. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 1098–1390). Philadelphia: Lippincott Williams & Wilkins.
5. Simon L.S. (2007). Osteoporosis. *Rheumatic Disease Clinics of North America* 33, 140–176.
6. Gass M., Dawson-Huges B. (2006). Preventing osteoporosis fractures: An overview. *American Journal of Medicine* 119(4A), 35–115.

7. WHO Technical Report Series. (2003). *Prevention and management of osteoporosis*. [Online] Available: http://whqlibdoc.who.int/trs/WHO_TRS_921.pdf. Accessed September 5, 2009.
8. U.S. Department of Health and Human Services. (2004). The frequency of bone disease. In *Bone health and osteoporosis: A report of the surgeon general*. [Online] Available: www.surgeongeneral.gov/library/bonehealth/chapter_4.html#Prevalence. Accessed September 5, 2009.
9. Lane N.E. (2006). Epidemiology, etiology, and diagnosis of osteoporosis. *American Journal of Obstetrics and Gynecology* 194, S3–S11.
10. Rosen C.J. (2005). Postmenopausal osteoporosis. *New England Journal of Medicine* 353, 595–603.
11. Gennari L., Bilezikian J.P. (2007). Osteoporosis in men. *Endocrinology and Metabolism Clinics of North America* 36, 399–419.
12. Stein E., Shane E. (2003). Secondary osteoporosis. *Endocrinology and Metabolism Clinics of North America* 32, 115–134.
13. Tebas P., Powderly W.G., Claxton S., et al. (2000). Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 14, F63–F67.
14. Beals K.A., Meyer N.L. (2007). Female athlete triad update. *Clinics in Sports Medicine* 26, 69–80.
15. Sweet M.G., Sweet J.M., Jeremiah M.P., et al. (2009). Diagnosis and treatment of osteoporosis. *American Family Physician* 79(3), 193–202.
16. Raisz L.C. (2005). Screening for osteoporosis. *New England Journal of Medicine* 353, 164–171.
17. U.S. Preventative Services Task Force. (2003). Screening for osteoporosis: Recommendations and rationale. *Annals of Internal Medicine* 137, 526–528.
18. National Osteoporosis Foundation. (2008). *Clinicians guide to prevention and treatment of osteoporosis*. Washington, DC: National Osteoporosis Foundation.
19. Cauley J.A., Robbins J., Chen Z., et al., for the Women's Health Initiative. (2003). Effects of estrogen plus progestin on risk of fracture and bone mineral density. *Journal of the American Medical Association* 290, 1729–1738.
20. Pateder D.B., Khanna A.J., Lieberman I.H. (2007). Vertebroplasty and kyphoplasty for the management of osteoporotic vertebral compression fractures. *Orthopedic Clinics of North America* 38, 409–418.
21. Holick M.F. (2007). Vitamin D Deficiency. *New England Journal of Medicine* 357(3), 266–281.
22. Holick M.F., Chen T.C. (2008). Vitamin D deficiency: A worldwide problem with health consequences. *American Journal of Clinical Nutrition* 87(Suppl), 1080D–1086D.
23. Berg E.E. (2004). Rickets. *Orthopaedic Nursing* 23(1), 53–55.
24. Nield L.S., Mahajan P., Joshi A., et al. (2006). Rickets: Not a disease of the past. *American Family Physician* 74, 619–630.
25. Misra M., Pacaud D., Petryk A., et al. (2008). Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. *Pediatrics* 122, 398–417.
26. Whyte M.P. (2006). Paget's disease of bone. *New England Journal of Medicine* 355(6), 593–600.
27. Schneider D., Hofmann M.T. (2002). Diagnosis and treatment of Paget's disease of bone. *American Family Physician* 65, 2069–2072.
28. Roodman G.D., Windle J.J. (2005). Paget disease of bone. *Journal of Clinical Investigation* 115, 200–208.
29. Tehlirian C.V., Bathon J.M. (2008). Rheumatoid arthritis: Clinical and laboratory manifestations. In Klippel J.H., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 114–121). New York: Springer.
30. Firestein G.S. (2005). Etiology and pathogenesis of rheumatoid arthritis. In Harris E.D., Budd R.C., Firestein G.S., et al. (Eds.), *Kelly's textbook of rheumatology* (7th ed., pp. 996–1042). Philadelphia: Elsevier Saunders.
31. Harris E.D. (2005). Clinical features of rheumatoid arthritis. In Harris E.D., Budd R.C., Firestein G.S., et al. (Eds.), *Kelly's textbook of rheumatology* (7th ed., pp. 1043–1078). Philadelphia: Elsevier Saunders.
32. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. (2002). Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis and Rheumatism* 46, 328–346.
33. Munnek M., deJong Z., Zwinderman A.H., et al. (2005). Effect of a high intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. *Arthritis Care and Research* 53, 410–417.
34. Oliver A.M., St. Clair E.W. (2008). Rheumatoid arthritis: Treatment and assessment. In Klippel J.H., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 133–141). New York: Springer.
35. Pietsky D.S. (2008). Systemic lupus erythematosus: Epidemiology, pathology, and pathogenesis. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 303–313). New York: Springer.
36. Edworthy S.M. (2005). Clinical manifestations of systemic lupus erythematosus. In Harris E.D., Budd R.C., Firestein G.S., et al. (Eds.), *Kelly's textbook of rheumatology* (7th ed., pp. 1201–1219). Philadelphia: Elsevier Saunders.
37. Kumar V., Abbas A.K., Fausto N., et al. (2010). *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 213–226). Philadelphia: Saunders Elsevier.
38. Buyon J.P. (2008). Systemic lupus erythematosus: Clinical and laboratory features. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 303–313). New York: Springer.
39. Petri M. (2005). Review of classification criteria for systemic lupus erythematosus. *Rheumatic Disease Clinics of North America* 31, 245–254.
40. Manzi S., Kao A.H. (2008). Systemic lupus erythematosus: Treatment and assessment. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 303–313). New York: Springer.
41. Seibold J.R. (2005). Scleroderma. In Harris E.D., Budd R.C., Firestein G.S., et al. (Eds.), *Kelly's textbook of rheumatology* (7th ed., pp. 1279–1299). Philadelphia: Elsevier Saunders.
42. Hinchcliff M., Varga J. (2008). Systemic sclerosis/scleroderma: A treatable multisystem disease. *American Family Physician* 78(8), 961–969.
43. Buch M.H., Seibold J.R. (2008). Systemic sclerosis: Treatment and assessment. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 359–362). New York: Springer.
44. Van Der Huede D. (2008). Ankylosing spondylitis: Clinical features. In Klippel J.R., Stone J.H., Crofford L.J., et al. *Primer on the rheumatic diseases* (13th ed., pp. 193–199). New York: Springer.
45. Braun J. (2008). Ankylosing spondylitis: Pathology and pathogenesis. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 200–208). New York: Springer.
46. Elyan M., Khan M.A. (2006). Diagnosing ankylosing spondylitis. *Journal of Rheumatology* 33(Suppl 78), 12–23.
47. Clegg D.O. (2006). Treatment of ankylosing spondylitis. *Journal of Rheumatology* 33(Suppl 78), 24–31.
48. Carter J.D., Huckson A.P. (2009). Reactive arthritis: Clinical aspects and medical management. *Rheumatic Disease Clinics of North America* 35, 21–44.
49. Gladman D.D. (2008). Psoriatic arthritis. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 170–177). New York: Springer.

50. Mease P.J. (2003). Current treatment of psoriatic arthritis. *Rheumatic Disease Clinics of North America* 29, 495–511.
51. Dieppe P. (2008). Osteoarthritis. Clinical features. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 224–228). New York: Springer.
52. Zhang Y., Jordon J.M. (2008). Epidemiology of osteoarthritis. *Rheumatic Disease Clinics of North America* 34, 515–529.
53. Felson D.T. (2006). Osteoarthritis of the knee. *New England Journal of Medicine* 354, 841–848.
54. Ling S.M., Rudolph K. (2006). Osteoarthritis. In Bartlett S.J., Bingham C.O., Maricic M.J., et al. (Eds.), *Clinical care in the rheumatic diseases* (3rd ed., pp. 127–134). Atlanta: Association of Rheumatology Health Professionals.
55. Hunter D.J., Lo G.H. (2008). The management of osteoarthritis: An overview and call to appropriate conservative treatment. *Rheumatic Disease Clinics of North America* 33, 689–712.
56. Sharma L. (2008). Osteoarthritis: Treatment. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 235–240). New York: Springer.
57. Clegg D.O., Reda D.J., Harris C.L., et al. (2006). Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *New England Journal of Medicine* 354, 795–808.
58. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. (2000). Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis and Rheumatology* 43, 1905–1915.
59. Lo G.H., LaValley M., McAllindon T., et al. (2003). Intra-articular hyaluronic acid in treatment of knee osteoarthritis: A meta-analysis. *Journal of the American Medical Association* 290, 3115–3121.
60. Wortman R.L., Kelley W.N. (2005). Gout and hyperuricemia. In Harris E.D., Budd R.C., Firestein G.S., et al. (Eds.), *Kelly's textbook of rheumatology* (7th ed., pp. 1402–1425). Philadelphia: Elsevier Saunders.
61. Eggebeen A.T. (2007). Gout: An update. *American Family Physician* 76, 801–812.
62. Lovell D.J. (2008). Juvenile idiopathic arthritis. In Klippel J.R., Stone J.H., Crofford L.J., et al. (Eds.), *Primer on the rheumatic diseases* (13th ed., pp. 142–148). New York: Springer.
63. Miller M.L., Cassidy J.T. (2007). Juvenile rheumatoid arthritis. In Kliegman R.M., Behrman R.E., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1001–1012). Philadelphia: Saunders Elsevier.
64. Pachman L.M. (2007). Juvenile dermatomyositis. In Kliegman R.M., Behrman R.E., Jenson H.B., et al. (Eds.), *Nelson textbook of pediatrics* (18th ed., pp. 1001–1012). Philadelphia: Saunders Elsevier.
65. Burgos-Vargas R. (2002). The juvenile-onset spondylarthritides. *Rheumatic Disease Clinics of North America* 28, 531–560.
66. Tutuncu Z., Kavanaugh A. (2007). Rheumatic disease in the elderly: Rheumatoid arthritis. *Rheumatic Disease Clinics of North America* 33, 57–70.
67. Wise C.M. (2007). Crystal-induced arthritis in the elderly. *Rheumatic Disease Clinics of North America* 33, 33–55.
68. Weyand C.M., Goronzy J.J. (2003). Giant-cell arteritis and polymyalgia rheumatica. *Annals of Internal Medicine* 139, 505–515.
69. Frearson R., Cassidy T., Newton J. (2003). Polymyalgia rheumatica and temporal arteritis: Evidence and guidelines for diagnosis and management in older people. *Age and Ageing* 32, 370–374.

UNIT 13

Integumentary Function

Structure and Function of the Skin
- *Epidermis*
  - Keratinocytes
  - Melanocytes
  - Langerhans Cells
  - Merkel Cells
- *Dermis*
  - Papillary Dermis
  - Reticular Dermis
  - Immune Cells
  - Blood Vessels
  - Innervation
- *Basement Membrane Zone*
- *Skin Appendages*
  - Eccrine and Apocrine Sweat Glands
  - Sebaceous Glands
  - Hair Follicles
  - Nails

Manifestations of Skin Disorders
- *Lesions and Rashes*
- *Pigmentary Skin Disorders*
- *Pruritus*
- *Dry Skin*
- *Variations in Dark-Skinned People*

Chapter 45

Structure and Function of the Skin

The skin, also called the *integumentum*, is one of the largest and most versatile organs in the body. It has a surface area of 1.5 to 2 square meters, weighs approximately 4 kg (9 pounds), and forms the major interface between the internal organs and the external environment. Besides providing a covering for the entire body surface, the skin performs may other functions, including protection against physical injury, sunlight, and microorganisms; prevention of loss of fluids from the internal environment; regulation of body temperature; reception of continual sensations from the environment, such as touch, temperature, and pain; and synthesis of vitamin D through the action of sunlight on the skin.

Structure and Function of the Skin

The skin and its appendages (sweat glands, hair follicles, and nails) constitute a complex organ with many cell types. The properties of the skin, such as the thickness of skin layers, the distribution of sweat glands, and the number and size of hair follicles, vary in different parts of the body. Nevertheless, certain properties are common to the skin on all areas of the body. Structurally, the skin consists of two main layers: a superficial and thinner epithelial tissue layer, called the *epidermis*, and a deeper and thicker connective tissue layer, called the *dermis*. The basement membrane zone is an interface between the dermis and epidermis (Fig. 45-1). A layer

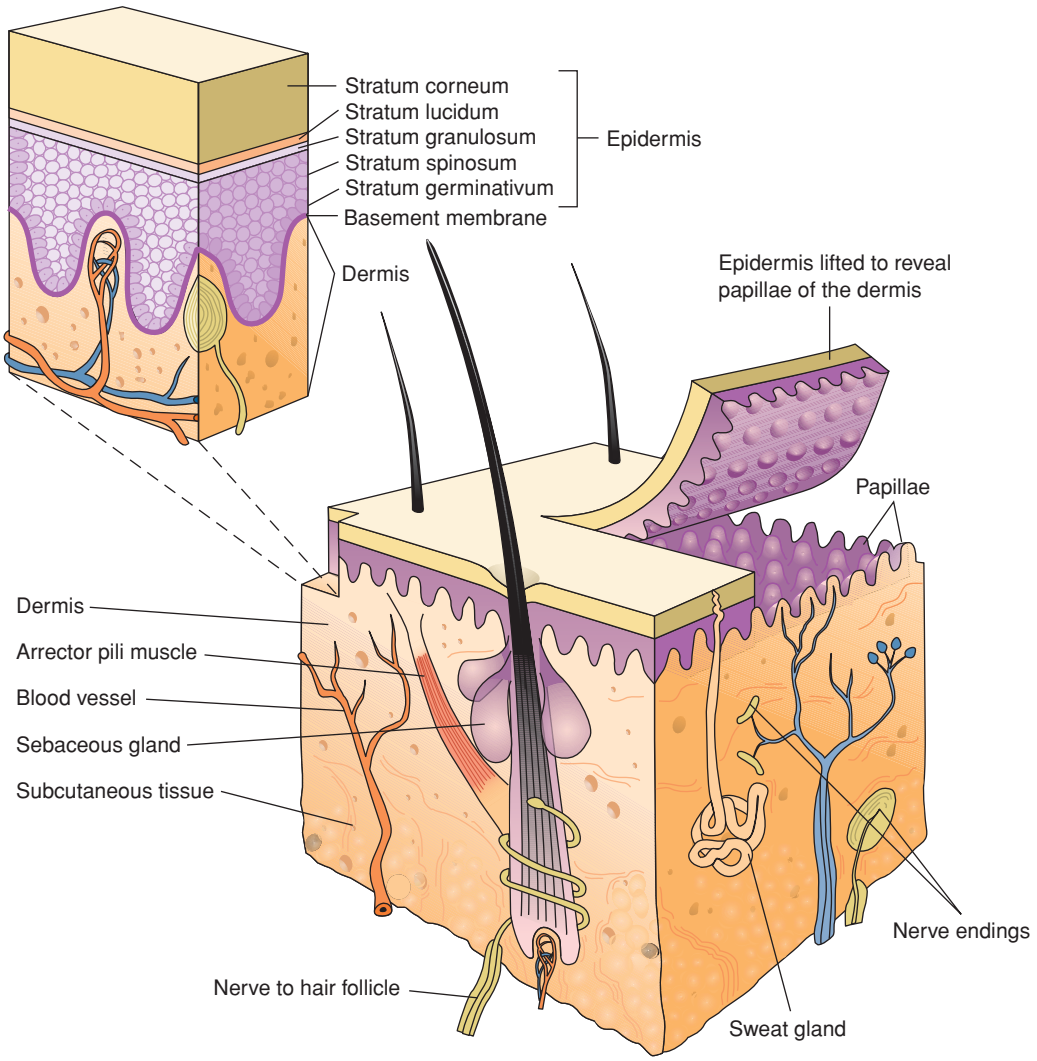


FIGURE 45-1. Three-dimensional view of the skin.

of subcutaneous tissue, sometimes called the *hypodermis*, serves as a storage site for fat and contains large blood vessels that supply the skin.

Epidermis

The functions of the skin depend largely on the properties of its epidermis, which is composed of stratified keratinized epithelium. The epidermis is composed of four types of cells: keratinocytes, melanocytes, Langerhans cells, and Merkel cells. The keratinocytes produce a fibrous protein called *keratin*, which is essential to the protective function of skin; the melanocytes produce a pigment called *melanin*, which is responsible for skin color, tanning, and protecting against ultraviolet radiation; the Langerhans cells link the epidermis to the immune system; and the Merkel cells provide sensory information.

Keratinocytes

The keratinocytes are the predominate cell type of the epidermis. These keratin-producing cells form five distinct

Organization of Skin Structures

- The skin has two layers, an outer epidermis and an inner dermis, separated by a basement membrane.
- The epidermis, which is avascular, is composed of four to five layers of stratified squamous keratinized epithelial cells that are formed in the deepest layer of the epidermis and migrate to the skin surface to replace cells that are lost during normal skin shedding.
- The basement membrane is a thin adhesive layer that cements the epidermis to the dermis. This is the layer involved in blister formation.
- The dermis is a connective tissue layer that separates the epidermis from the underlying subcutaneous fat layer. It contains the blood vessels and nerve fibers that supply the epidermis.

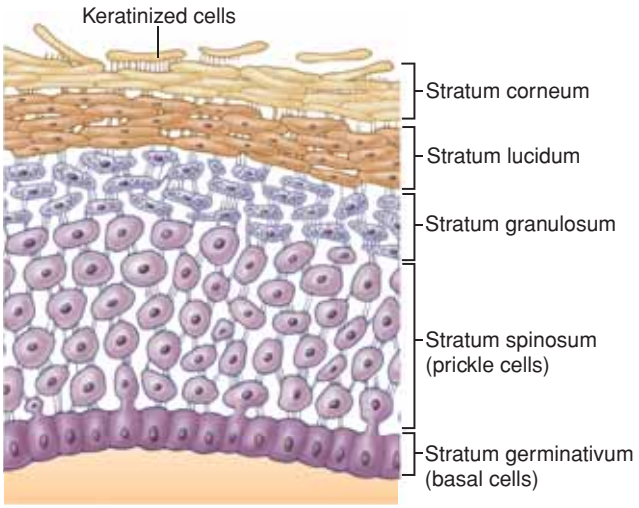


FIGURE 45-2. Epidermal cells. The basal cells undergo mitosis, producing keratinocytes that change their size and shape as they move upward, replacing cells that are lost during normal cell shedding.

layers, or *strata*, as they divide and mature: the stratum germinativum, the stratum spinosum, the stratum granulosum, the stratum lucidum, and the stratum corneum.

The deepest layer, the *stratum germinativum* or *stratum basale,* consists of a single layer of basal cells that are attached to the basal lamina in the basement membrane. The basal cells are the only epidermal cells that are mitotically active. All cells of the epidermis arise from this layer. As new cells form in the basal layer, the older cells change shape and are pushed upward toward the skin surface (Fig. 45-2). As these cells approach the surface, their cytoplasm is converted to keratin and they form flattened plates of dead cells on the skin surface. It normally takes 3 to 4 weeks for the epidermis to replicate itself. The rate of cell division in the stratum basale is greatly accelerated when the outer layers of the epidermis are stripped away as occurs in abrasions and burns.

The second layer, the *stratum spinosum,* is formed as cells from the basal cell layer move upward toward the skin surface. The stratum spinosum is two to four layers thick. The cells of this layer are commonly referred to as *prickle cells* because they develop a spiny appearance as their cell borders interact. The third layer, the *stratum granulosum,* consists of three to five layers of flattened keratinocytes. The nuclei and organelles of these cells begin to degenerate and keratin filaments become more apparent. A distinctive feature of cells in this layer is the appearance of dark staining granules of a protein called *keratohyalin,* which serve as a support for the keratin filaments. The *stratum lucidum,* the fourth layer, which lies just superficial to the stratum granulosum, is a thin, transparent layer mostly confined to the palms of the hands and soles of the feet. It consists of transitional cells that retain some of the functions of living skin cells from the layers below but otherwise resemble the cells of the stratum corneum.

The top or surface layer of the epidermis is the *stratum corneum*. The cells in the stratum corneum are made up of numerous layers of dead keratinized cells. The interior of the cells contain mostly keratin and keratohyalin. These cells are continuously shed and replaced by cells from the deeper strata. The stratum corneum is the layer that varies most in cell layers and thickness. It ranges from 15 layers of cells in areas such as the face to 25 or more layers on the arm. Specialized areas, such as the palms of the hand and soles of the feet, have 100 layers or more.

Melanocytes

Melanocytes are dendritic cells found scattered among the basal cells in the stratum basale. They function to produce pigment granules called *melanin,* the substance that gives skin its color. During embryonic life, melanocyte precursor cells migrate from the neural crest and enter the developing epidermis. A specific functional association is then established in which one melanocyte maintains an association with a given number of keratinocytes. This association is called the *dermal melanin unit*. The ratio of melanocytes to keratinocytes varies in different parts of the body and is constant in all races.

As dendritic cells, melanocytes are round to columnar cells with long undulating processes that extend between the keratinocytes of the stratum spinosum (Fig. 45-3). Melanocytes synthesize melanin from the amino acid tyrosine in the presence of an enzyme called *tyrosinase* that is activated by ultraviolet light. Synthesis of melanin occurs in membrane-bound structures called *premelanosomes,* which are derived from the Golgi complex. As melanin accumulates in the premelanosomes, they are transformed into mature melanin granules, called *melanosomes*. Premelanosomes are concentrated near the Golgi apparatus, nearly mature melanosomes near the base of the cell processes, and fully mature melanocytes

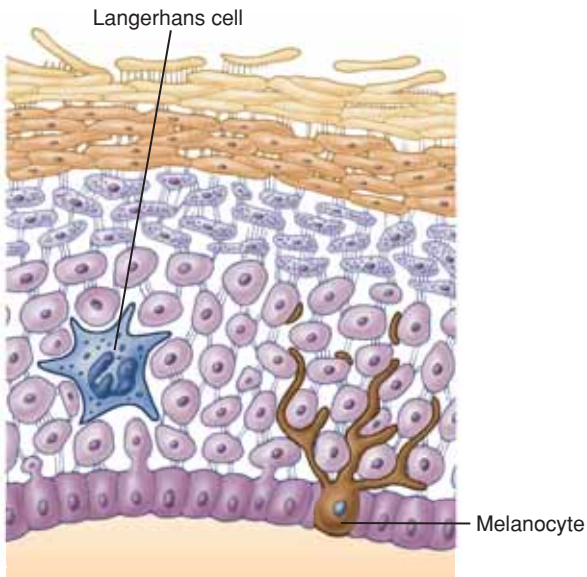


FIGURE 45-3. The melanocytes, which are located in the basal layer of the skin, produce melanin pigment granules that give skin its color. The melanocytes have threadlike, cytoplasm-filled extensions that are used in passing the pigment granules to the keratinocytes.

at the ends of the processes. Melanosomes and their melanin content are transferred to neighboring keratinocytes by pigment donation. This process involves the phagocytosis of the tips of the melanocyte process by keratinocytes. After pigment donation, the melanocyte process elongates and receives more melanosomes, and the process is repeated. Thus, a single melanocyte is able to provide melanin to all of the associated keratinocytes in its epidermal melanin unit.

Skin color is determined by the type, number, and size of the melanosomes transferred into the surrounding keratinocytes. Dark-skinned and light-skinned people have approximately the same number of melanocytes, but the production and packaging of pigment are different. In dark-skinned people, *larger* melanin-containing melanosomes are produced and transferred individually to the keratinocyte, whereas in light-skinned people, *smaller* melanosomes are produced and then packaged together in a membrane before being transferred to the keratinocyte.

There are two major forms of melanin: *eumelanin* and *pheomelanin*. Exposure to the sun's ultraviolet rays increases the production of eumelanin, a brownish-black pigment, which causes tanning to occur. The primary function of such melanin is to protect the skin by absorbing and scattering harmful ultraviolet rays, which are implicated in skin cancers. Localized concentrations of eumelanin are also responsible for the formation of freckles and moles. Pheomelanin, a reddish-yellow pigment, is particularly concentrated in the lips, nipples, glans penis, and vagina. Besides the skin, it is found in hair, particularly red hair. It has been suggested that the reason fair-haired individuals are more susceptible to skin cancers may be due to the enhanced photoreactivity of pheomelanin, as compared with eumelanin.

Langerhans Cells

Langerhans cells are a subtype of dendritic cells that reside in the epidermis (Fig. 45-4). They are antigen-presenting cells that originate in the bone marrow and are part of the mononuclear phagocytic system. Langerhans cells play a major role in functioning of the skin's immune system. Like macrophages, Langerhans cells express both major histocompatibility class (MHC) I and II molecules as well as receptors for immunoglobulins (see Chapter 15). It is postulated that the major function of the Langerhans cells found in the skin is to phagocytose and process foreign antigens, after which they migrate into regional lymph nodes, where they present the processed antigens to T cells (Fig. 45-4). As antigen-presenting cells, the Langerhans cells are involved in delayed-type hypersensitivity reactions such as contact dermatitis and other cell-mediated immune responses in the skin.

Merkel Cells

Merkel cells are epidermal cells that function in cutaneous sensation. They are interspersed among the keratinocytes of the stratum basale of the epidermis, and are particularly abundant in areas of the skin where sensory

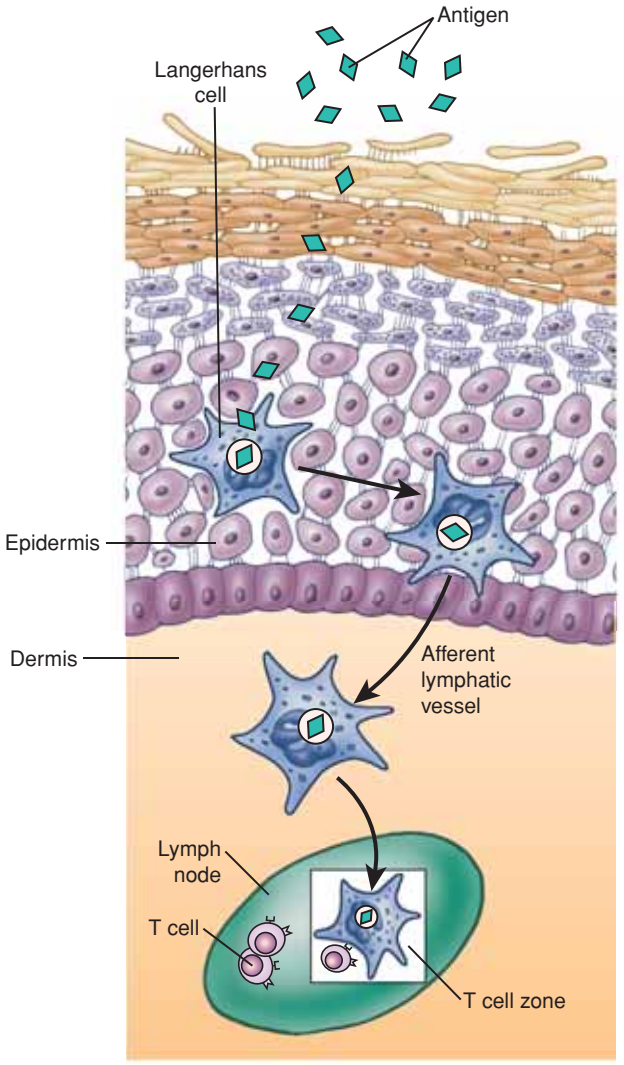


FIGURE 45-4. Langerhans cells.

perception is acute, such as the fingertips. They are usually found as single cells located parallel to the basement. Myelinated sensory neurons traverse the basement membrane to approximate the Merkel cell and form a Merkel cell–neuron complex. These complexes may function as tactile mechanoreceptors. Merkel cells display distinctive organelle and membrane-bound dense granules, suggesting that they possess neurosecretory function. These functions may include metabolic support of their associated neurons, neuron development, and regeneration after injury.

Dermis

The dermis is the connective tissue layer that separates the epidermis from the subcutaneous fat layer (see Fig. 45-1). It supports the epidermis and serves as its primary source of nutrition. The main component of the dermis is collagen, a group of fibrous proteins. Collagen represents 70% of dry skin weight and serves as the major stress-resistant material of the skin. Collagen is

rich in amino acids. Collagen fibers are loosely arranged in the papillary dermis, but are tightly bundled in the reticular dermis. The hair follicles and glandular structures are embedded in this layer and continue through the epidermis.

Based on its tissue structure, the dermis can be divided into both a superficial papillary dermis and a deeper reticular dermis. The two layers of the dermis contain immune cells and fibroblasts, blood vessels, and nerves.

Papillary Dermis

The papillary layer of the dermis is a thin superficial layer that interdigitates directly with the epidermis, but is separated from it by the basement membrane. It consists of collagen fibers and ground substance. This layer is densely covered with conical projections called *dermal papillae* (see Fig. 45-1). The basal cells of the epidermis project into the papillary dermis, forming *rete ridges*. It is believed that the dense structure of the dermal papillae serves to minimize the separation of the dermis and the epidermis. This layer of the dermis is richly vascularized. It contains capillaries, end arterioles, and venules that nourish the epidermal layers of the skin. Lymph vessels and nerve tissue also are found in this layer.

Reticular Dermis

The reticular layer of the dermis is the thicker area of the dermis and forms the bulk of the dermal layer. This is the tough layer in animal hides from which leather is made. The reticular dermis is characterized by a complex meshwork of three-dimensional collagen bundles interconnected with large elastic fibers and ground substance, a viscid gel that is rich in mucopolysaccharides. The collagen fibers are oriented parallel to the body's surface in any given area. Collagen bundles may be organized lengthwise, as on the abdomen, or in round clusters, as on the heel. The direction of surgical incisions is often determined by this organizational pattern.

Immune Cells

Once thought to be composed primarily of fibroblasts, it is now believed that one of the main cells of the dermis are dendritic cells, called *dermal dendrocytes*. Dermal dendrocytes are spindle-shaped cells that have both phagocytic and dendritic properties. They are believed to possess antigen-presenting functions and play an important part in the immunobiology of the dermis. In addition, it is possible that dermal dendrocytes may be able either to initiate or respond to immunologic events in the epidermis. Dermal dendrocytes also are thought to be involved in processes such as wound healing, blood clotting, and inflammation.

The dermis also contains macrophages, T cells and mast cells, and fibroblasts. Dermal macrophages and venular epithelial cells may present antigen to T cells in the dermis. Most of these T cells are previously activated or memory T cells. T-cell responses to macrophage- or endothelium-associated antigens in the dermis are probably more important in generating an immune response to antigen challenge in previously exposed persons than in initiating a response to a new antigen. The major type of T-cell–mediated immune response in the skin is delayed-type hypersensitivity (see Chapter 16).

Mast cells, which have a prominent role in immunoglobulin E–mediated immediate hypersensitivity, also are present in the dermis. These cells are strategically located at body interfaces such as the skin and mucous membranes and are thought to interact with antigens that come in contact with the skin.

Blood Vessels

The arterial vessels that nourish the skin form two plexuses (i.e., collections of blood vessels), one located between the dermis and the subcutaneous tissue and the other between the papillary and reticular layers of the dermis. The pink color of light skin results primarily from blood in the vessels of this latter plexus. Capillary flow that arises from vessels in this plexus also extends up and nourishes the overlying epidermis by diffusion. Blood leaves the skin through small veins that accompany the subcutaneous arteries. The lymphatic system of the skin, which aids in combating certain skin infections, also is limited to the dermis.

The skin is richly supplied with arteriovenous anastomoses in which blood flows directly between an artery and a vein, bypassing the capillary circulation. These anastomoses are important for temperature regulation. They can open up, letting blood flow through the skin vessels when there is a need to dissipate body heat, and close off, conserving body heat if the environmental temperature is cold.

Innervation

The innervation of the skin is complex. The dermis is well supplied with sensory receptors for temperature, pain, and tactile sensation (see Chapter 35), as well as nerves that supply the blood vessels, sweat glands, and arrector pili muscles.

The papillary layer of the dermis is supplied with free nerve endings that serve as nociceptors (i.e., pain receptors) and thermoreceptors. The dermis also contains encapsulated pressure-sensitive receptors that detect pressure and touch. The largest of these are the *pacinian corpuscles,* which are widely distributed in the dermis and subcutaneous tissue in the digits of the hands and breasts. These mechanoreceptors are specialized to perceive pressure, touch, and vibration. *Meissner corpuscles* are encapsulated mechanoreceptors specialized for tactile discrimination. They are concentrated on the fingertips and palms of the hands, where they account for about half of the tactile receptors. They are also located on the eyelids, lips, tongue, nipples, and skin of the foot and forearm. The deep dermis is supplied with small, oval mechanoreceptors called *Ruffini corpuscles*. They are slowly adapting receptors, responding to heavy pressure and joint movement. They are also believed to detect cold. The skin is also supplied by *Krause end bulbs*, nerve endings contained in a cylindrical or oval capsule. They are found most frequently in the oral cavity,

conjunctiva, and genitalia. Although their function is uncertain, they are thought to function as mechanoreceptors and heat detectors.

Most of the skin's blood vessels are innervated by the sympathetic nervous system. The sweat glands are innervated by cholinergic fibers but controlled by the sympathetic nervous system. Likewise, the sympathetic nervous system controls the arrector pili (pilomotor) muscles that cause elevation of hairs on the skin. Contraction of these muscles tends to cause the skin to dimple, producing "goose bumps."

Basement Membrane Zone

The basement membrane zone is a layer of intercellular and extracellular matrices that serves as an interface between the dermis and the epidermis. It separates the epithelium from the underlying connective tissue, anchors the epithelium to the loose connective tissue underneath, and serves as a selective filter for molecules moving between the two layers. It is also a major site of immunoglobulin and complement deposition in skin disease.

Most of the structures of the basal membrane zone are produced by cells of the epidermis. The basal lamina is the primary organizational structure of the basement membrane and is responsible for epithelial cell polarity as well as keratin gene expression. The ultrastructures of the basal lamina include the lamina lucida, lamina densa, hemidesmosomes, anchoring filaments, and microfilaments (Fig. 45-5). The *lamina lucida* is an electron-lucent layer where adherence proteins are located. It consists of fine anchoring filaments and a cell adhesion glycoprotein, called *laminin*, which plays a role in the organization of the macromolecules in the basement membrane zone and promotes attachment of cells to the extracellular matrix. The *lamina densa* contains an adhesive called *type IV collagen* as well as laminin. It is important in dermal–epidermal attachment. The tonofibril is a fiber similar to the keratin filament. Bundles of tonofibrils converge and terminate in the hemidesmosomes that serve as attachment sites for the dermis and epidermis. Because they form a continuous link between the intracellular tonofibrils of the epidermis and the extracellular basement membrane, the hemidesmosomes are also thought to be involved in relaying signals between the skin systems.

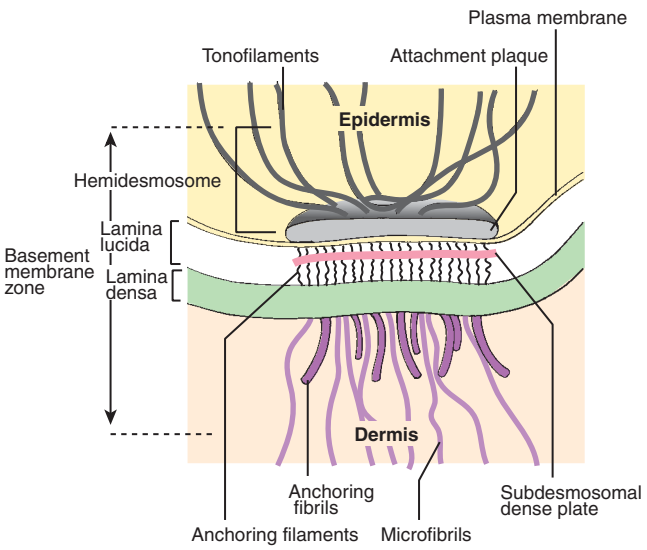


FIGURE 45-5. The dermal–epidermal interface and basement membrane layers. (Adapted from Rubin R., Strayer D.E. [Eds.]. [2008]. *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1004]. Philadelphia: Lippincott Williams & Wilkins.)

The basement membrane zone is often involved in skin disorders that cause bullae or blister formation. One of these disorders, bullous pemphigoid, is a blistering disease caused by antibodies against basement membrane proteins (Fig. 45-6). The blisters of bullous pemphigoid are large and tense and may appear on normal-appearing skin. The thighs and flexor tendons are most commonly affected. The disease is self-limited but chronic, and the person's general health is unaffected.

Skin Appendages

Skin appendages are derived from outgrowths of epidermal epithelium during development. They include the eccrine and apocrine sweat glands, sebaceous glands, hair follicles, and nails.

Eccrine and Apocrine Sweat Glands

There are two types of sweat glands: eccrine and apocrine. *Eccrine sweat glands* are simple tubular structures that originate in the dermis and open directly to the skin surface. They are numerous (several million), vary in density, and are located over the entire body surface. Their purpose is to transport sweat to the outer skin surface to regulate body temperature. *Apocrine sweat glands* are less numerous than eccrine sweat glands. They are larger and located deep in the dermal layer. They open through a hair follicle, even though a hair may not be present, and are found primarily in the axillae and groin. The major difference between these glands and the eccrine glands is that apocrine glands secrete an oily substance. In animals, apocrine secretions give rise to distinctive odors that enable animals to recognize the presence of others. In humans, apocrine secretions are sterile until mixed with the bacteria on the skin surface; they then produce what is commonly known as "body odor."

Sebaceous Glands

The sebaceous glands are located over the entire skin surface except for the palms, soles, and sides of the feet. They secrete a waxlike mixture of triglycerides, cholesterol, and secretory debris, called *sebum*. Sebum lubricates the hair and skin, prevents undue evaporation of moisture from the stratum corneum during cold weather, and helps to conserve body heat. The sebaceous glands are part of what is called the *pilosebaceous*

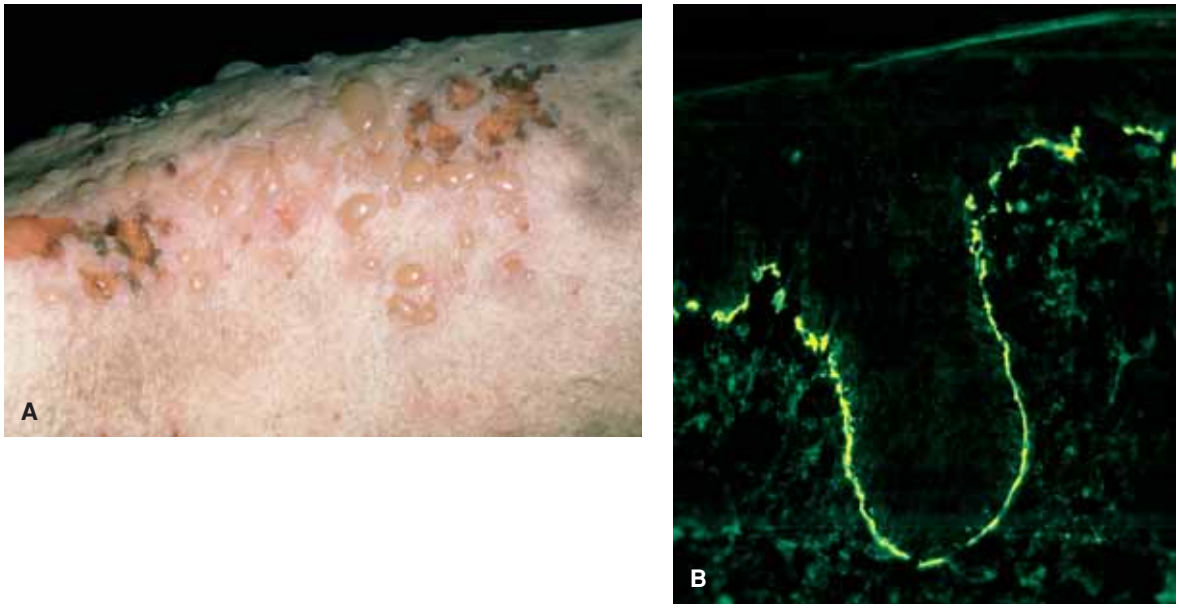


FIGURE 45-6. Bullous pemphigoid. **(A)** The skin shows multiple tense bullae on an erythematous base and erosions, distributed primarily on the medial thighs and trunk. **(B)** Direct immunofluorescence study discloses linear deposition of immunoglobulin G (and complement 3) along the dermal–epidermal junction. Ultrastructurally, these antibodies and complement are present in the lamina lucida. (From Storm C.A., Elder D.E. [2008]. The skin. In Rubin R., Strayer D.S. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [5th ed., p. 1020]. Philadelphia: Lippincott Williams & Wilkins.)

unit, with their ducts opening into the upper third of the hair follicle. The sebum produced by the sebaceous gland is the product of holocrine secretion. The entire cell produces and becomes filled with the fatty product while it simultaneously undergoes cell death as the product fills the cell. Both the secretory product and the cell are then discharged from the gland into the hair follicle. New cells are produced by mitosis of the basal cells in the gland.

Sebum production is under the control of genetic and hormonal influences. Sebaceous glands are relatively small and inactive until individuals approach adolescence. The glands then enlarge, stimulated by the rise in sex hormones. Gland size directly influences the amount of sebum produced, and the level of androgens influences gland size. The sebaceous glands are the structures that become inflamed in acne (see Chapter 46).

Hair Follicles

Hair is a filamentous, keratinized structure that originates from hair follicles in the dermis. Coloration of hair is attributable to the content and type of melanin that the hair contains. The entire hair structure consists of the hair follicle, sebaceous gland, hair muscle (arrector pili), and, in some instances, apocrine gland (Fig. 45-7). Most hair follicles are associated with sebaceous glands, and these structures combine to form the pilosebaceous unit. The arrector pili muscle, located under the sebaceous gland, provides a thermoregulatory function by contracting to cause goose bumps, thereby reducing the skin surface area that is available for the dissipation of body heat.

The hair follicle is divided into three parts: the infundibulum, which extends from the surface opening to the level of the opening for the sebaceous gland; the isthmus, which extends from the infundibulum to the level of the arrector pili muscle; and the expanded inferior

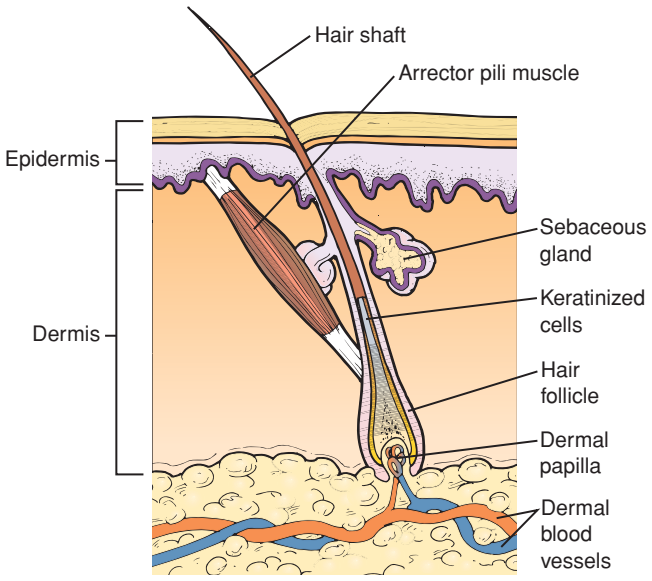


FIGURE 45-7. Parts of a hair follicle.

hair bulb, which is indented to conform to the shape of the dermal papillae occupying it. The dermal papillae contains a rich supply of nutrients and oxygen for the cells in the hair follicle.

Growth of the hair is centered in the bulb (i.e., base) of the hair follicle, and the hair undergoes changes as it is pushed outward. Hair growth goes through three cyclic phases: the anagen (growth), catagen (atrophy), and telogen (resting) phases. Anagen hair has long inner roots and outer root sheaths, is deeply rooted in the dermis, and is difficult to detach and does not come out with regular brushing. *Anagen* follicles are actively replicating and therefore especially susceptible to nutritional deficiencies and metabolic insults. The *catagen* phase represents degeneration of the root structure and migration of dermal papillae and the follicular unit toward the more superficial layers of the dermis. Catagen hair usually represents approximately 1% of all scalp hairs. *Telogen* hair has short, white, club-shaped roots. With formation of new anagen hair below the club, the developing follicle will eventually replace the telogen hair, leading to the shedding of approximately 50 to 100 hairs a day.

Nails

The nails are hardened keratinized plates, called *fingernails* and *toenails*, that protect the fingers and toes and enhance dexterity. The nails grow out from a curved transverse groove called the *nail groove*. The floor of this groove, called the *nail matrix*, is the germinal region of the nail plate (Fig. 45-8). The underlying epidermis, attached to the nail plate, is called the *nail bed*. Like hair, nails are the end product of dead matrix cells that are pushed outward from the nail matrix. Unlike hair, nails grow continuously rather than cyclically, unless permanently damaged or diseased. The epithelium of the fold of skin that surrounds the nail consists of the usual layers of skin. The stratum corneum forms the *eponychium* or cuticle. The nearly transparent nail plate provides a useful window for viewing the amount of oxygen in the blood, providing a view of the color of the blood in the dermal vessels. Changes or abnormalities of the nail can also serve to help diagnose skin or systemic diseases.

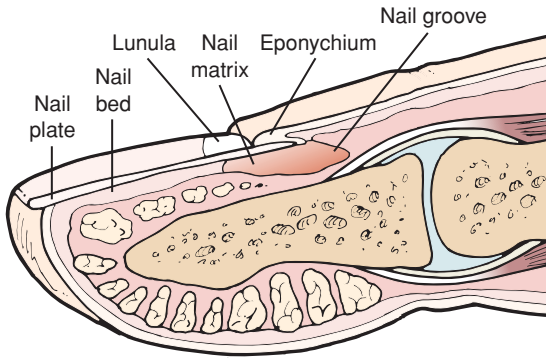


FIGURE 45-8. Parts of a fingernail.

In summary, the skin is primarily an organ of protection. It is the largest organ of the body and forms the major barrier between the internal organs and the external environment. The skin is richly innervated with pain, temperature, and touch receptors; it synthesizes vitamin D and plays an essential role in fluid and electrolyte balance. The skin is composed of two layers, the epidermis and the dermis, separated by a basement membrane.

The epidermis, the outermost layer of the skin, contains four to five layers, or strata. The major cells of the epidermis are the keratinocytes, Langerhans cells, Merkel cells, and melanocytes. The stratum germinativum, or basal layer, is the source of the cells in all five layers of the epidermis. The keratinocytes, which are the major cells of the epidermis, are transformed from viable keratinocytes to dead keratin as they move from the innermost layer of the epidermis (i.e., stratum germinativum) to the outermost layer (i.e., stratum corneum). The melanocytes are pigment-synthesizing cells that give skin its color; Langerhans cells are antigen-presenting cells that link the epidermis to the immune system; and Merkel cells are epidermal cells that function in cutaneous sensation.

The two layers of the dermis, the papillary dermis and the reticular dermis, provide the epidermis with support and nutrition and are the source of blood vessels, innervation, and skin appendages (i.e., sweat glands, sebaceous glands, hair follicles, and nails). The hypodermis, a layer of subcutaneous tissue, binds the dermis to the underlying organs and tissues of the body.

Manifestations of Skin Disorders

No two skin disorders look exactly alike, nor are they necessarily caused by the same agents. The appearance of many skin disorders may be further influenced by excessive itching, infection, or the effects of self-treatment. Skin color also may influence the appearance. Nevertheless, most skin disorders have some common characteristics that can be used to describe them. This section of the chapter covers lesions and rashes, pigmentary skin disorder, pruritus, dry skin, and variations in dark skin.

Lesions and Rashes

Rashes are temporary eruptions of the skin, such as those associated with childhood diseases, heat, diaper irritation, or drug-induced reactions. The term *lesion* refers to a traumatic or pathologic loss of normal tissue continuity, structure, or function. The components of a rash often are referred to as *lesions*. Skin lesions may occur as primary lesions arising in previously normal skin, or they may develop as secondary lesions resulting from other

disease conditions. Figure 45-9 illustrates various types of skin lesions.

Rashes and lesions may range in size from a fraction of a millimeter (e.g., the pinpoint spots of petechiae) to many centimeters (e.g., pressure ulcer). They may be blanched (white), erythematous (reddened), hemorrhagic or purpuric (containing blood), or pigmented (colored). A *macule* is a small (≤1.0 cm in diameter) flat spot, such as a freckle; a *papule* is an elevated (≥1.0 cm) superficial lesion. *Plaques* are elevated lesions (≥1 cm), often formed by the coalescence of papules. *Nodules* are solid marblelike lesions (>0.5 cm) that are deeper and firmer than a papule. A *wheal* is a somewhat irregular, relatively transient area of localized skin edema, such as a mosquito bite. *Lichenification* is a thickened and leathery roughening of the skin with increased visibility of the normal skin furrows and excoriations caused by scratching.

Blisters are circumscribed elevations of the skin caused by fluid under or within the epidermis. *Pustules* are circumscribed pus-filled elevations of the skin. *Vesicles* are small (<1.0 cm in diameter) and *bullae* are large (1.0 cm or larger in diameter) fluid-filled blisters (see Fig. 45-9). Friction blisters most commonly occur on the palmar and plantar surfaces of the hands and feet where the skin is constantly exposed to mechanical trauma, such as from shoes and household tools and appliances.

An *erosion* is a loss of the superficial epidermis, the surface of which is moist but does not bleed. An *ulcer* is a skin defect in which there has been loss of the epidermis and papillary layer of dermis. It may extend into the subcutaneous tissue, and often occurs in pathologically damaged tissue.

A *callus* is a hyperkeratotic plaque of skin due to chronic pressure or friction. It represents hyperplasia of the dead, keratinized cells that make up the cornified or horny layer of the skin. Increased cohesion between cells results in hyperkeratosis and decreased skin shedding. A callus may be filed down but is likely to recur if pressure continues in the localized area.

Corns (helomas) are small, well-circumscribed, conical, keratinous thickenings of the skin. They usually appear on the toes from rubbing or ill-fitting shoes. The corn may be either hard (heloma durum) with a central hard, horny core, or soft (heloma molle), as commonly seen between the toes. They may appear on the hands as an occupational hazard. The hard tissue at the center of the corn looks like a funnel with a broad top and a pointed bottom, hence the name "corn." Corns on the feet often are painful, whereas corns on the hands may be asymptomatic. Corns may be abraded or surgically removed, but they recur if the causative agent is not removed.

Pigmentary Skin Disorders

Pigmentary skin disorders involve the melanocytes. In some cases, there is an absence of melanin production, as in vitiligo or albinism. In other cases, there is an increase

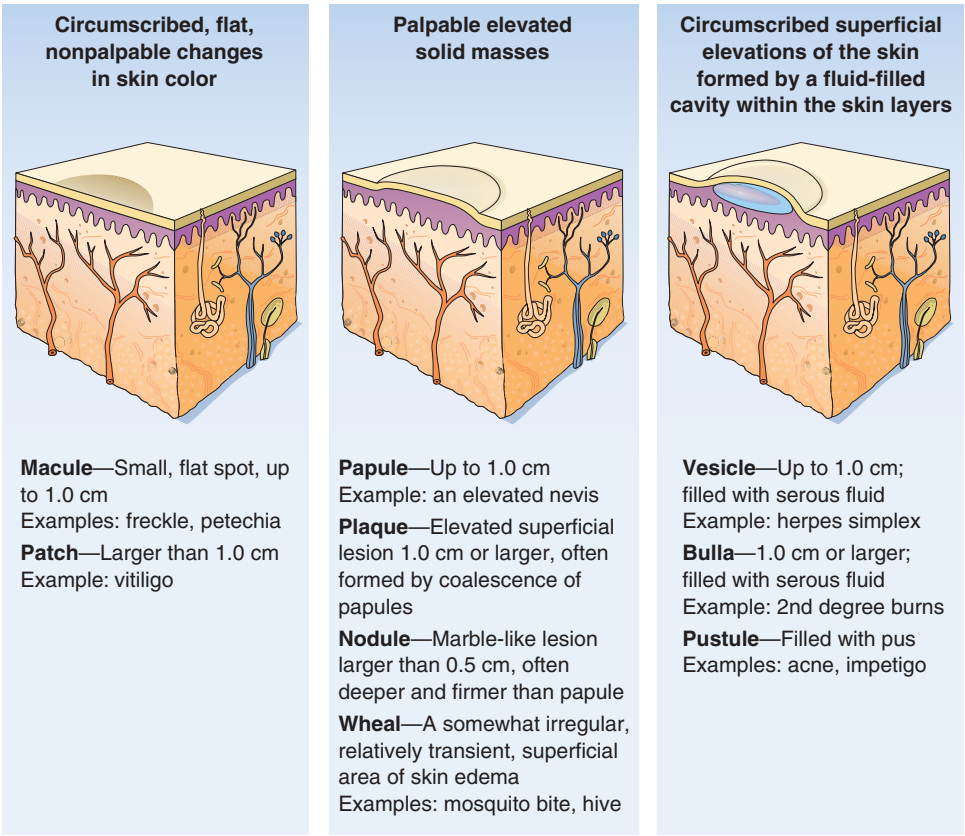


FIGURE 45-9. Primary lesions may arise in previously normal skin. Authorities vary somewhat on their definition of skin lesions by size. (Adapted from Bickley L.S., Szilagyi P.C. [2003]. *Bates' guide to physical assessment and history taking* [8th ed., p. 103]. Philadelphia: Lippincott Williams & Wilkins.)

in melanin or some other pigment, as in melasma. In either case, the emotional impact can be devastating.

Albinism, a genetic disorder in which there is complete or partial congenital absence of pigment in the skin, hair, and eyes, is found in all races. Although there are over 10 different types of albinism, the most common type is recessively inherited oculocutaneous albinism, in which there is a normal number of melanocytes but they lack tyrosinase, the enzyme needed for synthesis of melanin. It affects the skin, hair, and eyes. Individuals have pale or pink skin, white or yellow hair, and light-colored or sometimes pink eyes. Persons with albinism have ocular problems, such as extreme sensitivity to light and refractive problems. Treatment efforts for people with albinism are aimed at reducing their risk for skin cancer through protection from solar radiation and screening for malignant changes. Efforts to reduce the visual impact are important, such as glasses, preferential seating in classrooms, and large-print books.

Vitiligo is a pigmentary problem of concern to darkly pigmented persons of all races. It also affects white-skinned persons, but not as often, and the effects usually are not as socially problematic. The classic sign of vitiligo is the sudden appearance of white patches on the skin. The lesion is a depigmented macule with definite smooth borders on the face, axillae, neck, or extremities (Fig. 45-10). The patches vary in size from small macules to ones involving large skin surfaces. The large macular type is more common. Depigmented areas appear white, pale colored, or sometimes grayish-blue. Histologically, the depigmented areas may contain no melanocytes, greatly altered or decreased amounts of melanocytes, or, in some cases, melanocytes that no longer produce melanin. Although there are many treatment regimens for vitiligo, none is curative. Self-tanning lotions, skin stains, and cosmetics are used for camouflage. Micropigmentation (tattooing) has been done on smaller, recalcitrant areas, but it is often difficult to attain a correct color match. If extensive skin surfaces are involved, the treatment may be reversed and the pigmented areas bleached to match the remainder of the skin color. A melanocytotoxic agent is used to remove remaining melanocytes from skin areas.

FIGURE 45-10. Vitiligo of the forearm of a black person. (Neutrogena Skin Care Institute.) (From Sauer G.C., Hall J.C. [1996]. *Manual of skin diseases* [7th ed.]. Philadelphia: Lippincott-Raven.)

Melasma is a disorder characterized by darkened macules on the face. It is common in all skin types, but most prominent in brown-skinned people from Asia, India, and South America. It occurs in men but is more common in women, particularly during pregnancy or while using oral contraceptives. It may or may not resolve after giving birth or discontinuing hormonal birth control. Melasma is exacerbated by sun exposure. Treatment measures are palliative, mostly consisting of limiting exposure to the sun and using sunscreens. Bleaching agents, containing 2% to 4% hydroquinone, are standard treatments.

Pruritus

Pruritus is an unpleasant sensation of itch leading to the desire to scratch. Symptoms of pruritus range from mild to severe. In some persons, the condition may be so severe that it interrupts sleep and the general quality of life. While pruritus most commonly occurs in skin disorders, it may also occur with systemic disorders, such as chronic kidney disease, diabetes, and biliary disease.

Pruritus originates within the skin's free nerve endings, is carried by small myelinated type C nerve fibers to the dorsal horn of the spinal cord, and is then transmitted to the somatosensory cortex through the spinothalamic tract (see Chapter 35). Many chemicals have been found to produce the itch sensation, including histamine, serotonin, and cytokines. Substances such as bradykinin and bile salts act locally to stimulate the itch sensation. Prostaglandins are modulators of the itch response, lowering the threshold for other mediators. Opioids produce pruritus in a number of patients who receive them and narcotic antagonists have been used successfully to relieve pruritus. Regardless of cause, pruritus is often exacerbated by skin inflammation, dry or hot ambient temperatures, skin vasodilation, and psychological stressors. Pruritus can also have a neuropathic cause. The pruritus that occurs with herpes zoster (shingles) is an example of a pruritus with a neuropathic origin. Certain idiopathic types of pruritus have been attributed to peripheral neuropathies.

Scratching, the well-known response to itch, is a spinal reflex response that to varying degrees can be controlled by the individual. While providing momentary relief, scratching increases inflammation and stimulates nerve endings, leading to more itching and scratching. Repeated scratching also causes undesirable changes in the skin such as lichenification. Successful treatment of pruritus requires interruption of this cycle.

The focus of treatment measures for pruritus can be grouped into two categories: specific and nonspecific. Specific treatment involves finding and correcting the underlying disorder, thereby eliminating the itch sensation. Nonspecific measures involve the use of measures to relieve the itch sensation and prevent complications that arise from intense and persistent scratching.

Measures such as using the entire hand to rub over large areas and keeping the fingernails trimmed often can

relieve itch and prevent skin damage. Self-limited or seasonal cases of pruritus may respond to treatment measures such as moisturizing lotions, bath oils, and the use of humidifiers. Because vasodilation tends to increase itching, cold applications may provide relief. Cool showers before bed, light sleepwear, and cool home temperatures also may be helpful. Cooling over-the-counter anti-itch agents contain menthol, camphor, or phenol. These substances stimulate nerve fibers that transmit the sensation of cold, thereby masking the itch sensation. Mild cutaneous disorders, such as bug bites, are mediated by histamine; therefore, topical antihistamines tend to be the treatment of choice. Topical corticosteroids are effective as antipruritics, particularly when used for urticaria (hives) or insect bites.

However, because most cases of pruritus are not histamine related, their management should be directed at the underlying cause. For example, systemic antihistamines and corticosteroids may be indicated for persons with severe pruritus or atopic dermatitis. Topical capsaicin cream and topical aspirin have been used for localized chronic pruritic disorders. Other modalities that have been used for all cases of pruritus with varying degrees of success are phototherapy, acupuncture, antidepressant medications, behavior modification, and alternative therapies (herbal, nutritional, and reflex therapies). In persons with pruritus due to a systemic cause, itching gradually recedes as the primary condition improves.

Dry Skin

Dry skin, also called *xerosis,* may be a natural occurrence, as in the drying of skin associated with aging, or it may be symptomatic of an underlying systemic disease or skin disorder such as contact dermatitis. Most cases of dry skin are caused by dehydration of the stratum corneum. The effects of aging on skin dryness include a change in the composition of sebaceous gland secretions and a decrease in the secretion of moisture from the sweat glands. Aging is also accompanied by a decrease in skin capillaries as well as a flattening of the dermal rete ridges, resulting in less surface area for exchange of fluids between the dermis, epidermis, and skin surface.

Persons with dry skin often experience severe pruritus and discomfort, most commonly of the extremities. Other commonly involved areas include the back, abdomen, and waist. Dry skin appears rough and scaly; there may be increased wrinkles or lines. Skin drying also predisposes the skin to scratching, resulting in cracking, fissuring, and a number of other skin maladies.

Moisturizing agents are the cornerstone of treatment for dry skin. These agents exert their effects by repairing the skin barrier, increasing the water content of the skin, reducing transepidermal water loss, and restoring the lipid barrier's ability to attract, hold, and redistribute water. Moisturizing agents can be classified as emollients, humectants, and occlusives. *Emollients* are fatty acid–containing lotions that replenish the oils on the skin surface, but usually do not leave a residue on the skin. They have a short duration of action and need to be applied frequently. *Humectants* are the additives in lotions, such as α-hydroxy acids and urea, that draw out water from the deeper skin layers and hold it on the skin surface. However, the water that is drawn to the skin is transepidermal water, not atmospheric water; thus, continued evaporation from the skin can actually exacerbate dryness. α-Hydroxy acids are derived from fruits, hence the abundance of fruit additives in shampoos and lotions in over-the-counter preparations. Urea is a nitrogenous substance that has been quite effective in reducing xerosis when combined with lotions. It is a humectant at lower concentrations (10%), but in higher concentrations (20% to 30%) it is mildly keratolytic. Clinical trials of urea have indicated its utility compared with ammonium lactate (lactic acid) lotion and glycerin. *Occlusives* are thick creams that contain petroleum or some other moisture-proof material. They prevent water loss from the skin. They are the most effective agents for relieving skin dryness, but because of their greasiness and lack of cosmetic appeal, some people do not wish to use them.

Lotion or cream additives include corticosteroids or mild anesthetics, such as camphor, menthol, lidocaine, or benzocaine. These agents work by suppressing itching while moisturizing the skin. Using room humidifiers and keeping room temperatures as low as possible to prevent water loss from the skin also may be helpful. Soaps with moisturizers may be helpful. Glycerine soaps, although popular and visually appealing, are drying and can exacerbate the symptoms.

Variations in Dark-Skinned People

Some skin disorders common to people of African, Hispanic, or East Indian descent are not commonly found in those of European descent. Similarly, some skin disorders, such as skin cancers, affect light-skinned persons more commonly than dark-skinned persons. Because of these differences, serious skin disorders may be overlooked, and normal variations in darker skin may be mistaken for anomalies.

Skin color is determined by the melanin produced by the melanocytes. Although the number of melanosomes in dark and white skin is the same, black skin produces more melanin, and more quickly, than white skin. Because of their skin color, dark-skinned persons are better protected against skin cancer, premature wrinkling, and aging of the skin that occurs with sun exposure.

A condition common in people with dark skin is too much or too little color. Areas of the skin may darken after injury, such as a cut or scrape, or after disease conditions such as acne. These darkened areas may take many months or years to fade. Dry or "ashy" skin also can be a problem for people with dark skin. It often is uncomfortable, and it also is easily noticed because it gives the skin an ashen or grayish appearance. Although using a moisturizer may help relieve the discomfort, it may cause a worsening of acne in predisposed persons.

Normal variations in skin structure and skin tones often make evaluation of dark skin difficult. The darker pigmentation can make skin pallor, cyanosis, and

TABLE 45-1 Common Normal Variations in Dark Skin

Variation	Appearance
Futcher (Voigt) line	Demarcation between darkly pigmented and lightly pigmented skin in upper arm; follows spinal nerve distribution; common in black and Japanese populations
Midline hypopigmentation	Line or band of hypopigmentation over the sternum, dark or faint, lessens with age; common in Latin American and black populations
Nail pigmentation	Linear dark bands down nails or diffuse nail pigmentation, brown, blue, or blue-black
Oral pigmentation	Blue to blue-gray pigmentation of oral mucosa; gingivae also affected
Palmar changes	Hyperpigmented creases, small hyperkeratotic papules, and tiny pits in creases
Plantar changes	Hyperpigmented macules, can be multiple with patchy distribution, irregular borders, and variance in color

Developed from information in Rosen T., Martin S. (1981). *Atlas of black dermatology.* Boston: Little, Brown.

erythema more difficult to observe. Therefore, verbal histories must be relied on to assess skin changes. The verbal history should include the client's description of her or his normal skin tones. Changes in skin color, in particular hypopigmentation and hyperpigmentation, often accompany disorders of dark skin and are very important signs to observe when diagnosing skin conditions. Common variations in dark skin and nails are described in Table 45-1.

In summary, skin lesions and rashes are the most common manifestations of skin disorders. Rashes are temporary skin eruptions. Lesions result from traumatic or pathologic loss of the normal continuity, structure, or function of the skin. Rashes and lesions may vary in size and color; they may be flat (macule or patch), palpable (papule, plaque, or nodule), or fluid-filled elevations (vesicle or bullae). Erosions involve a loss of the superficial epidermis, and an ulcer a loss of the epidermis and papillary layer of dermis. Pigmentary skin disorders involve the melanocytes. In some cases, there is an absence of melanin production, as in vitiligo or albinism. In other cases, there is an increase in melanin or some other pigment, as in melasma.

Pruritus and dry skin are symptoms common to many skin disorders. Pruritus is an unpleasant sensation of itch leading to the desire to scratch that occurs as the result of skin disorders or systemic diseases such chronic kidney disease, diabetes, and biliary disease. Pruritus is a complex process that has its origin in free nerve endings and is transmitted via the spinothalamic tract to the cerebral cortex. Pruritus, or the sensation of itch, can result from stimulation of the peripheral itch receptors or by neuropathic mechanisms that alter transmission of the itch response. Dry skin, also called *xerosis,* may be a natural occurrence, as in the drying of skin associated with aging, or it may be symptomatic of an underlying systemic disease or skin disorder such as contact dermatitis. Normal variations in dark skin often make evaluation difficult and result in some disorders being overlooked.

REVIEW EXERCISES

1. Bullous pemphigoid is an autoimmune blistering disease caused by autoantibodies to constituents of the dermal–epidermal junction.

A. Explain how antibodies, which attack glycoproteins in the lamina lucida and their attachment to the hemidesmosomes, can cause blisters to form (hint: see Fig. 45-5).

2. "Allergy tests" involve the application of an antigen to the skin, either through a small scratch or intradermal injection.

A. Explain how the body's immune system is able to detect and react to these antigens.

BIBLIOGRAPHY

Boulais N. (2007). Merkel cells. *Journal American Academy of Dermatology* 57, 147–165.

Boulais N., Misery L. (2008). The epidermis: A sensory tissue. *European Journal of Dermatology* 18(2), 119–127.

Buchness M.R. (2006). A practical approach to basic skin care. *Women's Health in Primary Care* 9(8), 11–15.

Charlesworth E.N., Beltrani V.S. (2002). Pruritic dermatoses: Overview of etiology and therapy. *American Journal of Medicine* 113(Suppl 9A), 25S–33S.

Cheng A.S., Bayliss S.J. (2008). The genetics of hair shaft disorders. *Journal American Academy of Dermatology* 59, 1–22.

Choung C.M., Nickoloff B.J., Elias P.M., et al. (2002). What is the "true" function of the skin? *Experimental Dermatology* 11, 159–187.

Gartner L.P., Hiatt J.L. (2007). *Color textbook of histology* (3rd ed., pp. 327–344). Philadelphia: Saunders Elsevier.

Hood A.F., Kwan T.H., Mihm M.C., et al. (2002). *Primer of dermatopathology* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins.

Kirchner A., Stefan H., Schmelz M., et al. (2002). Influence of vagus nerve stimulation on histamine-induced itching. *Neurology* 59, 108–112.

Lotti T., Bianchi B., Ghersetich I., et al. (2002). Can the brain inhibit inflammation generated in the skin? The lesson of

gamma-melanocyte-stimulating hormone. *International Journal of Dermatology* 41, 311–318.
Millikan L.E. (2003). Alternative therapy in pruritus. *Dermatologic Therapy* 16, 175–180.
Moses S. (2003). Pruritus. *American Family Physician* 68(6), 1135–1145.
Njoo D.M., Westerhof W. (2001). Vitiligo: Pathogenesis and treatment. *American Journal of Clinical Dermatology* 2, 167–181.
Nordland J.J. (2007). The melanocyte and the epidermal melanin unit: An expanded concept. *Dermatology Clinics* 25, 271–281.
Roebuck H.L. (2006). For pruritus, combination therapy works best. *American Journal of Primary Health Care* 31(3), 12–13.
Ross M.H., Pawlina W. (2006). *Histology: A text and atlas* (5th ed., pp. 442–475). Philadelphia: Lippincott Williams & Wilkins.
Ständer S., Steinhoff M., Schmitz M., et al. (2003). Neurophysiology of pruritus. *Archives of Dermatology* 139, 1463–1470.
Storm C.A., Elder D.E. (2008). The skin. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 999–1006). Philadelphia: Lippincott Williams & Wilkins.
Taïeb A., Picardo M. (2009). Vitiligo. *New England Journal of Medicine* 360(2), 160–169.
Yosipovitch G., Fleischer A.B. (2003). Itch associated with skin disease: Advances in pathophysiology and emerging therapies. *American Journal of Clinical Dermatology* 4, 617–622.

Primary Disorders of the Skin
Infectious Processes
Superficial Fungal Infections
Bacterial Infections
Viral Infections
Pustular Disorders
Acne Vulgaris
Acne Conglobata
Rosacea
Allergic and Hypersensitivity Dermatoses
Atopic Dermatitis
Urticaria
Drug-Induced Skin Eruptions
Papulosquamous Dermatoses
Psoriasis
Pityriasis Rosea
Lichen Planus
Lichen Simplex
Ultraviolet Radiation, Thermal, and Pressure Injury
Ultraviolet Radiation
Ultraviolet Radiation Skin Damage
Thermal Injury
Classification of Burns
Systemic Complications
Emergency and Long-Term Treatment
Pressure Ulcers
Mechanisms of Development
Prevention and Treatment
Nevi and Skin Cancers
Nevi
Skin Cancer
Malignant Melanoma
Basal Cell Carcinoma
Squamous Cell Carcinoma
Age-Related Skin Manifestations
Skin Manifestations of Infancy and Childhood
Skin Disorders of Infancy
Pigmented and Vascular Birthmarks
Skin Manifestations of Common Infectious Diseases
Skin Manifestations and Disorders in the Elderly
Normal Age-Related Changes
Skin Lesions Common Among the Elderly

Chapter 46

Disorders of Skin Integrity and Function

The skin is a unique organ in that numerous signs of disease or injury are immediately observable on the skin. The skin serves as the interface between the body's internal organs and the external environment. Therefore, skin disorders represent the culmination of environmental forces and the internal functioning of the body. Sunlight, infectious organisms, chemicals, and physical agents all play a role in the pathogenesis of skin diseases. Although most disorders are intrinsic to skin, many are external manifestations of systemic disease. Thus, skin provides a valuable window for the recognition of many systemic disorders.

Primary Disorders of the Skin

Primary skin disorders are those originating in the skin. They include infectious processes, acne, rosacea, papulosquamous dermatoses, allergic disorders, and drug reactions. Although most of these disorders are not life-threatening, they can affect the quality of life.

Infectious Processes

Normally, the skin flora, sebum, immune responses, and other protective mechanisms defend against serious systemic infections. However, the skin frequently succumbs to attack by microorganisms, including fungi, bacteria, and viruses, whose primary clinical manifestations are in the skin.

Superficial Fungal Infections

Fungi are free-living, saprophytic, plantlike organisms, certain strains of which are considered part of the normal skin flora (see Chapter 14). There are two types of fungi, yeasts and molds. Yeasts, such as *Candida albicans,* grow as single cells and reproduce asexually. Molds grow in long filaments, called *hyphae*. Fungal infections of the skin or mycoses are commonly classified as deep fungal infection and superficial mycoses, more commonly known as *tinea*.[1,2] As opposed to deep fungal infections

Primary Skin Disorders

- Primary skin disorders are condition that have their origin in the skin.
- Infectious skin disorders are caused by viruses, bacteria, and fungi that invade the skin, incite inflammatory responses, and otherwise cause rashes and lesions that disrupt the skin surface.
- Disorders of the pilosebaceous unit include acne vulgaris, which occurs most frequently in adolescence and manifests as comedones, papulopustules, nodules, or in severe cases, cysts and scarring; and rosacea, which is a chronic acneform disorder of middle-aged and older persons.
- Allergic and hypersensitivity responses are caused by antigen-antibody responses resulting from sensitization to topical or systemic antigens.
- The papulosquamous dermatoses constitute a group of disorders characterized by scaling papules and plaques that result from uncontrolled keratinocyte proliferation.

of the skin, where the dermis, subcutaneous, and deeper tissues are primarily involved, superficial fungal infections are confined to the epidermis and its integuments, the hair and nails.

Most of the superficial mycoses, or *dermatophytoses*, are caused by the dermatophytes, a group of closely related fungi classified into three genera: *Microsporum* (*M. audouinii, M. canis, M. gypseum*), *Epidermophyton* (*E. floccosum*), and *Trichophyton* (*T. schoenleinii, T. violaceum, T. tonsurans, T. rubrum*).[1–3] Another way of classifying the dermatophytes is according to their ecologic origin—human, animal, or soil. *Anthropophilic* species (*M. audouinii, M. tonsurans, T. violaceum*) are parasitic in humans and are spread by other infected humans. *Zoophilic* species (*M. canis* and *T. mentagrophytes*) cause parasitic infections in animals, some of which can be spread to humans. *Geophilic* species originate in the soil, but may infect animals, which in turn serve to infect humans. The clinical purpose of identifying species of dermatophytes is to determine the possible cause of infection. There is also some consideration of prognostic value. The anthropophilic species tend to cause chronic infections that are difficult to treat, whereas the Zoophilic and Geophilic species tend to cause inflammatory lesions that respond well to therapy or occasionally resolve spontaneously.[1]

The fungi that cause superficial mycoses live on the dead keratinized cells of the epidermis. They emit an enzyme that enables them to digest keratin, which results in superficial skin scaling, nail disintegration, or hair breakage, depending on the location of the infection. Deeper reactions involving vesicles, erythema, and infiltration are caused by the inflammation that results from exotoxins liberated by the fungus. The superficial mycoses, more commonly known as *tinea* or *ringworm,* can affect various parts of the body, with lesions varying according to site and fungal species.

Diagnosis of superficial fungal infections is primarily done by microscopic examination of skin scrapings for fungal spores, the reproducing bodies of fungi.[2] Potassium hydroxide (KOH) preparations are used to prepare slides of skin scrapings. KOH disintegrates human tissue and leaves behind the threadlike filaments, or hyphae, that grow from the fungal spores. Cultures also may be done using a dermatophyte test medium or a microculture slide that produces color changes and allows for direct microscopic identification. The Wood light (ultraviolet [UV] light) is another method that can assist with the diagnosis of tinea. Some types of fungi (e.g., *M. canis* and *M. audouinii*) fluoresce yellow-green when the light is directed onto the affected area.

Treatment usually follows diagnosis confirmed by KOH preparation or culture, particularly if a systemic agent is to be used. Topical agents are commonly used in the treatment of tinea infections; however, success often is limited because of the lengthy duration of treatment, poor compliance, and high rates of relapse at specific body sites.

The topical fungal agents can be grouped by structure and function. The principal pharmacologic groups are the azoles and allylamines. The azoles are a group of synthetic antifungal drugs that act by inhibiting the fungal enzymes needed for the synthesis of ergosterol, which is an essential part of fungal cell membranes. In contrast to the azoles, the allylamines act by interrupting ergosterol synthesis, causing the accumulation of a metabolite that is toxic to the fungus. Many of the topical azoles are available as either over-the-counter or prescription preparations.[4] Members of this class include ketoconazole, miconazole, clotrimazole, econazole, miconazole, and oxiconazole. Two allylamines, naftifine and terbinafine, are available as topical preparations. Topical corticosteroids may be used in conjunction with topical antifungal agents to relieve itching and erythema secondary to inflammation.

The systemic (i.e., oral) antifungal agents include griseofulvin, the azoles, and the allylamines.[2,3] Griseofulvin is an antifungal agent derived from a species of penicillium, whose only use is in the systemic treatment of dermatophytosis. It acts by binding to the keratin of newly formed skin, protecting the skin from new infection. Because its action is to prevent new infections, it must be administered for 2 to 6 weeks to allow for skin and hair replacement. Nail infections often require months to allow for nail regrowth. Terbinafine is a synthetic allylamine that is used in the treatment of dermatophytosis. In contrast to griseofulvin, the synthetic agents are fungicidal (i.e., kill the fungus) and therefore are more effective over shorter treatment periods.

Some of the oral agents can produce serious side effects, such as hepatic toxicity, or interact adversely with other medications.

Tinea of the Body or Face. *Tinea corporis* (ringworm of the body) can be caused by any of the dermatophyte species, but is most frequently caused by *M. canis* and less commonly by *T. rubrum*. There has been an increase in *T. tonsurans* as the causative agent of tinea corporis as well. Although tinea corporis affects all ages, children seem most prone to infection. Transmission is most commonly from kittens, puppies, and other children who have infections.

The lesions vary, depending on the fungal agent. The most common types of lesions are oval or circular patches on exposed skin surfaces and the trunk, back, or buttocks (Fig. 46-1). Less common are foot and groin infections. The lesion begins as a red papule and enlarges, often with a central clearing. Patches have raised red borders consisting of vesicles, papules, or pustules. The borders are sharply defined, but lesions may coalesce. Pruritus, a mild burning sensation, and erythema frequently accompany the skin lesion.

Tinea faciale, or ringworm of the face, is an infection caused by *T. mentagrophytes* or *T. rubrum*. Tinea faciale may mimic the annular, erythematous, scaling, pruritic lesions characteristic of tinea corporis. It also may appear as flat erythematous patches. Topical antifungal agents usually are effective in treating tinea corporis and tinea faciale. Oral antifungal agents may be used in resistant cases.

Tinea of the Scalp. *Tinea capitis*, the most common type of fungal infection in children, is an infection of the scalp and hairshaft. Tina capitis can be divided into two types: primary (noninflammatory) and secondary (inflammatory). The noninflammatory type is caused primarily by *T. tonsurans*. Children between the ages of 3 and 14 years are primarily affected, with a higher incidence among people of African American or Hispanic descent.[5] The lower incidence among adults has been attributed to the higher content of fatty acids in the sebum after puberty. The primary lesions vary from grayish, round, hairless patches to balding spots. The lesions vary in size and are most commonly seen on the back of the head (Fig. 46-2). Mild erythema, crust, or scale may be present. The individual usually is asymptomatic, although pruritus may exist.

FIGURE 46-1. Tinea of the arm due to the dermatophytic fungus trichophyton rubrum. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

FIGURE 46-2. Ringworm or tinea of the scalp (tinea capitis) caused by the *Microsporum* species. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

The inflammatory type of tinea capitis is caused by virulent strains of *T. mentagrophytes, T. verrucosum,* and *M. gypseum*. The onset is rapid, and inflamed lesions usually are localized to one area of the head. The inflammation is believed to be a delayed hypersensitivity reaction to the invading fungus. The initial lesion consists of a pustular, scaly, round patch with broken hairs. A secondary bacterial infection is common and may lead to a painful, circumscribed, boggy, and an indurated lesion called a *kerion*. The highest incidence is among children and farmers who work with infected animals.

Both the noninflammatory and inflammatory forms of tinea capitis are treated with oral griseofulvin or synthetic antifungal agents that penetrate the hair shafts. Topical ointments or shampoos are sometimes indicated in addition to oral medications, both to decrease the spore population and to protect household members. Because of the lower fatty acid content in the sebum of young children, several of the topical antifungal agents are prepared with fatty acid bases. Wet packs, medicated shampoos, steroids, and antibiotics may be prescribed for secondary infections that occur.

Tinea of the Foot and Hand. *Tinea pedis* (athlete's foot) is the most common fungal dermatosis, primarily affecting the spaces between the toes, the soles, or the sides of the feet (Fig. 46-3). It is caused by *T. mentagrophytes* and *T. rubrum*. The lesions vary from a mildly scaling lesion to a painful, exudative, erosive, inflamed lesion with fissuring. Lesions often are accompanied by pruritus, pain, and foul odor. Some persons are prone

FIGURE 46-3. Chronic tinea of the sole caused by *Trichophyton rubrum.* (Schering Corp.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 248]. Philadelphia: Lippincott Williams & Wilkins.)

FIGURE 46-4. Onychomycosis due to *Trichophyton rubrum,* right and left great toes. (Courtesy Dr. Edwin P. Ewing, Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

to chronic tinea pedis. Mild forms are more common during dry environmental conditions. Exacerbations occur as a result of hot weather, sweating, and exercise or when the feet are exposed to moisture, occlusive shoes, and communal swimming.

Tinea of the hand (*Tinea manus*) is usually a secondary infection with tinea pedis as the primary infection. In contrast to other skin disorders, such as contact dermatitis and psoriasis, which affect both hands, tinea manus usually occurs only on one hand. The characteristic lesion is a blister on the palm or finger surrounded by erythema. Chronic lesions are scaly and dry. Cracking and fissuring may occur. The lesions may spread to the plantar surfaces of the hand. If chronic, tinea manus may lead to tinea of the fingernails.

Simple forms of tinea pedis and tinea manus are treated with topical applications of antifungals. Complex cases are treated with oral griseofulvin, ketoconazole, or terbinafine. Other treatment and preventive measures include careful cleaning and drying of affected areas.

Tinea of the Nails. *Tinea unguium* is a dermatophyte infection of the nails.[6] It is a subset of a condition called *onychomycosis,* which includes dermatophyte, nondermatophyte, and candidal infections of the nails. There is an increased incidence of fungal nail infections in recent years, probably reflecting better diagnostics, increased numbers of immunocompromised patients who have greater susceptibility, increased use of immunosuppressive drugs, increasing numbers of elderly people, worldwide travel, and increased use of communal bathing facilities.

Distal and lateral subungual onychomycosis, the most common form of tinea unguium, usually is caused by *T. rubrum* or *T. mentagrophytes.* Toenails are involved more commonly than fingernails because fingernails are more exposed to air. The infection often begins at the tip of the nail, where the fungus digests the nail keratin (Fig. 46-4). In some cases, the infection may begin from a crushing injury to a toenail or from the spread of tinea pedis. Initially, the nail appears opaque, white, or silver. The nail then turns yellow or brown. The condition often remains unchanged for years. During this time it may involve only one or two nails and may produce little or no discomfort. Gradually, the nail thickens and cracks as the infection spreads and includes the nail plate. Permanent discoloration and distortion result as the nail plate separates from the nail bed.

The standard for the diagnosis of fungal nail disease is a positive result on microscopic examination and culture of nail clippings with subungual debris. Treatment considerations include efficiency, cost, and possible side effects of the treatment. Treatment of tinea unguium usually requires oral antifungal therapy administered over a period of months. Persons with minimal toenail involvement and no associated symptoms may not require treatment. All of the oral agents require careful monitoring for side effects. A nail lacquer containing the antifungal agent ciclopirox is available for use in the topical management of mild to moderate infections of the fingernails and toenails caused by *T. rubrum.* A new nail may require 3 to 12 months to grow. Thus, people being treated with antifungal agents need to be reminded that the resolution of the infection requires 4 to 6 months for fingernails and longer for toenails.

Dermatophytid Reaction. A secondary skin eruption may occur in persons allergic to the fungus responsible for the dermatophytosis. This dermatophytid or allergic reaction may occur during an acute episode of a fungal infection. The most common reaction occurs on the hands in response to tinea pedis. The lesions are vesicles with erythema extending over the palms and fingers, sometimes extending to other areas (Fig. 46-5). Less commonly, a more generalized reaction occurs in which papules or vesicles erupt on the trunk or extremities. These eruptions may resemble tinea corporis. Lesions may become excoriated and infected with bacteria. Treatment is directed at the primary site of infection. The intradermal reaction resolves in most cases without intervention if the primary site is cleared.

FIGURE 46-5. Dermatophytid or id reaction on the fingers due to a tinea infection. An id immunologic reaction, also known as *autoeczematization,* is an itchy, vesicular rash produced in response to an intense inflammatory process that can be located in another region of the body. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

Candidal Infections. Candidiasis (moniliasis) is a fungal infection caused by *C. albicans*. This yeastlike fungus is a normal inhabitant of the gastrointestinal tract, mouth, and vagina (see Chapter 41). The skin problems result from the release of irritating toxins on the skin surface. *C. albicans* is found almost always on the surface of the skin; it rarely penetrates to the deeper layers of the skin. Some persons are predisposed to candidal infections by conditions such as diabetes mellitus, antibiotic therapy, pregnancy, oral contraceptive use, poor nutrition, and immunosuppressive diseases.[7] Oral candidiasis may be the first sign of infection with human immunodeficiency virus (HIV).

C. albicans thrives on warm, moist, intertriginous areas (i.e., between folds or adjacent surfaces) of the body. The rash is red with well-defined borders. Patches erode the epidermis, and there is scaling. Mild to severe itching and burning often accompany the infection. Severe forms of infection may involve pustules or vesiculopustules. In addition to microscopy, a candidal infection often can be differentiated from a tinea infection by the presence of satellite lesions. These satellite lesions are maculopapular and are found outside the clearly demarcated borders of the candidal infection. Satellite lesions often are diagnostic of diaper rash complicated by *Candida*. The appearance of candidal infections varies according to the site (see Chapter 41 for a discussion of vaginal candidiasis).

Diagnosis usually is based on microscopic examination of skin or mucous membrane scrapings placed in a KOH solution. Treatment measures vary according to the location. Preventive measures such as wearing rubber gloves are encouraged for persons with infections of the hands. Intertriginous areas often are separated with clean cotton cloth and allowed to air dry as a means of decreasing the macerating effects of heat and moisture. Topical and oral antifungal agents, such as clotrimazole, econazole, ketoconazole, and miconazole, are used in treatment depending on the site and extent of involvement.

Bacterial Infections

Bacteria are considered normal flora of the skin. Most bacteria are not pathogenic, but when pathogenic bacteria invade the skin, superficial or systemic infections may develop. Bacterial skin infections are commonly classified as primary or secondary infections. Primary infections are superficial skin infections such as impetigo. Secondary infections consist of deeper cutaneous infections, such as infected ulcers. Diagnosis usually is based on cultures taken from the infected site. Treatment methods include antibiotic therapy and measures to promote comfort and prevent the spread of infection.

Impetigo. Impetigo is a common, superficial bacterial infection caused by staphylococci or group A β-hemolytic streptococci, or both.[8,9] Impetigo is common among infants and young children, although older children and adults occasionally contract the disease. Impetigo initially appears as a small vesicle or pustule or as a large bulla on the face or elsewhere on the body. As the primary lesion ruptures, it leaves a denuded area that discharges a honey-colored serous liquid that hardens on the skin surface and dries as a honey-colored crust with a "stuck-on" appearance (Fig. 46-6). New vesicles erupt within hours. Pruritus often accompanies the lesions, and skin excoriations that result from scratching multiply the

FIGURE 46-6. Impetigo of the face. The lesions vary from small vesicles to large bullae that rupture and discharge a honey-colored serous liquid that hardens on the skin surface and dries as a honey-colored crust. (Abner Kurten, *Folia Dermatologica.* No. 2. Geigy Pharmaceuticals.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 187]. Philadelphia: Lippincott Williams & Wilkins.)

infection sites. Although a very low risk, a possible complication of untreated streptococcal impetigo is poststreptococcal glomerulonephritis (see Chapter 25). Topical mupirocin (Bactroban), which has few side effects, may be effective for limited infections. If the area is large or if there is concern about complications, systemic antibiotics are used.

Another form of impetigo exists, *bullous impetigo,* which is usually caused by *Staphylococcus aureus*.[9] Bullous impetigo is more common among children and occurs intermittently, with some cases transmitted among family members, but most often found among the institutionalized. Thin bullae erupt that appear clear to cloudy and coalesce. The bullae open, leaving the original bullous rim with central thin, flat, honey-colored crusts, or in some cases denuded areas. The face is often affected, but bullous impetigo may occur anywhere on the body. The treatment measures are the same as for nonbullous impetigo.

Cellulitis. Cellulitis is a deeper infection affecting the dermis and subcutaneous tissues.[8] It is usually caused by group A β-hemolytic streptococci or *S. aureus,* but can be caused by bacteria specific to certain activities, such as fish handling, swimming in fresh water, or swimming in salt water, or from animal bites or scratches. Preexisting wounds (e.g., ulcers, erosions) and tinea pedis are often portals of entry. Legs are the most common sites, followed by the hands and pinnae of the ears, but cellulitis may occur on many body sites. The lesion consists of an expanding red, swollen, tender plaque with an indefinite border, covering a small to wide area (Fig. 46-7). Cellulitis is frequently accompanied by fever, erythema, heat, edema, and pain. Cellulitis often involves the lymph system and, once compromised, repeat infections may impair lymphatic drainage, leading to chronically swollen legs, and eventually dermal fibrosis and lymphedema. Incorrectly treated, it may result in septicemia, nephritis, or death. Treatment measures (oral and intravenous antibiotics) are aimed at the invasive organisms and the extent of the infection.

FIGURE 46-7. Cellulitis on leg infected with *Staphylococcus aureus* and *Pseudomonas.*

Viral Infections

Viruses are intracellular pathogens that rely on live cells of the host for reproduction. They have no organized cell structure but consist of a deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) core surrounded by a protein coat. The viruses seen in skin lesion disorders tend to be DNA-containing viruses. Viruses invade the keratinocyte, begin to reproduce, and cause cellular proliferation or cellular death. The rapid increase in viral skin diseases has been attributed to the use of corticosteroid drugs, which have immunosuppressive properties, and the use of antibiotics, which alter the bacterial flora of the skin. As the number of bacterial infections has decreased, there has been a proportional rise in viral skin diseases.

Verrucae. Verrucae, or warts, are common benign papillomas caused by the DNA-containing human papillomavirus (HPV).[10–13] Transmission of HPV infection is largely by direct contact between individuals or by autoinoculation. As benign papillomas, warts represent an exaggeration of the normal skin structures. There is an irregular thickening of the stratum spinosum and greatly increased thickening of the stratum corneum. The classification of warts is based largely on morphology and location.

Although warts vary in appearance depending on their location, it is now recognized that the clinically distinct types of warts result not simply because of the anatomic sites in which they arise, but also because of the distinct type of HPV. There are more than 80 types of HPV found on the skin and mucous membranes of humans that cause several different kinds of warts, including skin warts and genital warts. Many of the HPV types that cause genital warts are sexually transmitted, some of which (types 6, 11, 16, and 18) may increase the risk of cervical cancer (discussed in Chapter 41).

Nongenital warts often occur on the hands and feet. They are commonly caused by HPV types 1, 2, 3, 4, 27, and 57, and are not considered precancerous lesions. They are classified as common warts, flat warts, and plantar or palmar warts. Common warts, or verrucae vulgaris, are the most common type. The lesions can occur anywhere, but most frequently occur on dorsal surfaces of the hands, especially the periungual area, where they appear as small, grayish-white to tan, flat to convex papules with a rough, pebblelike surface (Fig. 46-8). Verrucae plana, or flat warts, are common on the face or dorsal surfaces of the hands. These warts are slightly elevated, flat, smooth, tan papules that are slightly larger than verrucae vulgaris. Verrucae plantaris and verrucae palmaris (i.e., plantar and palmar warts, respectively) occur on the soles of the feet and palms of the hands, respectively. They appear as rough, scaly lesions that may reach 1 to 2 cm in diameter, coalesce, and be confused with ordinary calluses. HPV transmission usually occurs through breaks in skin integrity. For example, plantar warts, which occur on the soles of the feet, frequently are transmitted to the abraded, softened heels of children in swimming areas. Common hand warts can be transmitted by biting the cuticles surrounding the nail.

FIGURE 46-8. Common and periungual warts. (Reed & Carnrick Pharmaceuticals.) (From Sauer G.C., Hall J.C. [1996]. *Manual of skin diseases* [7th ed.]. Philadelphia: Lippincott-Raven.)

FIGURE 46-9. Recurrent herpes simplex of the face. (Dermik Laboratories, Inc.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 228]. Philadelphia: Lippincott Williams & Wilkins.)

Treatment is usually directed at inducing a "wart-free" period without producing scarring. Warts resolve spontaneously when immunity to the virus develops.[13] The immune response, however, may be delayed for years. Because of their appearance or discomfort, people usually desire their removal, rather than waiting for immunity to develop. Removal is usually done by applying a keratolytic agent, such as salicylic acid gel or plaster that breaks down the wart tissue, or by freezing with liquid nitrogen. Salicylic acid works by dissolving intercellular cement and producing desquamation of the horny layer of skin without affecting normal epidermal cells. Intralesional bleomycin injections have been effective for recalcitrant warts. Various types of laser surgery, electrosurgery, cryotherapy, immunotherapy (e.g., oral zinc sulfate), and antiviral therapy (e.g., cidofovir) also have been successful in wart eradication.

Herpes Simplex. Herpes simplex virus (HSV) infections of the skin and mucous membrane (i.e., cold sore or fever blister) are common.[14,15] Two types of HSV infect humans: type 1 and type 2. HSV-1 is usually associated with oropharynx infections (labial herpes), and the organism is spread by respiratory droplets or by direct contact with infected saliva. HSV-1 may also be transmitted to other parts of the body through occupational hazards, such as skin contact athletics, dentistry, and medicine. Genital herpes usually is caused by HSV-2 (see Chapter 41). HSV-1 genital infections and HSV-2 oral infections are becoming more common, perhaps because of oral–genital sex.

Infection with HSV-1 may present as a primary or recurrent infection. Primary HSV-1 symptoms include fever, sore throat, painful vesicles, and ulcers of the lips, tongue, palate, and buccal mucosa. Primary infection results in the production of antibodies to the virus so that recurrent infections are more localized and less severe. After an initial infection, the herpesvirus persists in the trigeminal and other dorsal root ganglia in the latent state, periodically reactivating in recurrent infections. The symptoms of a primary HSV-1 infection most often occur in young children (1 to 5 years of age). It is likely that many adults were exposed to HSV-1 during childhood and therefore have antibodies to the virus.

The recurrent lesions of HSV-1 usually begin with a burning or tingling sensation. Umbilicated vesicles and erythema follow and progress to pustules, ulcers, and crusts before healing (Fig. 46-9). Lesions are most common on the lips, face, mouth, nasal septum, and nose. When a lesion is active, HSV-1 is shed and there is risk of transmitting the virus to others. Pain is common, and healing takes place within 10 to 14 days. Precipitating factors may be stress, menses, or injury. In particular, UVB exposure seems to be a trigger for recurrence. Individuals who are immunocompromised may have severe attacks.

There is no cure for oropharyngeal herpes; most treatment measures are palliative.[14,15] Application of over-the-counter topical preparations containing antihistamines, antipruritics, and anesthetic agents along with aspirin or acetaminophen may be used to relieve pain. Topical medications are best applied gently with a cotton-tipped applicator to prevent increased viral shedding and viral inoculation to another anatomic site. Oral acyclovir, an antiviral drug that inhibits herpesvirus replication, may be used prophylactically to prevent recurrences. The antiviral drugs valacyclovir and famciclovir also may be used for prophylaxis. Sunscreen preparations applied to the lips can prevent sun-induced herpes simplex. Efforts to develop vaccines to prevent HSV infections are in process.[14]

Herpes Zoster. Herpes zoster (shingles) is an acute, localized vesicular eruption distributed over a dermatomal segment of the skin.[7,16,17] It is caused by the same herpesvirus, varicella-zoster, that causes chickenpox. It is believed to be the result of reactivation of a latent varicella-zoster virus infection that was dormant in the sensory dorsal root ganglia since a primary childhood infection. During an episode of herpes zoster, the reactivated virus travels from the ganglia to the skin of the corresponding dermatome. Although herpes zoster is not as contagious as chickenpox, the reactivated virus can be transmitted to nonimmune contacts.

The incidence of herpes zoster increases with age; it occurs most frequently in persons older that 60 years of age. The normal age-related decrease in cell-mediated immunity is thought to account for the increased viral activation in this age group. Other persons at increased risk because of impaired cell-mediated immunity are persons with conditions such as HIV infection and certain malignancies, and those receiving long-term corticosteroid treatment, cancer chemotherapy, and radiation therapy.

The lesions of herpes zoster typically are preceded by a prodrome consisting of a burning pain, a tingling sensation, extreme sensitivity of the skin to touch, and pruritus along the affected dermatome (see Chapter 35). Among the dermatomes, the most frequently involved are the thoracic (53%), the cervical (20%), the trigeminal (15%), and the lumbosacral (11%).[17] Prodromal symptoms may be present for 1 to 3 days or longer before the appearance of the rash. During this time, the pain may be mistaken for a number of other conditions, such as heart disease, pleurisy, musculoskeletal disorders, or gastrointestinal disorders.

The lesions appear as an eruption of vesicles with erythematous bases that are restricted to skin areas supplied by sensory neurons of a single or associated group of dorsal root ganglia (Fig. 46-10). In immunosuppressed persons, the lesions may extend beyond the dermatome. Eruptions usually are unilateral in the thoracic region, trunk, or face. New crops of vesicles erupt for 3 to 5 days along the nerve pathway. The vesicles dry, form crusts, and eventually fall off. The lesions usually clear in 2 to 3 weeks, although they can persist up to 6 weeks in some elderly persons.

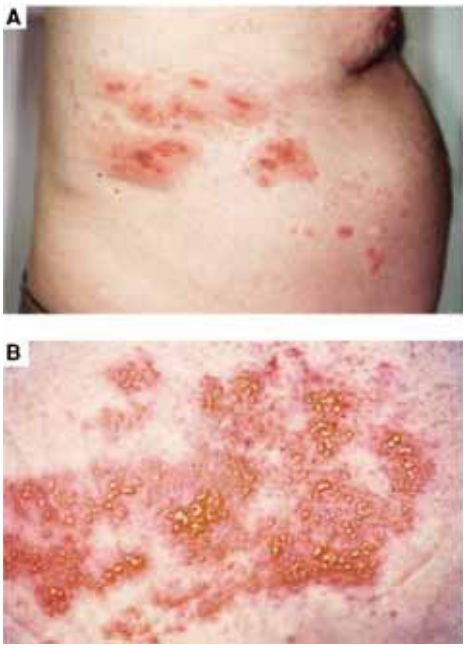


FIGURE 46-10. Acute herpes zoster. Panel **(A)** shows a cutaneous eruption in the right T7 dermatome. Panel **(B)** shows a close-up of fresh vesicular lesions. (From Gnann J.W., Whitley R.J. [2002]. Herpes zoster. *New England Journal of Medicine* 347, 341.)

Serious complications can accompany eruptions. Eye involvement can result in permanent blindness and occurs in a large percentage of cases involving the ophthalmic division of the trigeminal nerve (see Chapter 38). *Postherpetic neuralgia,* which is pain that persists longer than 1 to 3 months after the resolution of the rash, is an important complication of herpes zoster (discussed in Chapter 35). It is seen most commonly in persons older than 60 years of age, increasing age being the greatest risk factor. Affected persons complain of sharp, burning pain that often occurs in response to nonnoxious stimuli. Even the slightest pressure of clothing and bed sheets may elicit pain. It usually is a self-limited condition that persists for months, with symptoms abating over time.

The treatment of choice for herpes zoster is the administration of an antiviral agent (e.g., acyclovir, valacyclovir, famciclovir).[7] The treatment is most effective when started within 72 hours of rash development. When given in the acute vesicular stage, the antiviral drugs have been shown to decrease the amount of lesion development and pain. Narcotic analgesics, tricyclic antidepressants, gabapentin, anticonvulsant drugs, and nerve blocks have been used for management of postherpetic neuralgia. Local application of capsaicin cream or lidocaine patches may be used in selected cases. Palliative treatments, such as heat and gentle pressure, may also be helpful.

An effective live herpes zoster vaccine is available to prevent both herpes zoster and postherpetic neuralgia. The vaccine is recommended for use in people 60 years of age and older.[18]

Pustular Disorders

Acne Vulgaris

Acne vulgaris is a disorder of the pilosebaceous unit (see Chapter 45, Fig. 45-7) that results in formation of discrete papular or pustular lesions and may lead to scarring.[11,12,19–22] It can be cosmetically disfiguring and often psychologically disabling. Scarring can lead to lifelong problems in regard to self-esteem. Acne typically begins around puberty, as a result of increased androgen production. It may begin earlier and persist longer in females; however, overall the incidence and severity are greater in males. The disorder, which affects more than 85% of teenagers, is so common that many regard it as a "rite of passage" through adolescence.[12] Although acne is frequently considered a disorder of adolescence, a large percentage of young adults continue to show signs of the disorder.

Acne vulgaris is characterized by both noninflammatory and inflammatory lesions. The lesions are typically located on the face and neck and, to a lesser extent, on the back, chest, and shoulders. Noninflammatory lesions consist of *comedones* (whiteheads and blackheads). *Blackheads* are plugs of material that accumulate in sebaceous glands that open to the skin surface. The color of blackheads results from melanin that has moved

into the sebaceous glands from adjoining epidermal cells. *Whiteheads* are pale, slightly elevated papules with no visible orifice. Inflammatory lesions consist of papules, pustules, nodules, and, in severe cases, cysts. *Papules* are raised areas less than 5 mm in diameter. *Pustules* have a central core of purulent material. *Nodules* are larger than 5 mm in diameter and may become suppurative or hemorrhagic. Suppurative nodules often are referred to as *cysts* because of their resemblance to inflamed epidermal cysts. The inflammatory lesions are believed to develop from the escape of sebum into the dermis and the irritating effects of the fatty acids contained in the sebum.

The cause of acne vulgaris is largely unknown. It is considered a chronic inflammatory disease of the pilosebaceous unit. There is a hereditary factor; multiple generations of family members often experience it. Several factors are believed to contribute to acne, including (1) the influence of androgens on sebaceous gland activity; (2) increased proliferation of the keratinizing epidermal cells that form the sebaceous cells; (3) increased sebum production in relation to the severity of the disease; and (4) the presence of *Propionibacterium acnes,* the microorganism responsible for the inflammatory stage of the disorder. These factors are probably interrelated. Increased androgen production results in increased sebaceous cell activity, with resultant plugging of the pilosebaceous ducts. The excessive sebum provides a medium for *P. acnes* growth, and the organism contains lipases that break down the free fatty acids that produce the acne inflammation. *P. acnes* is also thought to form a biofilm (an extracellular polysaccharide lining in which the bacteria are encased) that acts as a protective barrier to antibiotic treatment (see Chapter 14), explaining why prolonged antibiotic treatments are necessary.[23] Acne may be triggered or worsened by external factors such as obstructions (e.g., head bands, collars), manipulation of the lesions, cosmetics, and occupational exposures.

The diagnosis of acne is based on history and physical examination. The severity of the acne is generally assessed by the number, type, and distribution of lesions.[19] Mild acne is usually characterized by the presence of a small number (generally <10) of open and closed comedones, with a few inflammatory papules; moderate acne by the presence of a moderate number (10 to 40) of erythematous papules and pustules (Fig. 46-11), usually limited to the face; and moderately severe acne by the presence of numerous papules and pustules (40 to 100) and occasionally larger, deeper, nodular inflamed lesions involving the face, chest, and back. Acne conglobata (to be discussed) is a severe chronic form of acne.

Treatment of acne focuses on clearing up existing lesions, preventing new lesions, and limiting scar formation.[19–22] Treatment measures include the use of topical antimicrobials, oral antibiotics, topical retinoids, and isotretinoin. Soaps are usually not effective in treating acne, and unless the skin is exceptionally oily, a mild soap should be used to avoid additional irritation that will limit the effectiveness of other topical treatments.

FIGURE 46-11. Moderate acne. Erythematous papules and pustules are the predominant lesions, and lesions are limited to the face. (From James W.D. [2005]. Acne. *New England Journal of Medicine* 352, 1464.)

Mild acne is usually treated with a topical preparation containing a combination of erythromycin or clindamycin and benzoyl peroxide. Topical antibiotics do not affect existing lesions but decrease the *P. acnes* on the skin, thereby reducing subsequent inflammation resulting from free fatty acid release and breakdown. Benzoyl peroxide, which is a bactericide, does not induce resistance, and when used with topical and oral antibiotics it protects against the development of this problem. Azelaic acid, products containing sodium sulfacetamide and sulfur, and salicylic acid preparations are also available. These agents are usually not considered as first-line therapies, but may be used in persons who cannot tolerate other topical agents.

Moderate to severe cases of acne may be managed with systemic antibiotics (e.g., tetracycline), topical vitamin A derivatives (retinoids), or oral retinoids (isotretinoin). Systemic antibiotics decrease *P. acnes* colonization and have intrinsic anti-inflammatory effects. The action of topical vitamin A (e.g., tretinoin) has been attributed to decreased cohesiveness of epidermal cells and increased epidermal cell turnover. This is thought to result in increased extrusion of open comedones and transformation of closed comedones into open ones. Isotretinoin is approved for treatment of recalcitrant cases of acne and cystic acnes. Although the exact mode of action is unknown, isotretinoin decreases sebaceous gland activity, prevents new comedones from forming, reduces the *P. acnes* count through sebum reduction, and has an anti-inflammatory effect. Because of its many side effects, it is used only in persons with severe acne. The oral retinoids are known teratogens and must not be used in women who are pregnant or may become pregnant.

Acne Conglobata

Acne conglobata occurs later in life as a chronic form of acne. Comedones, papules, pustules, nodules, abscesses, cysts, and scars occur on the back, buttocks,

and chest. Lesions occur to a lesser extent on the abdomen, shoulders, neck, face, upper arms, and thighs. The comedones or cysts have multiple openings, large abscesses, and interconnecting sinuses. Inflammatory nodules are not uncommon. Their discharge is odoriferous, serous or mucoid, and purulent. Healing often leaves deep keloidal lesions. Affected persons have anemia with elevated white blood cell counts, erythrocyte sedimentation rates, and neutrophil counts. The treatment is difficult and stringent. It often includes débridement, systemic corticosteroid therapy, oral retinoids, and systemic antibiotics.

Rosacea

Rosacea is a chronic skin disorder of middle-aged and older persons. The disease has a variety of clinical manifestations (blushing, presence of telangiectatic vessels, eruption of inflammatory papules and pustules) that primarily affect the central areas of the face. In the early stage of rosacea development, there are repeated episodes of blushing.[24–26] The blush eventually becomes a permanent dark red erythema on the nose and cheeks that sometimes extends to the forehead and chin (Fig. 46-12). This stage often occurs before 20 years of age. Ocular problems occur in at least 50% of persons with rosacea. Prominent symptoms include eyes that are itchy, burning, or dry; a gritty or foreign body sensation; and erythema and swelling of the eyelid. As the person ages, the erythema persists, and telangiectasia with or without acne components (e.g., comedones, papules, pustules, nodules, erythema, and edema) develops. After years of affliction, acne rosacea may develop into an irregular bullous hyperplasia (thickening of the skin) of the nose, known as *rhinophyma* (Fig. 46-13). Although rosacea is more common in women, rhinophyma is more common in men.

FIGURE 46-12. Papulopustular and ocular rosacea of moderate severity. The pustules are seen over the central portion of the face with sparing of the periocular area. Erythema and edema of the upper eyelids are also present. (From Powell F.C. [2005]. Rosacea. *New England Journal of Medicine* 352, 793–803.)

FIGURE 46-13. Chronic rosacea with rhinophyma. (Hoechst Marion Roussel Pharmaceuticals, Inc.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 149]. Philadelphia: Lippincott Williams & Wilkins.)

The cause of rosacea is unknown; however, it is believed to be a chronic inflammatory process involving the area surrounding the pilosebaceous units, accompanied by vascular instability with leakage of fluid and inflammatory mediators into the dermis. The lesions are accompanied by nonspecific perifollicular infiltrate of lymphocytes surrounded by dermal edema and dilated capillaries and terminal arterioles (telangiectases).[24] In the pustular phase, neutrophils may colonize the follicles, and follicular rupture may produce a granulomatous response. Rhinophyma is associated with hypertrophy of the sebaceous glands.

Rosacea is distinguished from acne vulgaris by the presence of the neurovascular component and absence of comedones. Treatment measures are similar to those used for acne vulgaris. Persons with rosacea are heat sensitive. They are instructed to avoid vascular stimulating agents such as heat, sunlight, hot liquids, foods, and alcohol. Topical metronidazole and azelaic acid creams have been effective. Topical antibiotics (e.g., clindamycin, erythromycin) have been useful, as well as systemic antibiotics (e.g., tetracycline and its derivatives). Pulsed dye laser therapy may be used for ablation of vessels in persons with prominent telangiectases. Rhinophyma can be treated by a number of surgical methods, including electrosurgery, laser ablation, dermabrasion, cryosurgery, and excision.

Allergic and Hypersensitivity Dermatoses

Allergic and hypersensitivity dermatoses involve the inflammatory response to multiple exogenous and endogenous agents. The disorders, which are usually characterized by epidermal edema with separation of epidermal cells, include atopic dermatitis, urticaria, drug-induced skin eruptions, and allergic contact dermatitis (discussed in Chapter 16).

Atopic Dermatitis

Atopic dermatitis (atopic eczema) is a highly pruritic chronic inflammatory skin disease. It usually begins early in life and often occurs in children with a personal or family history of other atopic disorders, such as allergic rhinitis and asthma.[27–29] A total of 45% of cases begin within the first 6 months of life, 60% begin during the first year, and 85% occur before the fifth year of life.[27] Up to 70% of these children have a spontaneous remission before adolescence. The hallmarks of atopic dermatitis are a chronic, relapsing form of skin inflammation; a disturbance in the epidermal barrier function that leads to increased transepidermal water loss and dry skin; and immunoglobulin E (IgE)-mediated sensitization to food and environmental antigens.[27–29] Whether the primary defect resides in an immunologic disturbance or a disorder of the epidermal barrier is uncertain. It has been suggested that an abnormal skin barrier allows increased antigen absorption and contributes to the hyperreactivity characteristic of atopic dermatitis.[27]

The lesions of atopic dermatitis are usually characterized by vesicle formation, oozing, and crusting with excoriations. Scratching causes crusted erosions. The clinical manifestations of the disorder can be divided into three stages that often vary with age.[27] In infancy the eczematous lesion usually appear on the checks and scalp (Fig. 46-14).

FIGURE 46-14. Atopic eczema on an infant's face and on a wrist. (Dome Chemicals.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 84]. Philadelphia: Lippincott Williams & Wilkins.)

The skin of the cheeks may be paler, with extra creases under the eyes, called *Dennie-Morgan folds*. During childhood, lesions involve flexures, the nape of the neck, and the dorsal aspects of the limbs.

Adolescents and adults usually have dry, red patches affecting the face, neck, and upper trunk, but without the thickening and discrete demarcation associated with psoriasis. The bends of the elbows and knees are usually involved. In chronic cases, the skin is dry, leathery, and lichenified. Persons with dark skin may have a papular eruption and poorly demarcated hypopigmentation patches on the cheeks and extremities. In persons with black skin, pigmentation may be lost from lichenified skin. Acute flares may present with red patches that are weepy, shiny, or lichenified (i.e., thickened, with prominent markings), and with plaques and papules. Itching may be severe and prolonged with both childhood and adult forms of atopic dermatitis. Secondary infections are common.

Treatment of atopic eczema is designed to target the underlying abnormalities: dryness, pruritus, infection, and inflammation.[28–30] Basic therapy begins with optimal skin care, addressing the skin barrier defect with continuous use of emollients and skin hydration, along with avoiding exposure to environmental irritants and foods that cause exacerbations of the symptoms. Nonspecific irritants include contact with clothing made from irritating synthetic or wool materials. Further irritants are soaps and hot water temperature during bathing or showering. Although there is no evidence that emollients improve atopic dermatitis directly, they are widely used to relieve the problem of dry skin and pruritus. A key feature of atopic dermatitis is severe dryness of the skin caused by dysfunction of the skin barrier with transepidermal water loss. This is accompanied by intense pruritus and inflammation.

Topical corticosteroids remain an important treatment for acute flare-ups but can cause local and systemic side effects. Potency of topical corticosteroids is classified by the potential for vasoconstriction. In general, only preparations that have weak or moderate potency are used on the face and genital areas, whereas those that have moderate or high potency are used on other areas of the body. Lower-potency corticosteroids may be sufficient on all areas of the body in younger children. One of the main concerns of topical corticosteroid use is skin thinning. Another concern is secondary adrenal suppression and the suppression of growth in children resulting from systemic absorption. Wet-wrap therapy, in which a wet dressing is applied over emollients in combination with topical antiseptics or topical corticosteroids, has been shown to be beneficial in some cases of severe atopic dermatitis.[30]

Systemic or adjuvant therapy is usually reserved for severe acute exacerbations. Short-term corticosteroids are also used during acute flare-ups with adult patients. Antihistamines may be used to relieve itching. Secondary infection with *S. aureus* is common and may be treated with systemic antimicrobial therapy. Phototherapy can be an important adjunct for severely affected adults and adolescents older than 12 years of age.[30]

Urticaria

Urticaria, or hives, is a common skin disorder characterized by the development of edematous wheals accompanied by intense itching.[31–33] The lesions typically appear as raised pink or red areas surrounded by a paler halo. They blanch with pressure and vary in size from a few millimeters to centimeters. Angioedema, which can occur alone or with urticaria, is characterized by nonpitting, nonpruritic, well-defined edematous swelling that involves subcutaneous tissues of the face, hands, feet, or genitals. It is more likely than urticaria to produce life-threatening swelling of the tongue and upper airways.

Urticaria can be acute or chronic and due to known or unknown causes. Numerous factors, both immunologic and nonimmunologic, can be involved in its pathogenesis. The urticarial wheal results from liberation of histamine from mast cells and basophils. Histamine causes hyperpermeability of the microvessels of the skin and surrounding tissue, allowing fluid to leak into the tissues, causing edema and wheal formation.

Acute immunologic urticaria is commonly the result of an IgE-mediated immune reaction that usually occurs within 1 hour of exposure to an antigen. The most common causes of acute urticaria are foods or drinks, medications (most notably penicillin and cephalosporin), insect stings, and exposure to pollens or chemicals. Although nonsteroidal anti-inflammatory drugs, including aspirin, do not normally cause urticaria, they may exacerbate the preexisting disease. In rare cases, urticaria is a manifestation of underlying disease, such as certain cancers, collagen diseases, and hepatitis. There is an association between chronic urticaria and autoimmune thyroid disease (e.g., Hashimoto thyroiditis, Graves disease, toxic multinodular thyroiditis).[33] A hereditary deficiency of a C1 (complement 1) inhibitor also can cause a condition called *hereditary angioneurotic edema*.

The physical urticarias are a specific form of chronic urticaria, in which specific physical stimuli reproducibly elicit wheals.[33] Physical urticarias are intermittent, usually last less than 2 hours, are produced by appropriate stimuli, have distinctive appearances and locations, and are seen most frequently in young adults. Dermographism, or skin writing, is one form of physical urticaria in which wheals appear in response to simple rubbing of the skin (Fig. 46-15). The wheals follow the pattern of the scratch or rubbing, appearing within 10 minutes and dissolving completely within 20 minutes. Other types of physical urticaria are induced by exercise (cholinergic), cold, delayed pressure, sunlight (solar), water (aquagenic), vibration, and heat (external localized). Appropriate challenge tests (e.g., application of an ice cube to the skin to initiate development of cold urticaria) are used to differentiate physical urticaria from chronic urticaria due to other causes.

Most types of urticaria are treated with antihistamines: drugs that block histamine type 1 (H_1) receptors and, less frequently, H_1 receptor blockers in combination with H_2 receptor blockers. They control urticaria by inhibiting vasodilation and the escape of fluid into the surrounding tissues. Usually nonsedating antihistamines that alleviate pruritus and decrease the incidence of hives, without producing drowsiness, are used. Leukotriene antagonists (zafirlukast and montelukast) may also be used. Oral corticosteroids may be used in the treatment of refractory urticaria. Tricyclic antidepressant drugs, particularly those with antihistamine actions, also may be used. Persons who have experienced angioedema of the larynx and pharynx should be counseled to carry a prescription of epinephrine in an autoinjectable instrument (e.g., EpiPen).[32]

Drug-Induced Skin Eruptions

Most drugs can cause a localized or generalized skin eruption. Topical drugs are usually responsible for localized contact dermatitis types of rashes, whereas systemic drugs cause generalized skin lesions. Although many drug-induced skin eruptions are morbilliform (i.e., measleslike) or exanthematous, they may mimic most of the skin disorders described in this chapter. Because the

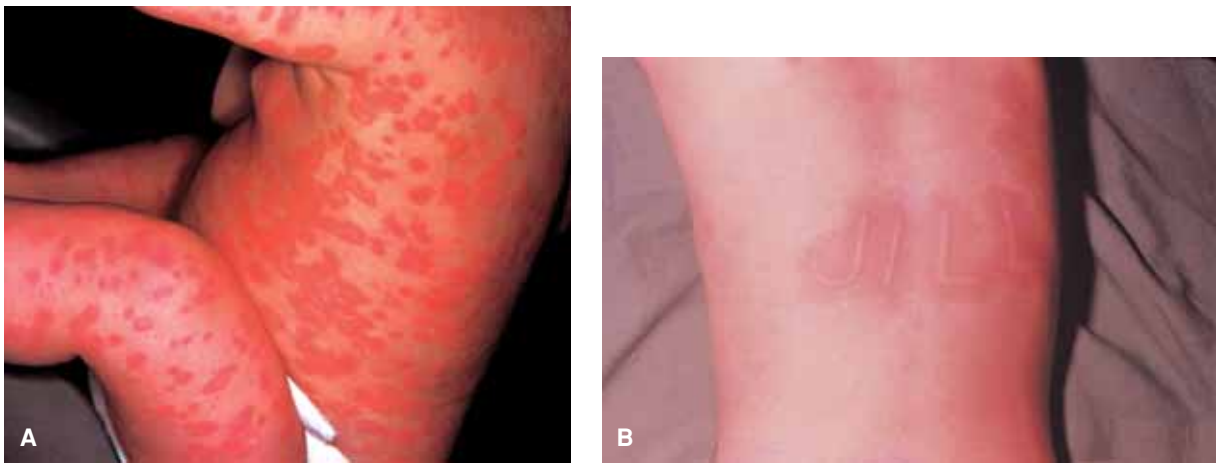


FIGURE 46-15. **(A)** Acute urticaria from penicillin in a 6-month-old-child. **(B)** Dermographism on flexor wrist. (Dermik Laboratories, Inc.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 126]. Philadelphia: Lippincott Williams & Wilkins.)

lesions vary greatly, the diagnosis depends almost entirely on an accurate patient report, including a full drug history. Early recognition and discontinuation of the drug are essential. Management of mild cases is aimed at eliminating the offending drug while treating the symptoms. Severe cases require prompt medical attention.

Some drug reactions result in epidermal cell detachment and bullae (fluid-filled blisters) formation. The skin detachment seen with bullous skin lesions is different from the desquamation (i.e., peeling) that occurs with other skin disorders. In the bullous disorders, there is full-thickness detachment of the entire epidermis from the dermis. This leaves the person vulnerable to multiple problems, including loss of body fluids and electrolytes, impaired body temperature control, and a greatly increased risk of infection. Three types of drug reactions that result in bullous skin lesions are erythema multiforme minor, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[7,34,35] *Erythema multiforme minor* is usually self-limiting. Cases involving less than 10% of the body surface area are called *Stevens-Johnson syndrome,* and detachment of more than 30% of the epidermis is labeled *toxic epidermal necrolysis,* with a 10% to 30% overlap of Stevens-Johnson syndrome and toxic epidermal necrolysis.[7,35]

Although the cause of erythema multiforme minor may be drug induced or unknown, it frequently occurs after infections, especially HSV infection. It is self-limiting, with a small amount of skin detachment at the lesion sites. Stevens-Johnson syndrome and toxic epidermal necrolysis are caused by a hypersensitivity reaction to drugs, the most common being sulfonamides, anticonvulsants, nonsteroidal anti-inflammatory drugs, antimalarial agents, and allopurinol. Although rare, Stevens-Johnson syndrome and toxic epidermal necrolysis have an annual incidence rate of 0.4 to 7 per 1 million people and a high mortality rate.[35] Recovery is based on the severity and quick, aggressive treatment.

The lesions of erythema multiforme minor and Stevens-Johnson syndrome are similar. The primary lesion of both is a round, erythematous papule, resembling an insect bite. Within hours to days, these lesions change into several different patterns. The individual lesions may enlarge and coalesce, producing small plaques, or they may change to concentric zones of color appearing as "target" or "iris" lesions (Fig. 46-16). The outermost rings of the target lesions usually are erythematous; the central portion usually is opaque white, yellow, or gray (dusky). In the center, small blisters on the dusky purpuric macules may form, giving them their characteristic targetlike appearance. Although there is wide distribution of lesions over the body surface area, there is a propensity for them to occur on the face and trunk.

Toxic epidermal necrolysis is the most serious type of drug reaction, with mortality rates of 25% to 35%.[35] The person experiences a prodromal period of malaise, low-grade fever, and sore throat. Within a few days, widespread erythema and large, flaccid bullae appear, followed by the loss of the epidermis, leaving a denuded and painful dermis. The skin surrounding the large denuded areas may have the typical targetlike lesions seen with Stevens-Johnson syndrome. Lateral pressure causes the surrounding skin to separate easily from the dermis (*Nikolsky sign*). The tracheobronchial mucosa and conjunctiva may be involved in severe cases with resultant scarring.[7] Ophthalmologic consultation is required when ocular involvement in present.

FIGURE 46-16. Erythema multiforme–like eruption on a patient's arm. Note the dusky, targetlike appearance. (Dermik Laboratories, Inc.) (From Sauer G.C., Hall J.C. [1996]. *Manual of skin diseases* [7th ed.]. Philadelphia: Lippincott-Raven.)

Treatment of erythema multiforme minor and less severe cases of Stevens-Johnson syndrome includes relief of symptoms using compresses, antipruritic drugs, and topical anesthetics. Corticosteroid therapy may be indicated in moderate cases, although its use is controversial. For severe cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, hospitalization is required for fluid replacement, respiratory care, administration of antibiotics and analgesics, and application of moist dressings. When large areas of skin are detached, the care is similar to that of thermal burn patients. Intravenous immunoglobulin may hasten the healing response of the skin. Generally, healing is a slow process, taking 6 weeks or more to regenerate skin. The mucous membranes heal slowly and follow-up treatment is often needed for ophthalmologic and mucous membrane sequelae. Discontinuation of the responsible drug and chemically related compounds is imperative, as are measures to prevent future exposures to the drug.

Papulosquamous Dermatoses

Papulosquamous dermatoses are a group of skin disorders characterized by scaling papules and plaques. Among the major papulosquamous diseases are psoriasis, pityriasis rosea, and lichen planus.

Psoriasis

Psoriasis is a common, chronic inflammatory skin disease, affecting approximately 2% of the population. Psoriasis

occurs worldwide, although the incidence is lower in warmer, sunnier climates. The average age of onset is in the third decade; its prevalence increases with age. Approximately one third of patients have a genetic history, indicating a hereditary factor. Childhood onset of the disease is more strongly associated with a family history than psoriasis occurring in adults older than 30 years of age. In rare cases, psoriasis is associated with arthritis (see Chapter 44).

The disease is usually manifested by raised, well-demarcated, erythematous plaques with adherent silvery scales.[11,12,36–38] Although the primary cause of psoriasis is uncertain, it is thought to be an immunologic disease with contributions from a genetic predisposition and environmental factors. It is not known if the inciting antigen is self or environmental. A genetic component is supported by population studies indicating a greater incidence of psoriasis among relatives of persons with the disease than among the general population. There is a strong association between psoriasis and the human leukocyte antigen (HLA)-C, particularly the HLA-Cw6 allele.[11] Immunologically, T lymphocytes may be the key to the pathogenesis of psoriasis.[39] Eruption of psoriatic lesions coincide with T-cell infiltration into the epidermis, and resolution of the lesions follows disappearance or reduction in epidermal T cells, suggesting a T-cell–mediated release of cytokines and growth factors that stimulate abnormal growth of keratinocytes and dermal blood vessels. Accompanying inflammatory changes are caused by infiltration of neutrophils and monocytes. Environmental stimuli may trigger the release of cytokines and growth factors from keratinocytes and other cells, with ensuing immune and inflammatory responses that lead to the full development of psoriatic lesions. For example, psoriatic lesions can be induced in susceptible individuals by trauma, a process known as the *Köbner phenomenon*.

Histologically, psoriasis is characterized by increased epidermal cell turnover with marked epidermal thickening, a process called *hyperkeratosis*. The granular layer (stratum granulosum) of the epidermis is thinned or absent, and neutrophils are found in the stratum corneum. There also is an accompanying thinning of the epidermal cell layer that overlies the tips of the dermal papillae, and the blood vessels in the dermal papillae become tortuous and dilated. These capillary beds show permanent damage even when the disease is in remission or resolved. The close proximity of the vessels in the dermal papillae to the hyperkeratotic scale accounts for multiple, minute bleeding points that are seen when the scale is lifted.

Psoriasis most frequently affects the elbows, knees, scalp, lumbosacral area, and intragluteal cleft. The primary lesions are sharply demarcated, thick, red plaques with a silvery scale that vary in size and shape (Fig. 46-17). In darker-skinned persons, the plaques may appear purple. There may be excoriation, thickening, or oozing from the lesions. A differential diagnostic finding is that the plaques bleed from minute points when removed, which is known as the *Auspitz sign*.

Treatment. The goals for psoriasis treatment focus on suppressing the hyperkeratosis, epidermal inflammation, and abnormal keratinocyte differentiation that are characteristic of the disease. Treatment measures are divided into topical and systemic approaches, the selection of which is dependent upon disease severity, as well as the person's age, sex, treatment history, and level of compliance. Usually, topical agents are used first in any treatment regimen

FIGURE 46-17. Psoriasis on the elbows of a 17-year-old girl. (Roche Laboratories.) (From Sauer G.C., Hall J.C. [1996]. *Manual of skin diseases* [7th ed.]. Philadelphia: Lippincott-Raven.)

and when less than 20% of the body surface is involved. Combination therapies tailored to the needs of the client are most effective.

Topical agents include emollients, keratolytic agents, coal tar products, corticosteroids, and calcipotriene.[38] Emollients hydrate and soften the psoriatic plaques. Petroleum-based products are more effective than water-based, but they are often less acceptable cosmetically to persons with psoriasis. Keratolytic agents are peeling agents. Salicylic acid is the most widely used. It softens and removes plaques. It has been used alone or in conjunction with other topical agents. Coal tar, the by-product of the processing of coke and gas from coal, is one of the oldest yet more effective forms of treatment. The exact mechanism of action of tar products is unknown, but side effects of the treatment are few. Newer preparations of coal tar lotions and shampoos are more aesthetically pleasing, but the odor remains a problem. *Calcipotriene* (a vitamin D derivative) *ointment* has been effective for the treatment of psoriasis. It inhibits epidermal cell proliferation and enhances cell differentiation. *Tazarotene,* a synthetic retinoid, also has been effective, but it is teratogenic and should be avoided in women of childbearing age.

Topical corticosteroids are widely used and relatively effective. They are generally more acceptable because they do not stain and are easy to use. Topical corticosteroids are available as low-, medium-, and high-potency preparations. Treatment usually is started with a medium-potency agent. Low-potency drugs usually are used on the face and areas of the body, such as the groin and axillary areas, where the skin tends to be thinner. High-potency preparations are reserved for treatment of thick chronic plaques that do not respond to less potent preparations. Although the corticosteroids are rapidly effective in the treatment of psoriasis, they are associated with flare-ups after discontinuation and they have many potential side effects. Their effectiveness is increased when used under occlusive dressings, but there is an increase in side effects.

Systemic treatments include phototherapy, photochemotherapy, methotrexate, corticosteroids, and cyclosporine. The positive effects of sunlight have long been established. Phototherapy with UVB is a widely used treatment. Newly developed narrow-band UVB radiation is reportedly more effective that broad-band UVB.[38] Photochemotherapy involves using a light-activated form of the drug methoxsalen. Methoxsalen, a psoralen or phototoxic drug, exerts its actions when exposed to UVA radiation in 320- to 400-nm wavelengths. The combination treatment regimen of psoralen and UVA is known by the acronym *PUVA*. Methoxsalen is given orally before UVA exposure. Activated by the UVA energy, methoxsalen inhibits DNA synthesis, thereby preventing cell mitosis and decreasing the hyperkeratosis that occurs with psoriasis. Although viewed as one of the safest therapies since its introduction in the 1970s, PUVA increases the risk for squamous cell carcinoma, and it may increase the risk for development of melanoma.

Methotrexate, which is used for cancer treatment, is an antimetabolite that inhibits DNA synthesis and prevents cell mitosis. Oral methotrexate has been effective in treating psoriasis when other approaches have failed. The drug has many side effects, including nausea, malaise, leukopenia, thrombocytopenia, and liver function abnormalities. Cyclosporine is a potent immunosuppressive drug used to prevent rejection of organ transplants. It suppresses inflammation and the proliferation of T cells in persons with psoriasis. Its use is limited to severe psoriasis because of serious side effects, including nephrotoxicity, hypertension, and increased risk of cancers. Intralesional cyclosporine also has been effective. Biologic agents (e.g., infliximab, etanercept, efalizumab, and alefacept) that target the activity of T lymphocytes and cytokines responsible for the inflammatory nature of psoriasis have proven effective.[7,38]

Pityriasis Rosea

Pityriasis rosea is a rash that primarily affects children and young adults. The origin of the rash is unknown, but is thought to be caused by an infective agent.[11,12,40] Numerous viruses have been investigated, thus far with no conclusive evidence. The incidence is highest in winter. Cases occur in clusters and among persons who are in close contact, indicating an infectious spread. However, there are no data to support communicability, suggesting it may be an immune response to any number of agents.

The characteristic lesion is an oval macule or papule with surrounding erythema (Fig. 46-18). The lesion spreads with central clearing, much like tinea corporis. This initial lesion is a solitary lesion called the *herald patch* and is usually on the trunk or neck. As the lesion enlarges and begins to fade (2 to 10 days), successive crops of lesions appear on the trunk and neck. The lesions on the back have a characteristic "Christmas tree" pattern. The extremities, face, and scalp may be involved. Mild to severe pruritus may occur. The disease is self-limited and usually disappears within 6 to 8 weeks. Treatment measures are palliative and include topical steroids, antihistamines, and colloid baths. Systemic corticosteroids may be indicated in severe cases.

FIGURE 46-18. Pityriasis rosea. Note oval herald patch (*arrow*) on the abdomen as well as a more generalized rash. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

Lichen Planus

The term *lichen* (Greek, "tree moss") refers to skin disorders characterized by small (2 to 10 mm), flat-topped papules with irregular, angulated borders. *Lichen planus* is a relatively common chronic pruritic disease.[7,41] It involves inflammation and papular eruption of the skin and mucous membranes. There are variations in the pattern of lesions (e.g., annular, linear) and differences in the sites (e.g., mucous membranes, genitalia, nails, scalp). The characteristic lesion is a purple, polygonal papule covered with a shiny, white, lacelike pattern (Fig. 46-19). The lesions appear on the wrist, ankles, and trunk of the body. Most persons who have skin lesions also have oral lesions, appearing as milky white lacework on the buccal mucosa or tongue. Other mucosal surfaces, such as the genital, nasal, laryngeal, otic, gastric, and anal areas, may also be affected. As with psoriasis, lichen planus lesions can develop on scratches or skin injuries (Köbner phenomenon).

The etiology of lichen planus is unknown, but it is believed to be an abnormal immune response in which epithelial cells are recognized as foreign. The disorder involves the epidermal–dermal junction with damage to the basal cell layer. Some cases of lichen planus have been linked to hepatitis C virus infections or medication use. The most common medication agents include gold, antimalarial agents, thiazide diuretics, beta blockers, nonsteroidal anti-inflammatory agents, quinidine, and angiotensin-converting enzyme inhibitors. Some persons with oral lichen planus have reacted to the mercury in dental amalgams to the extent that when the dental fillings were replaced, the lesions healed.[41]

Diagnosis is based on the clinical appearance of the lesions and the histopathologic findings from a punch biopsy. For most persons, lichen planus is a self-limited disease. Treatment measures include discontinuation of all medications, followed by treatment with topical corticosteroids and occlusive dressings. Antipruritic agents are helpful in reducing itch. Systemic corticosteroids may be indicated in severe cases. Photochemotherapy (i.e., PUVA) may also be used. Acitretin, an orally administered retinoid agent, also may be effective. Because retinoids are teratogenic, they should be avoided in women of childbearing age.

FIGURE 46-19. Lichen planus affecting both wrists. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

FIGURE 46-20. Localized lichen simplex chronicus of the leg. (Duke Laboratories, Inc.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 119]. Philadelphia: Lippincott Williams & Wilkins.)

Lichen Simplex

Lichen simplex chronicus is a localized lichenoid pruritic dermatitis resulting from repeated rubbing and scratching.[7] It is characterized by the occurrence of itchy, reddened, thickened, and scaly patches of dry skin (Fig. 46-20). Persons with the condition may have a single or, less frequently, multiple lesions. The lesions are seen most commonly at the nape of the neck, wrists, ankles, or anal area. The condition usually begins as a small pruritic patch, which after a repetitive cycle of itching and scratching develops into a chronic dermatitis. Because of the chronic itching and scratching, excoriations and lichenification with thickening of the skin develops, often giving the appearance of tree bark.

In summary, primary skin disorders are those originating in the skin. They include infectious processes, acne and rosacea, allergic and hypersensitivity disorders, and papulosquamous dermatoses. The skin is subject to invasion by a number of microorganisms, including fungi, bacteria, and viruses. Superficial fungal infections or *dermatophytoses* are commonly known as *tinea* or

ringworm. Tinea can affect the whole body (tinea corporis), scalp (tinea capitis), feet or hands (tinea pedis or manus), or nails (tinea unguium). Candidal skin infection due *C. albicans* occurs most often in persons with diabetes mellitus, those who are immunosuppressed, or those have been treated with broad-spectrum antibiotics. Impetigo, which is caused by staphylococci or β-hemolytic streptococci, is the most common superficial bacterial infection. Viruses are responsible for verrucae (warts), herpes simplex type 1 lesions (cold sores or fever blisters), and herpes zoster (shingles).

Noninfectious inflammatory skin conditions include acne and rosacea and the papulosquamous dermatoses. Acne is a disorder of the pilosebaceous unit. Acne vulgaris, which is a common skin disorder of adolescents and young adults, is thought to reflect increased sebum production and the presence of *P. acnes.* Allergic skin responses involve the body's immune system and are caused by hypersensitivity reactions to allergens such as environmental agents, drugs, and other substances. They include atopic dermatitis, urticaria, and drug-induced skin eruptions (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis).

The papulosquamous dermatoses, which are characterized by scaling papules and plaques, include psoriasis, pityriasis rosea, lichen simplex, and lichen planus. Psoriasis is a chronic proliferative skin disease characterized by epidermal hyperplasia. Lichen planus is a hypersensitivity reaction with lymphocytic infiltration at the dermal–epithelial junction.

Ultraviolet Radiation, Thermal, and Pressure Injury

- Because the skin covers the body, it is exposed to a number of potentially damaging agents in the external environment.
- The ultraviolet rays of sunlight have the potential for directly damaging skin cells, accelerating the effect of aging on the skin, and predisposing to the development of skin cancer.
- Prolonged pressure can interrupt blood flow, causing pressure ulcers.
- Thermal injury can damage skin and subcutaneous tissue and destroy the barrier function of the skin in terms of preventing the loss of body fluids and protecting against the entry of infectious organisms.

Ultraviolet Radiation, Thermal, and Pressure Injury

Ultraviolet Radiation

Sunlight is composed of a continuous spectrum of electromagnetic radiation that is divided into three main parts or wavelengths: ultraviolet (UV), visible, and infrared. The UV light region occurs between 200 and 400 nm (nm: one billionth of a meter).[42,43] The UV light region is divided into three categories depending on the wavelength: long-wave UVA (320 to 400 nm), medium-wave UVB (280 to 320 nm), and short-wave UVC (100 to 280 nm). The ozone layer effectively absorbs UV radiation up to 310 nm, absorbing all of UVC and much of UVB (95%) radiation. However, due to damage to the protective ozone layer, an increased amount of UVB is reaching the earth. The ozone layer does not absorb UVA.

Ultraviolet Radiation Skin Damage

UVA makes up more than 95% of the solar radiation that reaches us. Compared to UVB, this long-wave radiation penetrates deep into the dermis of the skin and is more effective in producing an immediate tan. UVB radiation is a minor, but more active constituent of sunlight. It is more genotoxic and about 1000 times more capable of causing sunburn than UVA light.[42] UVB acts mainly on the cells in the basal layer of the epidermis. It produces direct damage to the DNA and other nuclear proteins. It also provokes free radical production and induces a significant reduction in skin antioxidants, impairing the ability of the skin to protect itself against damage by the free radicals that are generated.

The acute effects of UVA and UVB are short lived and reversible. They include erythema, pigmentation, and injury to Langerhans cells and keratinocytes in the epidermis. These reactions differ depending on whether the inciting agent is UVA or UVB. For example, UVA-induced erythema occurs immediately, fades within hours, and is believed to be due to the "heat load." UVB-induced erythema has a delayed response, peaking within 6 to 24 hours after exposure to sunlight and fading over 1 or 2 days. Pigmentation or tanning induced by UVA and UVB is due to increased synthesis of melanin by melanocytes, along with increased transfer of the melanin to keratinocytes (see Chapter 45). Small doses of UVA produce transient, immediate darkening of the skin that fades within 2 hours, whereas higher doses of UVA can produce pigmentary changes lasting for several hours to days.[44] Tanning induced by UVB is protective against subsequent exposures, whereas tanning induced by UVA provides limited protection.

Skin damage induced by UVB is believed to be caused by the generation of reactive oxygen species and by damage to melanocytes.[43,44] Cellular proteins and DNA are primarily damaged because of their abundance and ability to absorb UVB radiation. Both UVA and UVB also deplete Langerhans cells and immune cells. It is believed that these effects prevent immune cells from detecting and removing sun-damaged cells with malignant potential. Both UVA and UVB are now considered causes of skin cancer. UVA may actually be more carcinogenic than UVB. Although it causes less sunburn, UVA is present during all daylight hours, year-round. Artificial sources of UVA, such as tanning beds and therapeutic solar

interventions (PUVA) for certain skin conditions, also produce the same effects as solar UVA in terms of skin cancer. This is of particular concern because of the increased use of indoor tanning, particularly among adolescents and young adults who are at greatest risk of melanoma.[45]

The UV rays of sunlight or other sources can be completely or partially blocked from the skin surface by sunscreens. There are two primary types of sunscreens available on the market—chemical (soluble) agents and physical (insoluble) agents.[46] Chemical agents (e.g., para-aminobenzoic acid [PABA] derivatives) protect the skin from absorbing sunlight, and physical agents (e.g., micronized titanium dioxide and microfine zinc) work by reflecting sunlight. The *sun protection factor* (SPF) rating of the various sunscreen products is based on their ability to obstruct UV radiation (UVR) absorption. The ratings usually are on a scale of 1 to 30+, with the higher ratings indicating greater blocking of UVR.[46] Products with a higher SPF screen out more UVB rays, which are primarily responsible for acute sun damage. Shielding the skin with protective clothing and hats or head coverings helps decrease UVR exposure.

Sunburn. Sunburn is caused by excessive exposure of the epidermal and dermal layers of the skin to UV radiation, resulting in an erythematous inflammatory reaction.[47] Sunburn ranges from mild to severe. Mild sunburn consists of various degrees of skin redness. The burn continues to develop for 24 to 72 hours, occasionally followed by peeling skin in 3 to 8 days. Some peeling and itching may continue for several weeks. Inflammation, blistering, weakness, chills, fever, malaise, and pain often accompany severe forms of sunburn. Scaling and peeling follow any overexposure to sunlight. Dark skin also burns and may appear grayish or gray-black. Severe sunburns are those that cover large portions of the body with blisters or are accompanied by a high fever or intense pain.

Mild to moderate sunburns are treated with anti-inflammatory medications, such as aspirin or ibuprofen, until redness and pain subside. Cold compresses, cool baths, and applying a moisturizing cream, such as aloe, to affected skin help treat the symptoms. Steroid and nonsteroidal agents are used depending on the severity of the burn. Blisters should not be broken to preserve the protective layer of the skin, hasten the healing process, and decrease the risk of infection. Extensive second- and third-degree sunburns may require hospitalization and specialized burn care techniques, as described in the section on thermal injury.

Drug-Induced Photosensitivity. Some drugs are classified as photosensitive drugs because they produce an exaggerated response to UVR when the drug is taken in combination with sun exposure.[48] Examples include some of the anti-infective agents (sulfonamides, tetracyclines, nalidixic acid), antihistamines (cyproheptadine, diphenhydramine), antipsychotic agents (phenothiazines, haloperidol), diuretics (thiazides, acetazolamide, amiloride), hypoglycemic agents (sulfonylureas), and nonsteroidal anti-inflammatory drugs (phenylbutazone, ketoprofen, naproxen).

Thermal Injury

About 1.2 million people in the United States require medical care for burns each year, with 51,000 requiring hospitalization. Between 30% and 40% of these are children younger than 15 years of age, with an average age of 32 months.[49] Thermal burns are caused by a number of sources. Flame burns occur because of exposure to direct fire. Scald burns result from hot liquids spilled or poured on the skin surface.

The effects and complications of burns fully illustrate the essential function that the skin performs in protecting the body from the many damaging elements in the environment while serving to maintain the constancy of the body's internal environment. The massive loss of skin tissue not only predisposes to attack by microorganisms that are present in the environment, but also allows for the massive loss of body fluids and their contents, interferes with temperature regulation, challenges the immune system, and imposes excessive demands on the metabolic and reparative processes that are needed to restore the body's interface with the environment.

Classification of Burns

Burns are typically classified according to the depth of involvement as first-degree, second-degree, and third-degree burns.[49–51] The depth of a burn is largely influenced by the duration of exposure to the heat source and the temperature of the heating agent. *First-degree burns* (superficial partial-thickness burns) involve only the outer layers of the epidermis. They are red or pink, dry, and painful. There usually is no blister formation. A mild sunburn is an example. The skin maintains its ability to function as a water vapor and bacterial barrier and heals in 3 to 10 days. First-degree burns usually require only palliative treatment, such as pain relief measures and adequate fluid intake. Extensive first-degree burns on infants, the elderly, and persons who receive radiation therapy for cancer may require more care.

Second-degree burns involve both the epidermis and dermis. *Second-degree partial-thickness burns* involve the epidermis and various degrees of the dermis. They are painful, moist, red, and blistered. Underneath the blisters is weeping, bright pink or red skin that is sensitive to temperature changes, air exposure, and touch. The blisters prevent the loss of body water and superficial dermal cells. Excluding excision of large burn areas, it is important to maintain intact blisters after injury because they serve as a good bandage and may promote wound healing. These burns heal in approximately 1 to 2 weeks.

Second-degree full-thickness burns involve the entire epidermis and dermis. Structures that originate in the subcutaneous layer, such as hair follicles and sweat glands, remain intact. These burns can be very painful because the pain sensors remain intact. Tactile sensation may be absent or greatly diminished in the areas of deepest destruction. These burns appear as mottled pink, red,

TABLE 46-1 American Burn Association Grading System for Burn Severity and Disposition

	Type of Burn		
	Minor	***Moderate***	***Major***
Criteria	<10% TBSA in adult <5% TBSA in young (<10 years) or old (>50 years) <2% Full-thickness burn	10%–20% TBSA in adult 5%–10% TBSA in young or old 2%–5% Full-thickness burn High-voltage injury Suspected inhalation injury Circumferential burn Concomitant medical problem predisposing to infection (e.g., diabetes, sickle cell disease)	>20% TBSA in adult >10% TBSA in young or old >5% Full-thickness burn High-voltage burn Known inhalation injury Any significant burn to face, eyes, ears, genitalia, hands, feet, or major joints Significant associated injuries (e.g., major trauma)
Disposition	Outpatient management	Hospital admission	Referral to burn center

TBSA, total body surface area.

From American Burn Association. (1990). Hospital and prehospital resources for optimal care of patients with burn injury: Guidelines for development and operation of burn centers. *Journal of Burn Care and Rehabilitation* 11, 98–104.

or waxy white areas with blisters and edema. The blisters resemble flat, dry tissue paper, rather than the bullous blisters seen with superficial partial-thickness injury. After healing, in approximately 1 month, these burns maintain their softness and elasticity, but there may be the loss of some sensation. Scar formation is usual. These burns heal with supportive medical care aimed at preventing further tissue damage, providing adequate hydration, and ensuring that the granular bed is adequate to support reepithelialization.

Third-degree full-thickness burns extend into the subcutaneous tissue and may involve muscle and bone. Thrombosed vessels can be seen under the burned skin, indicating that the underlying vasculature is involved. Third-degree burns vary in color from waxy white or yellow to tan, brown, deep red, or black. These burns are hard, dry, and leathery. Edema is extensive in the burn area and surrounding tissues. There is no pain because the nerve sensors have been destroyed. However, there is no such thing as a "pure" third-degree burn. Third-degree burns are almost always surrounded by second-degree burns, which are surrounded by an area of first-degree burns. The injury sometimes has an almost targetlike appearance because of the various degrees of burn. Full-thickness burns wider than 1.5 inches usually require skin grafts because all the regenerative (i.e., dermal) elements have been destroyed. Smaller injuries usually heal from the margins inward toward the center, the dermal elements regenerating from the healthier margins. However, regeneration may take many weeks and leave a permanent scar, even in smaller burns.

In addition to the depth of the wound, the extent of the burn also is important. Extent is measured by estimating the amount of total body surface area (TBSA) involved.[49–51] Several tools exist for estimating the TBSA. For example, the *rule of nines* counts anatomic body parts as multiples of 9% (the head and neck is 9%, each arm 9%, each leg 18%, anterior trunk 18%, posterior trunk 18%), with the perineum 1%. The Lund and Browder chart includes a body diagram table that estimates the TBSA by age and anatomic part. Children are more accurately assessed using this method because it takes into account the difference in relative size of body parts. The estimates of TBSA are then converted to the American Burn Association Classification of Extent of Injury (Table 46-1).

Other factors, such as age, location, other injuries, and preexisting conditions, are taken into consideration for a full assessment of burn injury.[51–55] These factors can increase the assessed severity of the burn and the length of treatment. For example, a first-degree burn is reclassified as a more severe burn if other factors are present, such as burns to the hands, face, and feet; inhalation injury; other trauma; or existence of psychosocial problems. Genital burns almost always require hospitalization because edema may cause difficulty urinating and the location complicates maintenance of a bacteria-free environment.

Systemic Complications

Burn victims often are confronted with hemodynamic instability, impaired respiratory function, a hypermetabolic response, and sepsis.[52–54] The magnitude of the response is proportional to the extent of injury, usually reaching a plateau when approximately 60% of the body is burned. In addition to loss of skin, burn victims often have associated injuries or illnesses. The treatment challenge is to provide immediate resuscitation efforts and long-term maintenance of physiologic function. Pain and emotional problems are additional challenges faced by persons with burns.

Hemodynamic Instability. Hemodynamic instability begins almost immediately with injury to capillaries in

the burned area and surrounding tissue. Fluid is lost from the vascular, interstitial, and cellular compartments. Because of a loss of vascular volume, major burn victims often present in the emergency department in a form of hypovolemic shock (Chapter 20) known as *burn shock*. Because proteins from the blood are lost into the interstitial compartment, generalized edema, including pulmonary edema, can be severe.

Respiratory System Dysfunction. Another injury commonly associated with burns is smoke inhalation and postburn lung injury. Victims often are trapped in a burning structure and inhale significant amounts of smoke, carbon monoxide, and other toxic fumes. Water-soluble gases, such as ammonia, sulfur dioxide, and chlorine, that are found in smoke from burning plastics and rubber react with mucous membranes to form strong acids and alkalis that induce ulceration of the mucous membrane, bronchospasm, and edema. Lipid-soluble gases, such as nitrous oxide and hydrogen chloride, are transported to the lower airways, where they damage lung tissue. There also may be thermal injury to the respiratory passages. Manifestations of inhalation injury include hoarseness, drooling and inability to handle secretions, hacking cough, and labored and shallow breathing. Serial blood gases show a fall in the partial pressure of arterial oxygen (PO_2). Signs of mucosal injury and airway obstruction often are delayed for 24 to 48 hours after a burn. Other pulmonary conditions, such as pneumonia, pulmonary embolism, or pneumothorax, may occur secondarily to the burn.

Hypermetabolic Response. The stress of burn injury increases metabolic and nutritional requirements. Secretion of stress-related hormones such as catecholamines and cortisol is increased in an effort to maintain homeostasis. Heat production is increased in an effort to balance heat losses from the burned area. Hypermetabolism, characterized by increased oxygen consumption, increased glucose use, and protein and fat wasting, is a characteristic response to burn trauma and infection. The hypermetabolic state peaks at approximately 7 to 17 days after the burn, and tissue breakdown diminishes as the wounds heal. Nutritional support is essential to recovery from burn injury. Enteral and parenteral hyperalimentation may be used during this time to deliver sufficient nutrients to prevent tissue breakdown and postburn weight loss.

Sepsis. A significant complication of the acute phase of burn injury is sepsis. It may arise from the burn wound, pneumonia, urinary tract infection, infection elsewhere in the body, or the use of invasive procedures or monitoring devices. The burn site is an ideal growth area for microorganisms; the serum and debris provide nutrients, and the burn injury compromises blood flow. Immunologically, the skin is the body's first line of defense. When the skin is no longer intact, the body is open to bacterial infection. Destruction of the skin also prevents the delivery of cellular components of the immune system to the site of injury. There also is loss of normal protective skin flora and a shift to colonization by more pathogenic flora.

Emergency and Long-Term Treatment

Regardless of the type of burn, the first step in any burn situation is to stop the burning process, cool the burn, provide pain relief, and cover the burn.[53,54] Active cooling removes the heat and prevents progression of the burn. Immersion or irrigation with lukewarm water for at least 20 minutes can be extremely helpful. Immediate submersion is more important than removal of clothing, which may delay cooling the involved areas. The application of ice or cold water is not recommended because it can further limit blood flow to an area, turning a partial-thickness into a full-thickness burn.

Depending on the depth and extent of the burn, medical treatment is necessary. Emergency care consists of resuscitation and stabilization with intravenous fluids while maintaining cardiac and respiratory function. Once hospitalized, the immediate treatment regimen focuses on continued maintenance of cardiorespiratory function, pain alleviation, wound care, and emotional support. After hemodynamic and pulmonary stability have been established, treatment is directed toward initial care of the wound. Treatment of the burn wound focuses on protection from desiccation and further injury of those burn areas that reepithelialize in 7 to 10 days (superficial second-degree burns). "Nature's own blister" is the best protection for these burns. Topical antimicrobial preparations (e.g., silver sulfadiazine) and dressings are used to cover the wound when the blister has been broken. Wounds that will not heal spontaneously in 7 to 10 days (deep second-degree and third-degree burns) are usually treated by excision and skin grafts. The sloughed tissue, or *eschar,* produced by the burn is excised as soon as possible. This decreases the chance of infection and allows the skin to regenerate faster.

Burns that encircle the entire surface of the body or a body part (e.g., arms, legs, torso) act like tourniquets and can cause major tissue damage to the muscles, tendons, and vasculature under the area of the leathery eschar skin. These burns are called *circumferential burns*. The eschar is incised longitudinally (escharotomy), and sometimes a fasciotomy (surgical incision through the fascia of the muscle) is performed.

Systemic infection remains a leading cause of morbidity among persons with extensive burns. Continuous microbiologic surveillance is necessary; protective isolation measures are often instituted. There is an increasing trend toward use of prophylactic antibiotic treatment in persons with major burns.

Skin grafts are surgically implanted as soon as possible, often at the same time the burn tissue is excised, to promote new skin growth, limit fluid loss, and act as a dressing.[56] Skin grafts can be permanent or temporary, and split thickness or full thickness. Permanent skin grafts are used over newly excised tissue. Temporary skin grafts are used to cover a burned area until the tissue underneath it has healed. Various sources of skin grafts exist: *autograft* (skin obtained from the person's own

body), *homograft* (skin obtained from another human being, alive or recently dead), and *heterograft* (skin obtained from another species, such as pigs). The best choice is autografting when there is enough uninterrupted skin on the person's body. The thickness of these grafts depends on the donor site and the needs of the burn patient. A *split-thickness skin graft* is one that includes the epidermis and part of the dermis. A split-thickness skin graft can be sent through a skin mesher that cuts tiny slits into the skin, allowing it to expand up to nine times its original size. These grafts are used frequently because they can cover large surface areas and there is less autorejection. *Full-thickness skin grafts* include the entire thickness of the dermal layer. They are used primarily for reconstructive surgery or for small deep areas. The donor site of a full-thickness skin graft requires a split-thickness skin graft to help it heal.

Two-layered synthetic skin grafts (*Apligraf, Integra*) are now available.[57] Synthetic skin grafts generally are composed of a layer of silicone, mimicking the properties of the epidermis, and a layer or matrix of fibers. Skin cells attach to the fibers, enabling dermal skin growth. Once the dermal skin has regenerated, the silicone layer is removed and a thin epidermal skin graft is applied, thus requiring less skin grafting overall.

Other treatment measures include positioning, splinting, and physical therapy to prevent contractures and maintain muscle tone. Because the normal body response to disuse is flexion, the contractures that occur with a burn are disfiguring and cause loss of limb or appendage use. Once the wounds have healed sufficiently, elastic pressure garments, sometimes for the full body, often are used to prevent hypertrophic scarring.

Pressure Ulcers

Pressure ulcers are ischemic lesions of the skin and underlying structures caused by unrelieved pressure that impairs the flow of blood and lymph. Pressure ulcers often are referred to as *decubitus ulcers* or *bedsores*. The word *decubitus* comes from the Latin term meaning "lying down." However, a pressure ulcer may result from pressure exerted in the seated or the lying position. Pressure ulcers are most likely to develop over a bony prominence, but they may occur on any part of the body that is subjected to external pressure, friction, or shearing forces. Several subpopulations are at particular risk, including persons with quadriplegia, elderly persons with restricted activity and hip fractures, and persons in the critical care setting.

Mechanisms of Development

Four factors contribute to the development of pressure ulcers: (1) pressure, (2) shearing forces, (3) friction, and (4) moisture.[58–60] External pressures that exceed capillary pressure interrupt blood flow in the capillary beds. When the pressure between a bony prominence and a support surface exceeds the normal capillary filling pressure, capillary flow essentially is obstructed. If this pressure is applied constantly for 2 hours, oxygen deprivation coupled with an accumulation of metabolic end products leads to irreversible tissue damage. Although 32 mm Hg has been traditionally accepted as the amount of pressure necessary to compress capillaries and interrupt blood flow, this is highly variable among individuals.[58] Persons with impaired circulation require less pressure to interrupt circulation. The same amount of pressure causes more damage when it is distributed over a small area than over a larger area.

Whether a person is sitting or lying down, the weight of the body is borne by tissues covering the bony prominences. More than 95% of pressure ulcers are located on the lower part of the body, most often over the sacrum, the coccygeal area, the ischial tuberosities, and the greater trochanters.[59] Pressure over a bony area is transmitted from the surface to the underlying dense bone, compressing all of the intervening tissue. As a result, the greatest pressure occurs at the surface of the bone and dissipates outward in a conelike manner toward the surface of the skin (Fig. 46-21). Thus, extensive underlying tissue damage can be present when a small superficial skin lesion is first noticed.

Altering the distribution of pressure from one skin area to another prevents tissue injury. Pressure ulcers most commonly occur in persons with conditions such as spinal cord injury in which normal sensation and movement to effect redistribution of body weight are impaired. Normally, persons unconsciously shift their

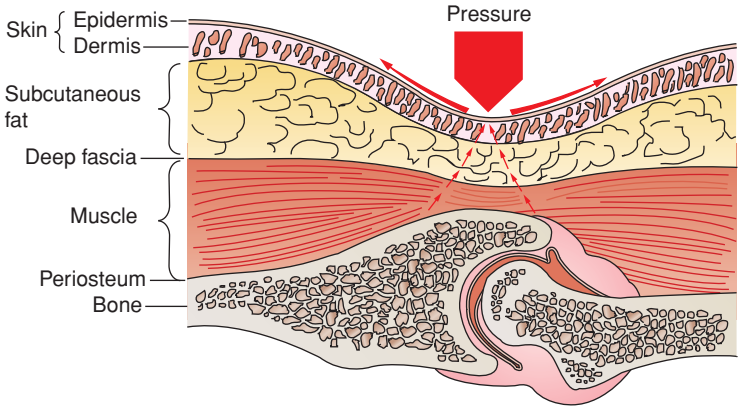


FIGURE 46-21. Pressure over a bony prominence compresses all intervening soft tissue, with a resulting wide, three-dimensional pressure gradient that causes various degrees of tissue damage. (From Shea J.D. [1975]. Pressure sores: Classification and management. *Clinical Orthopedics and Related Research* 112, 90.)

weight to redistribute pressure on the skin and underlying tissues. For example, during the night, people turn in their sleep, preventing ischemic injury of tissues that overlie the bony prominences that support the weight of the body; the same is true for sitting for any length of time. The movements needed to shift the body weight are made unconsciously, and only when movement is restricted do people become aware of discomfort.

Shearing forces are caused by the sliding of one tissue layer over another with stretching and angulation of blood vessels, causing injury and thrombosis. Shear occurs when the skeleton moves, but the skin remains fixed to an external surface, such as occurs with transfer from a stretcher to a bed or pulling a person up in bed. The same thing happens when the head of the bed is elevated, causing the torso to move toward the foot of the bed while friction and moisture cause the skin to remain fixed to the bed linens. *Friction* contributes to pressure ulceration by damaging the skin at the epidermal–dermal interface. It occurs as persons who are bedridden use their elbows and heels to aid in movement. *Moisture* contributes to pressure ulcer formation by weakening the cell wall of individual skin cells and by changing the protective pH of the skin. This makes the skin more susceptible to pressure, shear, and friction injury.

Prevention and Treatment

The prevention of pressure ulcers is preferable to their treatment.[60] Preventative measures include identifying at-risk persons who need preventive measures and the specific factors placing them at risk, maintaining and improving tissue tolerance to prevent injury, and protecting the skin and underlying tissue against the adverse effects of external mechanical forces (i.e., pressure, friction, shear). Risk factors contributing to the development of pressure ulcers are those related to sensory perception and the ability to respond meaningfully to pressure-related discomfort, level of skin moisture, urine and fecal continence, nutrition and hydration status, mobility, and circulatory status.

Prevention Methods. Methods for preventing pressure ulcers include frequent position changes, meticulous skin care, and frequent and careful observation to detect early signs of skin breakdown. Moisture macerates and injures skin. Sources of moisture include sweat, wound drainage, urine, and feces. Both urinary and fecal incontinence increase the risk of pressure ulcers. Food crumbs, intravenous tubing, and other debris in the bed can greatly increase local skin pressure points. Adequate hydration of the stratum corneum appears to protect the skin against mechanical insult. The prevention of dehydration improves the circulation. It also decreases the concentration of urine, thereby minimizing skin irritation in persons who are incontinent, and it reduces urinary problems that contribute to incontinence. Maintenance of adequate nutrition is important. Anemia and malnutrition contribute to tissue breakdown and delay healing after tissue injury has occurred.

Staging and Treatment. Pressure ulcers can be staged using four categories.[61] *Stage I ulcers* are characterized by a defined area of persistent redness in lightly pigmented skin or an area of persistent redness with blue or purple hues in darker skin. *Stage II ulcers* represent a partial-thickness loss of skin involving the epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion, a blister, or a shallow crater. *Stage III ulcers* represent a full-thickness skin loss involving damage and necrosis of subcutaneous tissue that may extend down to but not through underlying fascia. The ulcer manifests as a deep crater with or without undermining of adjacent tissue. *Stage IV ulcers* involve full-thickness skin loss and necrosis with extensive destruction or damage to the underlying subcutaneous tissues that may extend to involve muscle, bone, and supporting structures (e.g., tendon or joint capsule).

After skin breakdown has occurred, special treatment measures are needed to prevent further ischemic damage, reduce bacterial contamination and infection, and promote healing. Treatment methods are selected based on the stage of the ulcer.[60–62] Stage I ulcers usually are treated with frequent turning and measures to remove pressure. Stage II or III ulcers with little exudate are treated with semipermeable or occlusive dressings. Occlusive dressings are credited with preventing the loss of wound fluid and maintaining a moist environment that is necessary for epithelial cell migration. Wound fluid is thought to contain a variety of growth factors that enhance wound healing. Occlusive dressings may also relieve wound pain and prevent bacterial contamination. There are several types of occlusive dressings available, including polymer films, hydrogels, hydrocolloids, biomembranes, and absorbing granules. The available products differ in their permeability to water vapor and wound protection, and each has advantages and disadvantages.

Necrotic debris increases the possibility of bacterial infection and delays wound healing. Stage III ulcers with exudate and necrotic debris and stage IV ulcers usually require débridement (i.e., removal of necrotic tissue and eschar). This can be done surgically, with wet-to-dry dressings, or through the use of proteolytic enzymes. Stage IV wounds often require packing to obliterate dead space and are covered with nonadherent dressings. Stage IV ulcers may require surgical interventions, such as skin grafts or myocutaneous flaps.

In summary, repeated exposure to the UV rays of the sun predisposes to sunburn, premature aging of the skin (wrinkling, degenerative changes, and irregularities in pigmentation), and skin cancer. Solar and artificial sources of UV radiation, such as from a tanning bed, contribute to the amount of radiation to which human beings are exposed. Sunburn, which is caused by excessive exposure to UV radiation, is an erythematous inflammatory reaction, ranging from mild to severe. Photosensitive drugs can also produce an exaggerated response to UV radiation when they are taken in combination with sun

exposure. Sunscreens are protective agents that work by either reflecting sunlight or preventing its absorption.

Burns cause damage to skin structures, ranging from first-degree burns, which damage the epidermis, to third-degree full-thickness burns, which extend into the subcutaneous tissue and may involve muscle and bone. The extent of injury is determined by the thickness of the burn and the total body surface area involved. In addition to skin involvement, burn injury can cause hemodynamic instability with hypovolemic shock, inhalation injury with respiratory involvement, a hypermetabolic state, and sepsis. Treatment methods vary with the severity of injury and include immediate resuscitation and maintenance of physiologic function, wound cleaning and débridement, application of antimicrobial agents and dressings, and skin grafting.

Pressure ulcers are caused by ischemia of the skin and underlying tissues. They result from external pressure, which disrupts blood flow, or shearing forces, which cause stretching and injury to blood vessels. Pressure ulcers are divided into four stages, according to the depth of tissue involvement. The prevention of pressure ulcers is preferable to their treatment. The goals of prevention should include identifying at-risk persons who need prevention along with the specific factors placing them at risk, maintaining and improving tissue tolerance to pressure to prevent injury, and protecting against the adverse effects of external mechanical forces (i.e., pressure, friction, and shear).

Nevi and Skin Cancers

Nevi

Nevi, or moles, are common congenital or acquired tumors of the skin that are benign. Almost all adults have nevi, some in greater numbers than others. Nevi can be pigmented or nonpigmented, flat or elevated, and hairy or nonhairy.

Melanocytic nevi are pigmented skin lesions resulting from proliferation of melanocytes in the epidermis or dermis.[11,12] Melanocytic nevi are tan to deep brown, uniformly pigmented, small papules with well-defined, rounded borders (Fig. 46-22A). They are formed initially by melanocytes with their long dendritic extensions that are normally interspersed among the basal keratinocytes (see Chapter 45, Fig. 45-3). The melanocytes are transformed into round or oval melanin-containing cells that grow in nests or clusters along the dermal–epidermal junction. Because of their location, these lesions are called *junctional nevi* (see Fig. 46-22B). Most junctional nevi eventually grow into the surrounding dermis as nests or cords of cells. *Compound nevi* contain epidermal and dermal components. In older lesions, the epidermal nests may disappear entirely, leaving *dermal nevi.* Compound and dermal nevi usually are more elevated than junctional nevi.

Another form of nevus, the *dysplastic nevus,* is important because of its capacity to transform into malignant melanoma.[11,12,63] Although the association between nevi and malignant melanoma was made over 175 years ago, it was not until 1978 that the role of dysplastic nevi as precursors to malignant melanoma was described in detail.[11] Dysplastic nevi are usually larger than other nevi (often >5 mm in diameter). Their appearance is a flat, slightly raised plaque with a pebbly surface, or a targetlike lesion with a darker, raised center and irregular border (Fig. 46-23). They vary in shade from brown and red to flesh tones. A person may have hundreds of these lesions. Although dysplastic nevi can give rise to melanoma, the vast majority are stable and never progress, suggesting that they are best viewed as markers for melonoma risk. Dysplastic nevi have been documented in multiple members of families prone to development of malignant melanoma.

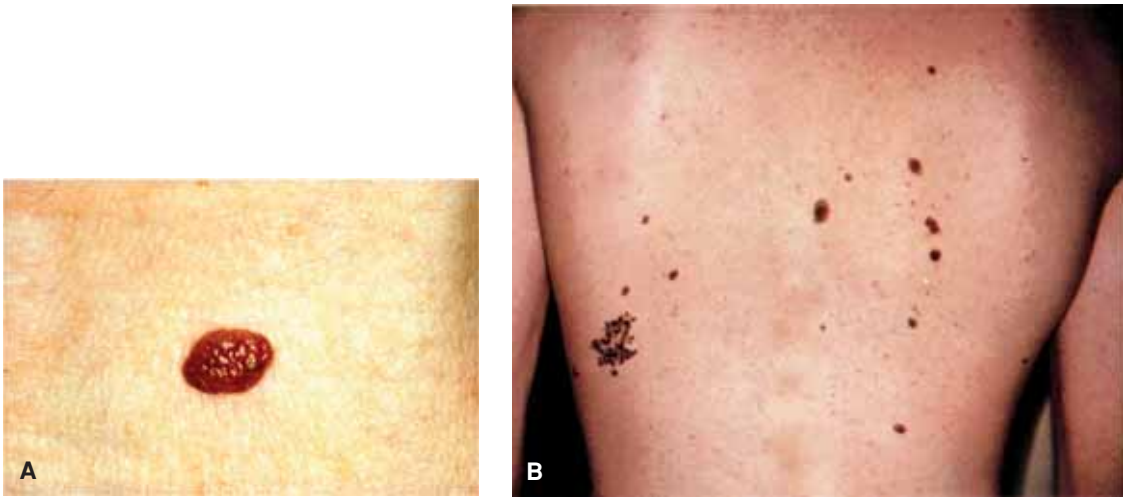


FIGURE 46-22. **(A)** Normal mole, with no different shades of brown, black, or tan. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.) **(B)** Junctional nevi on the back of a 16-year-old patient. (Owen Laboratories, Inc.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 397]. Philadelphia: Lippincott Williams & Wilkins.)

FIGURE 46-23. Dysplastic nevi. Lesion has a dark brown "pebbly" elevated surface against a lighter tan, macular background. The irregular, indistinct margin helps to distinguish it from the small congenital pattern nevus, which some dysplastic nevi closely resemble. Its distinct morphology, rather than its size (6 × 6 mm), identifies it as a dysplastic nevus. (From National Cancer Institute Visuals. [Online] Available: http://visualsonline.cancer.gov/browseaction.cfm?topicid=g11.)

Skin Cancers

- Increased and unprotected exposure to the ultraviolet rays of sunlight produces sunburn and increases the risk for development of skin cancer.
- The melanocytes, which protect against sunburn through increased production of melanin and suntanning, are particularly vulnerable to the adverse effects of unprotected exposure to ultraviolet light. Malignant melanoma, which is a malignant tumor of melanocytes, is a rapidly progressive and metastatic form of skin cancer.
- Basal cell carcinoma and squamous cell carcinoma, which also reflect the effects of increased sun exposure, are less aggressive forms of skin cancer and are more easily cured.

Because of the possibility of malignant transformation, any mole that undergoes a change warrants immediate medical attention. The changes to observe and report are changes in size, thickness, or color; itching; and bleeding.

Skin Cancer

Skin cancer represents the most common malignancy in white-skinned people in the Western world.[64] The majority of skin cancers are nonmelanomas, either basal cell or squamous cell carcinoma. Although melanoma represents a small subset of skin cancers, it is the most deadly. Not only is melanoma more deadly, but also its incidence is increasing faster than any other malignancy.[65] The rising incidence of melanoma and other skin cancer has been attributed to increased sun exposure associated with social and lifestyle changes.

The factors linking sun exposure to skin cancer are not completely understood, but both total cumulative exposure and altered patterns of exposure are strongly implicated. Basal cell and squamous cell carcinomas are often associated with total cumulative exposure to UV radiation. Thus, basal cell and squamous cell carcinomas occur more commonly on maximally sun-exposed parts of the body, such as the face and back of the hands and forearms. Melanomas occur most commonly on areas of the body that are exposed to the sun intermittently, such as the back in men and the lower legs in women.[64] They are more common in persons with indoor occupations whose exposure to sun is limited to weekends and vacations. Excessive childhood sun exposure is an important risk factor for melanoma, particularly blistering sunburns.

Malignant Melanoma

Malignant melanoma is a malignant tumor of the melanocytes.[11,12,64–68] It is a rapidly progressing, metastatic form of cancer. The dramatic increase in the incidence of malignant melanoma over the past several decades has been credited to increased UV light exposure, including tanning salons. Other risk factors include a family history of malignant melanoma, fair hair and skin, tendency to freckle, and a history of blistering sunburns as a child. Still other significant risk factors for melanoma are atypical moles/dysplastic nevus syndrome, immunosuppression, and prior PUVA therapy.

Roughly 90% of malignant melanomas in whites occur on sun-exposed skin. However, in darker-skinned people melanomas often occur on non–sun-exposed areas, such as the mucous membranes and subungual, palmar, and plantar surfaces. Malignant melanomas differ in size and shape. Usually, they are slightly raised and black or brown. Borders are irregular and surfaces are uneven. Most appear to arise from preexisting nevi or new molelike growths (Fig. 46-24). There may be surrounding erythema, inflammation, and tenderness. Periodically, melanomas ulcerate and bleed. Dark melanomas are often mottled with shades of red, blue, and white. These three colors represent three concurrent processes: melanoma growth (blue), inflammation and the body's attempt to localize and destroy the tumor (red), and scar tissue formation (white).

Four types of melanomas have been identified based on their radial and vertical growth progression: lentigo maligna, superficial spreading, acral lentiginous, and nodular.[11] Radial growth describes the horizontal spread of the melanoma within the epidermis and superficial

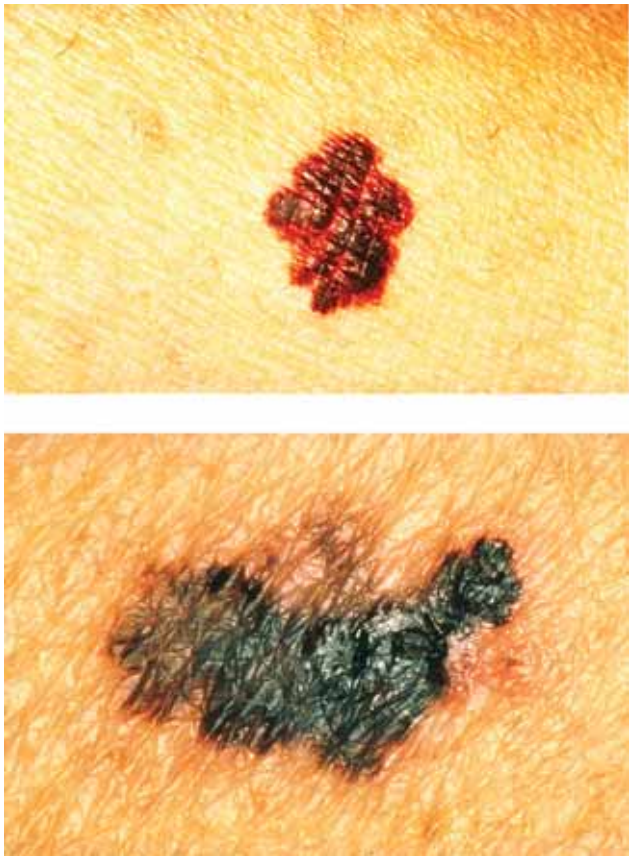


FIGURE 46-24. Melanoma lesions, demonstrating the ABCD rule: A (asymmetry), B (irregular borders), C (different colors), and D (diameter change in size). (From National Cancer Institute Visuals. [Online] Available: http://visualsonline.cancer.gov/browseaction.cfm?topicid=g11.)

dermis. During this initial stage, the tumor seems to lack the ability to metastasize. Lentigo maligna melanomas, superficial spreading melanomas, and acral lentiginous melanomas are tumors that are in the radial growth phase. *Lentigo maligna melanomas* are flat slow-growing nevi that may remain in the radial growth phase for several decades. They are seen primarily on sun-exposed skin of elderly persons. *Superficial spreading melanoma,* the most common type of melanoma, is seen most commonly in persons who sunburn easily and have intermittent sun exposure. It is characterized by a raised-edged nevus with lateral growth and a disorderly appearance in color and outline. It typically ulcerates and bleeds with growth. *Acral lentiginous melanoma* has an appearance similar to that of lentigo maligna, and is seen primarily on the palms, soles, nail beds, and mucous membranes. It occurrence is unrelated to sun exposure.

After a variable and unpredictable period of time, melanomas shift from a radial to vertical growth phase, during which the tumor cells invade downward into the deeper dermis layers.[11] This growth phase is heralded by the nodular phase and correlates with the emergence of a clone of cells with metastatic potential. *Nodular melanomas* are raised, dome-shaped lesions that can occur anywhere on the body. They are commonly a uniform blue-black color and tend to look like blood blisters. Nodular melanomas tend to rapidly invade the dermis from the start, with no apparent horizontal growth phase.

Early detection is critical with malignant melanoma. Regular self-examination of the total skin surface in front of a well-lighted mirror provides a method for early detection. It requires that a person undress completely and examine all areas of the body using a full mirror, handheld mirror, and handheld hair dryer (to examine the scalp). An *ABCD* rule has been developed to aid in early diagnosis and timely treatment of malignant melanoma.[68] The acronym stands for *a*symmetry, *b*order irregularity, *c*olor variegation, and *d*iameter greater than 6 mm (1/4 inch or pencil eraser size). People should be taught to watch for these changes in existing nevi or the development of new nevi, as well as other alterations such as bleeding or itching. Because of the existence of small-diameter melanomas (i.e., <6 mm in diameter), it has been suggested that people routinely screen their skin for all possible manifestations of skin cancer. Since their description over 20 years ago, evidence has accumulated to add an E for "evolving" to the ABCD rule.[68] The E for evolving is intended to encourage the recognition of melanomas at an earlier stage by emphasizing the dynamic nature of their growth.

Diagnosis of melanoma is based on biopsy findings from a lesion.[11,64,65,67] Because most melanomas initially metastasize to regional lymph nodes, additional information may be obtained through lymph node biopsy. Consistent with other cancerous tumors, melanoma is commonly staged using the TNM (tumor, lymph node, and metastasis) staging system (see Chapter 7) or the American Joint Committee on Cancer Staging System for Cutaneous Melanoma, in which the tumor is rated 0 to 4, depending on numerous factors, including extent of tumor invasion, ulceration, and metastasis.[11] Ulceration and invasion of the tumor into the deeper skin tissue result in a poorer prognosis. The degree and number of lymph nodes involved correlate well with overall survival.

Treatment of melanoma is usually surgical excision, the extent of which is determined by the thickness of the lesion, invasion into the deeper skin layers, and spread to the regional lymph nodes.[64,65,67] Deep, wide excisions with elective removal of lymph tissue and the use of skin grafts were once the hallmarks of treatment. When diagnosed in a premetastatic phase, melanoma is now treated in ambulatory settings, lessening the cost and inconvenience of care. Current capability allows for mapping lymph flow to a regional lymph node that receives lymphatic drainage from tumor sites on the skin. This lymph node, which is called the *sentinel lymph node,* is then sampled for biopsy. If tumor cells have spread from the primary tumor to the regional lymph nodes, the sentinel node will be the first node in which tumor cells appear. Therefore, sentinel node biopsy can be used to test for the presence of melanoma cells and determine if radical lymph node dissection is necessary. When nodes are positive, consideration is also given to systemic adjuvant

therapy. Although no effective chemotherapy is available for melanoma, interferon alfa-2b is a biologic therapy available for adjuvant treatment of melanoma. At this time, however, the use of interferon is controversial. Clinical trials with other therapies, including combination chemotherapies, vaccines, and hyperthermic isolation limb perfusion, are ongoing.[64,65,67]

Basal Cell Carcinoma

Basal cell carcinoma is a neoplasm of the nonkeratinizing cells of the basal layer of the epidermis.[11,69] It is the most common invasive cancer in humans, with nearly 1 million estimated new cases each year in the United States.[11] Basal cell carcinomas have a tendency to occur in fair-skinned persons with a history of significant long-term sun exposure. They are most frequently seen on the head and neck, most often occurring on skin that has hair.

Basal cell carcinomas are slow-growing tumors that extend wide and deep if left untreated, but rarely metastasize. Advanced lesions are often present as invasive and ulcerative lesions. Risk factors for extensive spread include a tumor diameter greater than 2 cm, location on the central part of the face or ears, long-standing duration, incomplete excision, and perineural or perivascular involvement.

Histologically, the tumor cells resemble those in the normal basal layer from the epidermis or follicular epithelium and do not occur on mucosal surfaces.[11,69] There are two types of basal cell carcinoma, determined by their pattern of growth: superficial basal cell carcinomas originating from the epidermis and extending upward, and nodular basal cell carcinomas in which the tumor grows downward into the dermis. *Nodular basal cell carcinoma,* the classic type, presents as a small, flesh-colored or pink, smooth, translucent nodule that enlarges over time (Fig. 46-25). Telangiectatic vessels frequently are seen beneath the surface. Over the years, there is a central depression that forms and develops into an ulcer surrounded by the original shiny, waxy border. *Superficial basal cell carcinoma* presents as a scaly erythematous patch or plaque. Both nodular and superficial forms may contain melanin, imparting a brown, blue, or black color to the lesions.

Since basal cell carcinoma is highly curable if detected and treated early, all suspected lesions should undergo biopsy for diagnosis. The treatment depends on the site and extent of the lesion. The most important treatment goal is complete elimination of the lesion. Also important is the maintenance of function and optimal cosmetic effect. Curettage with electrodesiccation, surgical excision, irradiation, laser, cryosurgery, and chemosurgery are effective in removing all cancerous cells. Immune therapy, gene therapy, and photodynamic therapy are emerging treatments. Persons should be checked at regular intervals for recurrences.

FIGURE 46-25. Nodular basal cell carcinoma, which presents as a reddish-brown papule, often with telangiectatic blood vessels, and a central depression with rolled borders. (From National Cancer Institute Visuals. [Online]

Squamous Cell Carcinoma

Squamous cell carcinomas are the second most common malignant tumors arising on sun-exposed sites in older people, exceeded only by basal cell carcinoma. The increase in the incidence of squamous cell carcinomas is consistent with increased UV exposure. There is also a strong occupational hazard link to the development of squamous cell carcinoma: persons exposed to arsenic (i.e., Bowen disease), industrial tars, coal, and paraffin have an increased likelihood of contracting squamous cell carcinoma. Men are twice as likely as women to have squamous cell carcinoma. Black persons are rarely affected.

Squamous cell cancers are composed of tumor cells that resemble the epidermal cells of the stratum spinosum to varying degrees and extend into the adjacent dermis.[11,70] There are two types of squamous cell carcinoma: intraepidermal (termed in situ carcinoma) and invasive carcinoma. *Intraepidermal squamous cell carcinoma* remains confined to the epidermis for a long time. However, at some unpredictable time, it penetrates the basement membrane to the dermis and metastasizes to the regional lymph nodes. It then converts to *invasive squamous cell carcinoma.* The invasive type of squamous cell carcinoma can develop from intraepidermal carcinoma or from a premalignant lesion (e.g., actinic keratoses). It may be slow growing or fast growing with metastasis.

Squamous cell carcinoma is a red-scaling, keratotic, slightly elevated lesion with an irregular border, usually

FIGURE 46-26. Squamous cell carcinoma of the right ear. This lesion is 1.2 × 0.7 in diameter. It was treated with micrographic surgery because of its location at a site associated with high risk and its history of rapid growth. (From Alam M., Ratner D. [2001]. Cutaneous squamous-cell carcinoma. *New England Journal of Medicine* 344[15], 980.)

with a shallow chronic ulcer (Fig. 46-26). The lesions usually lack the pearly rolled border and superficial telangiectases found on basal cell carcinomas. Later, lesions grow outward, show large ulcerations, and have persistent crusts and raised erythematous borders. The lesions occur on sun-exposed areas of the skin, particularly the nose, forehead, helix of the ear, lower lip, and back of the hand. Invasive squamous cell carcinoma has the potential to recur and metastasize. Chief among the risk factors for tumor recurrence and metastasis are the size and location of the tumor.[70] Large lesions (>2 cm in diameter), tumors of the lip and ear, tumors arising in injured or chronically diseased skin, and rapidly growing lesions are at particular risk.

Treatment measures are aimed at the removal of all cancerous tissue using methods such as electrosurgery, excision surgery, chemosurgery, or radiation therapy. After treatment, the person is observed for the remainder of his or her life for signs of recurrence.

In summary, nevi or moles usually are benign neoplasms of the skin. Because they may undergo cancerous transformation, any mole that undergoes a change warrants immediate medical attention. There has been an alarming increase in skin cancers over the past few decades. Repeated exposure to the UV rays of the sun has been implicated as the principal cause of skin cancer.

Malignant neoplasms of the skin include melanoma, basal cell carcinoma, and squamous cell carcinoma. Malignant melanoma is a malignant tumor of the melanocytes. It is a rapidly progressing, metastatic form of cancer. Clinically, malignant melanoma of the skin usually is asymptomatic. The most important clinical sign is the change in size, shape, and color of pigmented skin lesions, such as moles. As the result of increased public awareness, melanomas are being diagnosed at an earlier stage, when they can be cured surgically. Squamous cell carcinoma and basal cell carcinoma are of epidermal origin.

Basal cell carcinoma, which is a neoplasm of the nonkeratinizing cells of the basal layer of the epidermis, is the most common skin cancer in light-skinned people. They are slow-growing tumors that rarely metastasize. Squamous cell cancers are composed of tumor cells that resemble the epidermal cells of the stratum spinosum to varying degrees and extend into the adjacent dermis. Squamous cell carcinoma may remain confined to the epidermis for a period of time, but at some unpredictable time, it becomes invasive and metastasizes to the regional lymph nodes. Chief among the risk factors for tumor invasion and metastasis are the size and location of the tumor. Large lesions (>2 cm in diameter), tumors of the lip and ear, tumors arising in injured or chronically diseased skin, and rapidly growing lesions are at particular risk.

Age-Related Skin Manifestations

Skin Manifestations of Infancy and Childhood

Skin Disorders of Infancy

Infancy connotes the image of perfect, unblemished skin. For the most part, this is true. However, several congenital skin lesions, such as mongolian spots, hemangiomas, and nevi, are associated with the early neonatal period. There are also several acquired skin conditions, including diaper dermatitis, prickly heat, and cradle cap, that are relatively common in infants.

Diaper Dermatitis. Irritant diaper dermatitis, or *diaper rash,* is a form of contact dermatitis caused by the interaction of several factors, including prolonged contact of the skin with a mixture of urine and feces.[49,71] The appearance of diaper rash ranges from simple (i.e., widely distributed macules on the buttocks and anogenital areas) to severe (i.e., beefy, red, excoriated skin surfaces in the diaper area). Secondary infections with bacteria and yeasts are common; discomfort may be marked because of intense inflammation. Such conditions as contact dermatitis, seborrheic dermatitis, candidiasis, and atopic dermatitis should be considered when the eruption is persistent and recalcitrant to simple therapeutic measures.

Diaper dermatitis often responds to simple measures, including frequent diaper changes with careful cleansing of the irritated area to remove all waste products. Feces in particular should be removed from the skin as soon as possible after the diaper has been soiled. Because soap and lipid solvents remove protective lipids from the stratum corneum, using water or an alcohol-free baby wipe is recommended. Exposing the irritated area to air is helpful. It has been shown that application of a barrier ointment after each diaper change is a valuable component of therapy. Topical corticosteroid therapy is usually effective, but should be used cautiously because infants absorb proportionately greater quantities through their skin than adults. Antifungal therapy should not be used routinely, only when *Candida* infection is established or suspected. Antibacterial agents should not be used because it is known that bacterial infections are usually not involved in diaper dermatitis, and the normal microflora should be preserved.

Intractable and severe cases of diaper dermatitis should be seen by a health care provider for treatment of any secondary infections. Secondary candidal or other skin manifestations discussed in this chapter may occur in the diaper area. It is important to differentiate between normal diaper dermatitis and more serious skin problems.

Prickly Heat. Prickly heat (heat rash) results from constant maceration of the skin because of prolonged exposure to a warm, humid environment. Maceration leads to midepidermal obstruction and rupture of the sweat glands (Fig. 46-27). Although commonly seen during infancy, prickly heat may occur at any age. The treatment includes removing excessive clothing, cooling the skin with warm water baths, drying the skin with powders, and avoiding hot, humid environments.

Cradle Cap. Cradle cap is a greasy crust or scale formation on the scalp. It usually is attributed to infrequent and inadequate washing of the scalp. Cradle cap is treated using mild shampoo and gentle combing to remove the scales. Sometimes oil can be left on the head for minutes to several hours, softening the scales before scrubbing. Other emulsifying ointments or creams may be helpful in difficult cases. The scalp may need to be rubbed firmly to remove the buildup of keratinized cells. Recalcitrant cases need to be seen by a health care practitioner; serious or chronic forms of seborrheic dermatitis may exist.

FIGURE 46-27. Prickly heat in a 6-week-old infant. (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 441]. Philadelphia: Lippincott Williams & Wilkins.)

Pigmented and Vascular Birthmarks

Pigmented birthmarks represent abnormal migration or proliferation of melanocytes. For example, *mongolian spots* are caused by selective pigmentation. They usually occur on the buttocks or sacral area and are seen commonly in Asian and black persons. *Nevi* or moles are small, tan to brown, uniformly pigmented solid macules. *Melanocytic nevi* are formed initially from aggregates of melanocytes and keratinocytes along the dermal–epidermal border. *Congenital melanocytic nevi* are collections of melanocytes that are present at birth or develop within the first year of life. They present as macular, papular, or plaquelike pigmented lesions of various shades of brown, with a black or blue focus. The texture of the lesions varies and they may be with or without hair. They usually are found on the hands, shoulders, buttocks, entire arm, or trunk of the body. Some involve large areas of the body in garmentlike fashion. They usually grow proportionately with the child. Congenital melanocytic nevi are clinically significant because of their association with malignant melanoma.

Vascular birthmarks are cutaneous anomalies of angiogenesis and vascular development.[72,73] Two types of vascular birthmarks commonly are seen in infants and small children: bright red, raised hemangiomas of infancy and flat, reddish-purple port-wine stains.

Hemangiomas of infancy (formerly called *strawberry hemangiomas*) are small, red lesions that are noticed shortly after birth.[49,72] Hemangiomas of infancy are generally benign vascular tumors produced by proliferation of endothelial cells. They are seen in approximately 10% of children in the first year of life, with about 60% being located on the head and neck.[72] Although they can occur anywhere on the body, they can be life-threatening when they occur in the airway. Approximately 30% of these lesions are present at birth, and the remainder develop within a few weeks after birth.[72] Hemangiomas of infancy typically undergo an early period of proliferation during which they enlarge, followed by a period of slow involution during which the growth is reversed until complete resolution. Most hemangiomas of infancy disappear before 5 to 9 years of age without leaving an appreciable scar. A small percentage of hemangiomas develop complications. Ulceration, the most frequent complication, can be painful and carries the risk of infection, hemorrhage, and scarring. Some are located in anatomic regions associated with other anomalies requiring careful monitoring and early intervention.

FIGURE 46-28. Port-wine stain on the face of a boy. (Ortho Dermatology Corp.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 280]. Philadelphia: Lippincott Williams & Wilkins.)

Port-wine stains are pink or red patches that can occur anywhere on the body and are very noticeable (Fig. 46-28). They represent slow-growing capillary malformations that grow proportionately with the child and persist throughout life.[49] There is progressive dilation of the dermal capillaries, which initially is confined to the immediate epidermis, with gradual involvement of deeper dermal blood vessels, although the greater number is always in the upper dermis. Distribution of lesions on the face roughly corresponds to the sensory branches of the trigeminal nerve. The development of a port-wine stain may follow trauma. Port-wine stains usually are confined to the skin, but may be associated with vascular malformations of the eye, resulting primarily in glaucoma, or leptomeningeal involvement, leading to cognitive disorders, seizures, and other neurologic deficits (Sturge-Weber syndrome). Cover-up cosmetics are used in an attempt to conceal the disfiguring effects. Laser surgery has revolutionized the treatment of port-wine stains.

Skin Manifestations of Common Infectious Diseases

Infectious childhood diseases that produce rashes include exanthem subitum, rubella, rubeola, varicella, and scarlet fever.[49,74] Although these diseases are seen less frequently because of successful immunization programs and the use of antibiotics, they still occur. Because they are seen less frequently than in the past, they may be misdiagnosed or their diagnosis may be delayed.

Roseola Infantum. Roseola infantum (exanthem subitum or sixth disease) is a contagious disease caused by human herpes virus type 6 (HHV-6), and less frequently HHV-7. Because HHV-6 is the etiologic agent, the condition is often referred to as *sixth disease*. Primary HHV-6 infection occurs early in life. More than 95% of roseola cases occur in children younger than 3 years of age, with a peak at 6 to 15 months of age.[75] Transplacental antibodies likely protect most infants until 6 months of age. Roseola produces a characteristic maculopapular rash covering the trunk and spreading to the appendages. The rash is preceded by an abrupt onset of high fever (≤105°F), inflamed tympanic membranes, and coldlike symptoms usually lasting 3 to 4 days. These symptoms improve at approximately the same time the rash appears. Because infants with roseola exhibit a unique constellation of symptoms over a short time, the infection may be confused with other childhood exanthems. Blood antibody titers may be taken to determine the actual diagnosis. In most cases, there are no long-term effects from this disease. Infants who spike high temperatures should be seen by their health care providers.

Rubella. Rubella (i.e., 3-day measles or German measles) is a childhood disease caused by the rubella virus.[49,74] It is characterized by a diffuse, punctate, macular rash that begins on the trunk and spreads to the arms and legs (Fig. 46-29). Mild febrile states occur (usually <100°F). Postauricular, suboccipital, and cervical lymph node adenopathy is common. Coldlike symptoms usually accompany the disease in the form of cough, congestion, and coryza (i.e., nasal discharge).

Rubella usually has no long-lasting sequelae; however, the transmission of the disease to pregnant women early in their gestation periods may result in congenital rubella syndrome. Among the clinical signs of congenital

FIGURE 46-29. Rash of rubella on a child's back. Distribution is similar to measles (rubeola), but not as intense. (From Centers for Disease Control and Prevention Public Health Image Library. [Online] Available: http://phil.cdc.gov/Phil/home.asp.)

rubella syndrome are cataracts, microcephaly, mental retardation, deafness, patent ductus arteriosus, glaucoma, purpura, and bone defects. Most states have laws requiring immunization to prevent transmission of rubella. Immunization is accomplished by live-virus injection. Rubella vaccination has close to a 100% immunity response in treated children. Many states require a second preschool or later dose of rubella vaccine to increase immunity. Cases and outbreaks of rubella occur in the United States, especially among foreign-born unvaccinated adults.

Rubeola. Rubeola (measles, 7-day measles) is an acute, highly communicable viral disease caused by a morbillivirus.[49,74] The characteristic rash is macular and blotchy; sometimes the macules become confluent (Fig. 46-30). The rubeola rash usually begins on the face and spreads to the appendages. There are several accompanying symptoms: a fever of 100°F or greater, *Koplik spots* (i.e., small, irregular red spots with a bluish-white speck in the center) on the buccal mucosa, and mild to severe photosensitivity. The patient commonly has coldlike symptoms, general malaise, and myalgia. In severe cases, the macules may hemorrhage into the skin tissue or onto the outer body surface. This form is called *hemorrhagic measles*. The course of measles is more severe in infants, adults, and malnourished children. The World Health Organization recommends vitamin A treatment for measles in developing countries to reduce morbidity and mortality. There may be severe complications, including otitis media, pneumonia, and encephalitis. Antibody titers are determined for a conclusive diagnosis of rubeola. Measles is a disease preventable by vaccine, and immunization is required by law in the United States.

FIGURE 46-30. Child with measles (rubeola) showing the characteristic conjunctivitis, coryza, and red, blotchy rash that appear around day 3 of illness, first on the face and then becoming more generalized. (From Centers for Disease Control and Prevention Public Health Image Library.

FIGURE 46-31. Blisterlike lesions of varicella (i.e., chickenpox) on the face of a young child. (From Centers for Disease Control and Prevention Public Health Image Library.

Varicella. Varicella (chickenpox) is a common communicable childhood disease. It is caused by the varicella-zoster virus, which also is the agent in herpes zoster (shingles). The characteristic skin lesion occurs in three stages: macule, vesicle, and granular scab.[49,74] The macular stage is characterized by development within hours of macules over the trunk, spreading to the limbs, buccal mucosa, scalp, axillae, upper respiratory tract, and conjunctiva (Fig. 46-31). During the second stage, the macules form vesicles with depressed centers. The vesicles break open and a scab forms during the third stage. Crops of lesions occur successively, so that all three forms of the lesion usually are visible by the third day of the illness.

Mild to extreme pruritus accompanies the lesions, which can lead to scratching and subsequent development of secondary bacterial infections. Chickenpox also is accompanied by coldlike symptoms, including cough, coryza, and sometimes photosensitivity. Mild febrile states usually occur, typically beginning 24 hours before lesion outbreak. Side effects, such as pneumonia, septic complications, and encephalitis, are rare.

Varicella in adults may be more severe, with a prolonged recovery rate and greater chances for development of varicella pneumonitis or encephalitis. Immunocompromised persons may experience a chronic, painful form of the infection.

Live attenuated varicella vaccine has been demonstrated to have a lower efficacy than vaccines for rubella and rubeola in preventing the disease. There has been a dramatic decrease in varicella morbidity and mortality since 1995, when the varicella vaccine was introduced in the United States. However, outbreaks of mild cases of varicella, called *breakthrough varicella,* have occurred in vaccinated populations. The breakthrough infection is difficult to diagnose because the maculopapular rash does not have the classic sign of vesicles. One dose of the vaccine is required by law in the United States; however, a second dose is now recommended to address what is called *primary vaccine failure*. It is believed that a single dose of varicella vaccine

may only prime the host response, without inducing protective immunity.[76]

Skin Manifestations and Disorders in the Elderly

Elderly persons experience a variety of age-related skin disorders and exacerbations of earlier skin problems. Aging skin is believed to involve a complex process of actinic (solar) damage, normal aging, and hormonal influences. Actinic changes primarily involve increased occurrence of lesions on sun-exposed surfaces of the body.

Normal Age-Related Changes

Normal skin changes associated with aging are seen on areas of the body that have not been exposed to the sun.[77,78] They include thinning of the dermis and the epidermis, diminution in subcutaneous tissue, a decrease and thickening of blood vessels, and a decrease in the number of melanocytes, Langerhans cells, and Merkel cells. The keratinocytes shrink, but the number of dead keratinized cells at the surface increases. This results in less padding and thinner skin, with color and elasticity changes. The skin also loses its resistance to environmental and mechanical trauma. Tissue repair takes longer.

With aging, there is also less hair and nail growth, and there is permanent hair pigment loss. Hormonally, there is less sebaceous gland activity, although the glands in the facial skin may increase in size. Hair growth reduction also may be hormonally influenced. Although the reason is poorly understood, the skin in most elderly persons older than 70 years of age becomes dry, rough, scaly, and itchy. When there is no underlying pathologic process, it is called *senile pruritus*. Itching and dryness become worse during the winter, when the need for home heating lowers the humidity.

The aging of skin, however, is not just a manifestation of age itself. Most skin changes associated with the elderly are the result of cumulative actinic or environmental damage. For example, the wrinkled, leathery look of aged skin, as well as odd scars and ecchymotic spots, are due to solar elastotic degenerative change.

Skin Lesions Common Among the Elderly

Among the most common benign skin lesions in the elderly are skin tags, seborrheic keratoses, solar lentigines, and vascular lesions.[78] Most are actinic manifestations; they occur as a result of exposure to sun and weather over the years.

Skin Tags. *Skin tags* are soft, brown or flesh-colored papules. They occur on any skin surface, but most frequently the neck, axilla, and intertriginous areas. They range in size from a pinhead to the size of a pea. Skin tags have the normal texture of the skin. They are benign and can be removed with scissors or electrodesiccation for cosmetic purposes.

FIGURE 46-32. Large seborrheic keratoses on the hand of an 84-year-old woman. (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 409]. Philadelphia: Lippincott Williams & Wilkins.)

Seborrheic Keratosis. A keratosis is a circumscribed overgrowth of the horny layer of keratinocytes. *Seborrheic keratoses* are common benign tumors that arise spontaneously and are particularly numerous on the trunk, although they can also occur on the extremities, head, and neck. In people of color, multiple small lesions on the face are termed dermatoses papulosa nigra. The lesions characteristically appear as round, flat, coin-shaped waxy plaques that vary in diameter from a few millimeters to several centimeters in diameter (Fig. 46-32). Seborrheic keratoses are benign, but they must be watched for changes in color, texture, or size, which may indicate malignant transformation.

Actinic Keratosis. *Actinic keratoses* are the most common premalignant skin lesions that develop on sun-exposed areas. The lesions usually are less than 1 cm in diameter and appear as dry, brown, scaly areas, often with a reddish tinge. Actinic keratoses often are multiple and more easily felt than seen (Fig. 46-33). They often are indistinguishable from squamous cell carcinoma without biopsy. Actinic keratoses may accumulate dense scale on the surface of the skin and become hyperkeratotic (i.e., developing cutaneous growths of fingernail-type tissue that grow into hornlike appendages). This form is more prominent and palpable. Often, there is a weathered appearance to the surrounding skin. Slight changes, such as enlargement or ulceration, may indicate malignant transformation. Roughly 20% of actinic keratoses convert to squamous cell carcinomas. There is controversy regarding the classification of actinic keratoses. Some believe them to be capable of converting to cancerous growths,[79] some believe them to be on a continuum of cancerous growth,[80] and still others believe that actinic keratoses do not convert or progress to cancerous cells, but that they are actual early malignancies.[81]

Actinic keratoses are removed with cryosurgery, electrodesiccation, or lasers. When surgery is not indicated,

FIGURE 46-33. Multiple actinic keratoses of the face of an 80-year-old man. (Dermik Laboratories, Inc.) (From Hall J.C. [2006]. *Sauer's manual of skin diseases* [9th ed., p. 277]. Philadelphia: Lippincott Williams & Wilkins.)

they are treated with topical chemotherapy agents, such as 5-fluorouracil or imiquimod creams, which erode the lesions.

Solar Lentigines. Lentigines are small (5- to 10-mm), benign, oval or round, tan-brown macules or patches resulting from localized hyperplasia of melanocytes. *Solar lentigines,* also referred to as *liver spots,* are tan to brown, benign spots that gradually appear on sun-exposed areas, particularly the dorsum of the hand. They do not fade with cessation of sun exposure. Like all pigmented lesions, they should be evaluated. If the pigmentation is homogenous and they are symmetric and flat, they are most likely benign. Solar lentigines can be treated with a topical bleaching agent such as hydroquinone (e.g., Eldoquin, Solaquin), laser therapy, or cryotherapy.

Lentigo maligna (i.e., Hutchinson freckle) is a slowly progressive (≤20 years) preneoplastic disorder of melanocytes. It occurs on sun-exposed areas, particularly the face. The lesion is a pigmented macule with a well-defined border and grows to 5 cm or sometimes larger. As it grows over the years, it may become slightly raised and wartlike. If untreated, a true malignant melanoma often develops. Surgery, curettage, and cryotherapy have been effective at removing the lentigines. Careful monitoring for conversion to melanoma is important.

Vascular Lesions. Vascular lesions include angiomas, telangiectases, and venous lakes. *Cherry angiomas* are smooth, cherry-red or purple, dome-shaped papules that occur in nearly all people older than 30 years of age. They usually are found on the trunk and are generally benign unless there is a sudden appearance of many cherry angiomas. *Telangiectases* are single dilated blood vessels, capillaries, or terminal arteries that appear on areas exposed to sun or harsh weather, such as the cheeks and the nose. They occur individually or in clusters, measure 1 cm or less, are nonpalpable, and easily blanch. They can become large and disfiguring. Pulsed dye lasers have been effective in removing them. *Venous lakes* are small, dark blue, slightly raised papules that have a lake-like appearance. They occur on exposed body parts, particularly the backs of the hands, ears, and lips. They are smooth and compressible. Venous lakes can be removed by electrosurgery, laser therapy, or surgical excision if a person desires.

In summary, some skin problems occur in specific age groups. Common in infants are diaper rash, prickly heat, and cradle cap. Infectious childhood diseases that are characterized by rashes include roseola infantum, rubella, rubeola, and varicella. Vaccines are available to protect against rubella, rubeola, and varicella.

With aging, there is thinning of the dermis and the epidermis, diminution in subcutaneous tissue, loss and thickening of blood vessels, and slowing of hair and nail growth. Dry skin is common among the elderly, becoming worse during the winter months. Among the skin lesions seen in the elderly are skin tags, keratoses, lentigines, and vascular lesions.

REVIEW EXERCISES

1. The mother of a 7-year-old boy notices that he is scratching his head frequently. On close examination she notices a grayish, round, and roughened area, where the hair has broken off. Examination by the child's pediatrician produces a diagnosis of tinea capitis.

- **A.** Explain the cause of the infection and propose possible mechanisms for spread of this infection in school-age children, particularly during winter months.
- **B.** Referring to Chapter 14, explain the preference of the superficial mycoses (dermatophytoses) for the skin-covered areas of the body.
- **C.** What methods are commonly used in the diagnosis of superficial fungal infections?

2. A 75-year-old woman presents with severe burning pain and a vesicular rash covering a strip over the rib cage on one side of the chest. She is diagnosed with herpes zoster or shingles.

- **A.** What is the source of this woman's rash and pain?
- **B.** Explain the dermatomal distribution of the lesions.

3. Psoriasis is a chronically recurring papulosquamous skin disorder, characterized by circumscribed red, thickened plaques with an overlying silvery-white scale.

A. Explain the development of the plaques in terms of epidermal cell turnover.
B. Persons with psoriasis are instructed to refrain from rubbing or scratching the lesions. Explain the rationale for these instructions.
C. Among the methods used in the treatment of psoriasis are the use of topical keratolytic agents and corticosteroid skin preparations. Explain how these two different types of agents exert their effect on the plaque lesions.

4. During the past several decades there has been an alarming increase in the incidence of skin cancers, including malignant melanoma, that has been attributed to increased sun exposure.

A. Explain the possible mechanisms whereby ultraviolet radiation promotes the development of malignant skin lesions.
B. Cite two important clinical signs that aid in distinguishing a dysplastic nevus from a malignant melanoma.

REFERENCES

1. Murray P.R., Rosenthal K.S., Kobayashi G.S., et al. (2002). *Medical microbiology* (4th ed., pp. 639–650). St Louis: Mosby.
2. Hainer B.J. (2003). Dermatophyte infections. *American Family Physician* 67(1), 101–108.
3. Andrews M.D., Burns M. (2008). Common tinea infections in children. *American Family Physician* 77(10), 1415–1420.
4. Weinstein A. (2002). Topical treatment of common superficial tinea infections. *American Family Physician* 65(10), 2095–2102.
5. Habif T.P., Campbell J.L., Chapman M.S., et al. (Eds.). (2005). *Skin disease: Diagnosis and treatment* (pp. 258–261). Philadelphia: Mosby.
6. deBerke D. (2009). Fungal nail infections. *New England Journal of Medicine* 360(20), 2108–2116.
7. Berger T.G. (2009). Dermatologic disorders. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis & treatment* (58th ed., pp. 90–146). New York: McGraw-Hill.
8. Lopez F.A., Lartchenko S. (2006). Skin and soft tissue infections. *Infectious Disease Clinics of North America* 20, 759–772.
9. Cole C.C., Gazewood J. (2007). Diagnosis and treatment of impetigo. *American Family Physician* 75(6), 859–864.
10. Sterling J.C. (2004). Virus infections. In Burns T., Breathnach S., Cox N., et al. (Eds.), *Rook's textbook of dermatology* (7th ed., Vol. 2, p. 25.38). Malden, MA: Blackwell.
11. Lazar A.J.F., Murphy G.F. (2010). The skin. In Kumar V., Abbas A.K., Fausto N., et al. (Eds.), *Robbins and Cotran pathologic basis of disease* (8th ed., pp. 1185–1204). Philadelphia: Saunders Elsevier.
12. Storm C.A., Elder D.E. (2008). The skin. In Rubin R., Strayer D.S. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (5th ed., pp. 999–1056). Philadelphia: Lippincott Williams & Wilkins.
13. Bacelieri R., Johnson S.M. (2005). Cutaneous warts. *American Family Physician* 72(4), 647–652.
14. Fathzadeh M., Swartz R.A. (2007). Human herpes simplex virus infections: Epidemiology, pathogenesis, symptomatology, diagnosis, and management. *Journal American Academy Dermatology* 57, 737–763.
15. Cernik C., Gullina K., Brodell R.T. (2008). The treatment of herpes simplex infections. *Archives of Internal Medicine* 168(11), 1137–1144.
16. Weinberg J.M. (2007). Herpes zoster, natural history, and common complications. *Journal American Academy of Dermatology* 57, S130–S135.
17. Schmader K. (2007). Herpes zoster and postherpetic neuralgia in older adults. *Clinics in Geriatric Medicine* 23, 613–632.
18. Heymann W.R. (2008). The herpes zoster vaccine. *American Academy of Dermatology* 58, 872–873.
19. James W.D. (2005). Acne. *New England Journal of Medicine* 352, 1463–1472.
20. Feldman S., Careccia R.E., Barkham K.L. (2004). Diagnosis and treatment of acne. *American Family Physician* 69, 2123–2130, 2135–2136.
21. Yan A.C. (2006). Current concepts on acne management. *Adolescent Medicine Clinics* 17, 613–637.
22. Zaenglein A.L., Thiboutot D.M. (2006). Expert committee for acne management. *Pediatrics* 138, 1188–1199.
23. Burkhart C.N., Burkhart C.G. (2003). Microbiology's principle of biofilms as a major factor in the pathogenesis of acne vulgaris. *International Journal of Dermatology* 42, 925–927.
24. Powell F.C. (2005). Rosacea. *New England Journal of Medicine* 352(8), 793–803.
25. Buechner S.A. (2005). Rosacea: An update. *Dermatology* 210, 100–108.
26. Blount B.W., Pelletter A.L. (2002). Rosacea: A common, yet commonly overlooked, condition. *American Family Physician* 66, 435–442.
27. Bieber T. (2008). Atopic dermatitis. *New England Journal of Medicine* 358 (14), 1483–1494.
28. Boguniewicz M. (2005). Atopic dermatitis: Beyond the itch that rashes. *Immunology and Allergy Clinics of North America* 25, 333–351.
29. Simpson E.L., Hanifin J.M. (2006). Atopic dermatitis. *Medical Clinics of North America* 90, 149–167.
30. Akdis C.A., Akdis M., Bieber T., et al., PRACTALL Consensus Group. (2006). Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy* 61, 969–987.
31. Amar S.M., Dreskin S.C. (2008). Urticaria. *Primary Care Clinics in Office Practice* 35, 141–157.
32. Muller B.A. (2004). Urticaria and angioedema: A practical approach. *American Family Physician* 69, 1123–1128.
33. Kozel M.M.A., Sabroe R.A. (2004). Chronic urticaria. *Drugs* 64, 2615–2636.
34. Roujeau J.G., Sters R.S. (1994). Severe adverse cutaneous reactions to drugs. *New England Journal of Medicine* 331(19), 1271–1284.
35. Khalili B., Bahna S.L. (2006). Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Annals of Allergy, Asthma, & Immunology* 97, 272–281.
36. Schön M.P., Boehncke W-H. (2005). Psoriasis. *New England Journal of Medicine* 352(18), 1899–1912.
37. Nestle F.O., Kaplan D.H., Barker J. (2009). Psoriasis. *New England Journal of Medicine* 361(15), 496–509.
38. Lebwohl M. (2003). Psoriasis. *Lancet* 363, 1197–1204.
39. Lowes M.A., Lew W., Krueger J.G. (2004). Current concepts in the immunopathogenesis of psoriasis. *Dermatology Clinics* 22, 349–369.
40. Stulberg D.L., Wolfrey J. (2004). Pityriasis rosea. *American Family Physician* 69, 87–94.
41. Katta R. (2000). Lichen planus. *American Family Physician* 61, 3319–3328.

42. Svobodova A., Wlterova D., Vostalova J. (2006). Ultraviolet light induced alterations to the skin. *Biomedical Publications Medical Faculty Polacky Olomonac Czech Republic* 150(1), 25–38.
43. Marrot L., Meunier J-R. (2008). Skin DNA photodamage and its biological consequences. *Journal American Academy Dermatology* 58(5), 39–48.
44. Moyal D., Fourtanier A. (2004). Acute and chronic effects of UV on skin: What are they and how to study them? In Rigel D.S., Weiss R.A., Lim H.W., et al. (Eds.), *Photoaging* (pp. 15–32). New York: Marcel Dekker.
45. Junkins-Hopkins J.M. (2010). Tanning and skin cancer. *Journal American Academy of Dermatology* 62(3), 854–856.
46. Lim H.W., Thomas L., Rigel D.S. (2004). Photoprotection. In Rigel D.S., Weiss R.A., Lim H.W., et al. (Eds.), *Photoaging* (pp. 73–88). New York: Marcel Dekker.
47. Han A., Mailbach H.E. (2004). Management of acute sunburn. *American Journal of Clinical Dermatology* 5(1), 39–47.
48. Morrison W.L. (2004). Photosensitivity. *New England Journal of Medicine* 350(11), 1111–1117.
49. Behrman R.E., Kliegman R.M, Jenson H.B., et al. (Eds.). (2007). *Nelson textbook of pediatrics* (18th ed., pp. 450–458, 1327–1301, 1366–1372, 1380–1383, 2667–2672, 2693–2694). Philadelphia: Saunders Elsevier.
50. Moelieken B.RW., Nemer J.A. (2009). Disorders due to physical agents. In McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis & treatment* (48th ed., pp. 1376–1379). New York: McGraw-Hill.
51. Gömez R., Cancio L.C. (2007). Management of burn wounds in the emergency department. *Emergency Medical Clinics of North America* 25, 135–146.
52. Ipakichi K., Arbabi S. (2006). Advances in burn critical care. *Critical Care Medicine* 34(9 Suppl), S239–S244.
53. Monafo W.W. (1996). Initial management of burns. *New England Journal of Medicine* 335, 1581–1585.
54. Gordon M., Goodwin C.W. (1997). Initial assessment, management, and stabilization. *Nursing Clinics of North America* 32, 237–249.58.
55. Morgan E.D., Bledsoe S.C., Barker J. (2000). Ambulatory management of burns. *American Family Physician* 62, 2015–2030.
56. Orgill D.P. (2009). Excision and skin grafting of thermal burns. *New England Journal of Medicine* 360(9), 891–901.
57. Parenteau N. (1999). Skin: The first tissue-engineered products. *Scientific American* 280(4), 83–84.
58. Arnold M.C. (2003). Pressure ulcer prevention and management. *AACN Clinical Issues* 14, 411–428.
59. Maklebust J. (2005). Pressure ulcers: The great insult. *Nursing Clinics of North America* 40, 365–389.
60. Bluestein D., Javaheri A. (2008). Pressure ulcers: Prevention, evaluation, and management. *American Family Physician* 78(10), 1186–1196.
61. National Pressure Ulcer Advisory Panel. (2003). *Staging report*. [Online] Available: http://www.npuap.org/archive/positn6.htm. Accessed September 22, 2005.
62. Cannon B.C., Cannon J.P. (2004). Management of pressure ulcers. *American Journal of Health-System Pharmacists* 61, 1895–1905.
63. Naeyaert J.M., Brohez L. (2003). Dysplastic nevi. *New England Journal of Medicine* 349(23), 2233–2240.
64. Rager E.L., Bridgeford E.E. (2005). Cutaneous melanoma: Update on prevention, screening, diagnosis, and treatment. *American Family Physician* 72(2), 269–276.
65. Fritsch P. (2007). Skin diseases in Europe. *European Journal of Dermatology* 17(2), 559–560.
66. Miller A.J., Mihrn M.C. (2006). Melanoma. *New England Journal of Medicine* 355(1), 51–65.
67. Markovic S.N. (2007). Melanoma Study Group Mayo Clinic Cancer Center: Malignant melanoma in the 21st century, part 2: Staging, prognosis, and treatment. *Mayo Clinic Proceedings* 63(4), 490–513.
68. Abbasi N.R., Shaw H.M., Rigel D.S., et al. (2004). Early diagnosis of cutaneous melanoma. *Journal of the American Medical Association* 292, 2771–2776.
69. Rubin A.I., Chen E.H., Ratner D. (2005). Basal-cell carcinoma. *New England Journal of Medicine* 353(21), 3262–3269.
70. Alam M., Ratner D. (2001). Cutaneous squamous-cell carcinoma. *New England Journal of Medicine* 344(13), 975–983.
71. Kazaks E.L., Lane A.T. (2000). Diaper dermatitis. *Pediatric Clinics of North America* 47, 909–918.
72. MacArthur C. J. (2006). Head and neck hemangiomas of infancy. *Current Opinion in Otolaryngology & Head & Neck Surgery* 14, 397–405.
73. Metry D. (2004). Update on hemangiomas of infancy. *Current Opinion in Pediatrics* 16, 373–377.
74. Weisberg S.S. (2007). Measles. Rubella. Varicella infections. *Disease of the Month* 53, 471–477, 515–518, 522–528.
75. Zerr D.M., Meier A.S., Selke S.S., et al. (2005). A population-based study of primary human herpesvirus 6 infection. *New England Journal of Medicine* 352, 753–755.
76. Arvin A., Gershon A. (2006). Control of varicella: Why is a two-dose schedule necessary? *Pediatric Infectious Disease Journal* 25, 475–476.
77. Year M., Gilchrest B.A. (2001). Skin aging postulated mechanisms and consequent changes in structure and function. *Clinics in Geriatric Medicine* 17(4)1–12.
78. Gay C., Thiese M.S. (2003). Geriatric dermatology. *Clinics in Family Practice* 5(3), 771–789.
79. Berman B., Villa A.M., Ramirez C.C. (2006). Mechanisms of action of new treatment modalities for actinic keratosis. *Journal of Drugs in Dermatology* 5, 167–173.
80. Gold M.H., Nestor M.S. (2006). Current treatments of actinic keratosis. *Journal of Drugs in Dermatology* 5(2 Suppl), 17–25.
81. Anwar J., Wrone D.A., Kimyai-Asadi A., et al. (2004). The development of actinic keratosis into invasive squamous cell carcinoma: Evidence and evolving classification schemes. *Clinics in Dermatology* 22, 189–196.

Glossary

Abduction The act of abducting (moving or spreading away from a position near the midline of the body or the axial line of a limb) or the state of being abducted.
Abrasion The wearing or scraping away of a substance or structure, such as the skin, through an unusual or abnormal mechanical process.
Abscess A collection of pus that is restricted to a specific area in tissues, organs, or confined spaces.
Accommodation The adjustment of the lens (eye) to variations in distance.
Acromion The lateral extension of the spine of the scapula, forming the highest point of the shoulder. (Adjective: acromial)
Acuity The clearness or sharpness of perception, especially of vision.
Adaptation The adjustment of an organism to its environment, physical or psychological, through changes and responses to stress of any kind.
Adduction The act of adducting (moving or drawing toward a position near the midline of the body or the axial line of a limb) or the state of being adducted.
Adhesin The molecular components of the bacterial cell wall that are involved in adhesion processes.
Adrenergic Activated by or characteristic of the sympathetic nervous system or its neurotransmitters (i.e., epinephrine and norepinephrine).
Aerobic Growing, living, or occurring only in the presence of air or oxygen.
Afferent Bearing or conducting inward or toward a center, as an afferent neuron.
Agglutination The clumping together of particles, microorganisms, or blood cells in response to an antigen–antibody reaction.
Agonist A muscle whose action is opposed by another muscle (antagonist) with which it is paired; or a drug or other chemical substance that has affinity for or stimulates a predictable physiologic function.
Akinesia An abnormal state in which there is an absence or poverty of movement.
Allele One of two or more different forms of a gene that can occupy a particular locus on a chromosome.
Alveolus A small saclike structure, as in the alveolus of the lung.
Amblyopia A condition of vision impairment without a detectable organic lesion of the eye.
Amine An organic compound containing nitrogen.
Amorphous Without a definite form; shapeless.
Amphoteric Capable of reacting chemically as an acid or a base.
Ampulla A saclike dilatation of a duct, canal, or any other tubular structure.
Anabolism A constructive metabolic process characterized by the conversion of simple substances into larger, complex molecules.
Anaerobic Growing, living, or occurring only in the absence of air or oxygen.
Analog A part, organ, or chemical having the same function or appearance but differing in respect to a certain component, such as origin or development.
Anaplasia A change in the structure of cells and in their orientation to each other that is characterized by a loss of cell differentiation, as in cancerous cell growth.
Anastomosis The connection or joining between two vessels; or an opening created by surgical, traumatic, or pathologic means.
Androgen Any substance, such as a male sex hormone, that increases male characteristics.
Anergy A state of absent or diminished reaction to an antigen or group of antigens.
Aneuploidy A variation in the number of chromosomes within a cell involving one or more missing chromosomes rather than entire sets.
Aneurysm An outpouching or dilation in the wall of a blood vessel or the heart.
Ankylosis Stiffness or fixation of separate bones of a joint, resulting from disease, injury, or surgical procedure. (Verb: ankylose)
Anorexia Lack or loss of appetite for food. (Adjective: anorexic)
Anoxia An abnormal condition characterized by the total lack of oxygen.
Antagonist A muscle whose action directly opposes that of another muscle (agonist) with which it is paired, or a drug or other chemical substance that can diminish or nullify the action of a neuromediator or body function.
Anterior Pertaining to a surface or part that is situated near or toward the front.
Antigen A substance that generates an immune response by causing the formation of an antibody or reacting with antibodies or T-cell receptors.
Apex The uppermost point, the narrowed or pointed end, or the highest point of a structure, such as an organ.
Aphagia A condition characterized by the refusal or the loss of ability to swallow.
Aplasia The absence of an organ or tissue due to a developmental failure.
Apnea The absence of spontaneous respiration.
Apoptosis A mechanism of programmed cell death, marked by shrinkage of the cell, condensation of chromatin, formation of cytoplasmic blebs, and fragmentation of the cell into membrane-bound bodies eliminated by phagocytosis.
Apraxia Loss of the ability to carry out familiar, purposeful acts or to manipulate objects in the absence of paralysis or other motor or sensory impairment.
Articulation The place of connection or junction between two or more bones of a skeletal joint.
Ascites An abnormal accumulation of serous fluid in the peritoneal cavity.
Asepsis The condition of being free or freed from pathogenic microorganisms.

Astereognosis A neurologic disorder characterized by an inability to identify objects by touch.
Asterixis A motor disturbance characterized by a hand-flapping tremor, which results when the prolonged contraction of groups of muscles lapses intermittently.
Ataxia An abnormal condition characterized by an inability to coordinate voluntary muscular movement.
Athetosis A neuromuscular condition characterized by the continuous occurrence of slow, sinuous, writhing movements that are performed involuntarily. (Adjective: athetoid)
Atopy Genetic predisposition toward the development of a hypersensitivity or an allergic reaction to common environmental allergens.
Atresia The absence or closure of a normal body orifice or tubular organ, such as the esophagus.
Atrophy A wasting or diminution of size, often accompanied by a decrease in function, of a cell, tissue, or organ.
Autocrine A mode of hormone action in which a chemical messenger acts on the same cell that secretes it.
Autophagy Segregation of part of the cell's own damaged cytoplasmic material within a vacuole and its disposal.
Autosome Any chromosome other than a sex chromosome.
Axillary Of or pertaining to the axilla, or armpit.
Bacteremia The presence of bacteria in the blood.
Bactericide An agent that destroys bacteria. (Adjective: bactericidal)
Bacteriostat An agent that inhibits bacterial growth. (Adjective: bacteriostatic)
Ballismus An abnormal condition characterized by violent flailing motions of the arms and, occasionally, the head, resulting from injury to or destruction of the subthalamic nucleus or its fiber connections.
Baroreceptor A type of sensory nerve ending such as those found in the aorta and the carotid sinus that is stimulated by changes in pressure.
Basal Pertaining to, situated at, or forming the base; or the fundamental or the basic.
Benign Not malignant; or of the character that does not threaten health or life.
Bipolar neuron A nerve cell that has a process at each end—an afferent process and an efferent process.
Bolus A rounded mass of food ready to swallow or such a mass passing through the gastrointestinal tract; or a concentrated mass of medicinal material or other pharmaceutical preparation injected all at once intravenously for diagnostic purposes.
Borborygmus The rumbling, gurgling, or tinkling noise produced by the propulsion of gas through the intestine.
Bruit A sound or murmur heard while auscultating an organ or blood vessel, especially an abnormal one.
Buccal Pertaining to or directed toward the inside of the cheek.
Buffer A substance or group of substances that prevents change in the concentration of another chemical substance.
Bulla A thin-walled blister of the skin or mucous membranes greater than 5 mm in diameter containing serous or seropurulent fluid.
Bursa A fluid-filled sac or saclike cavity situated in places in the tissues at which friction would otherwise develop, such as between certain tendons and the bones beneath them.
Cachexia A condition of general ill health and malnutrition, marked by weakness and emaciation.
Calculus A stony mass formed within body tissues, usually composed of mineral salts.
Capsid The protein shell that envelops and protects the nucleic acid of a virus.
Carcinogen Any substance or agent that causes the development or increases the incidence of cancer.
Carpal Of or pertaining to the carpus, or wrist.
Caseation A form of tissue necrosis in which the tissue is changed into a dry, amorphous mass resembling crumbly cheese.
Catabolism A metabolic process through which living organisms break down complex substances to simple compounds, liberating energy for use in work, energy storage, or heat production.
Catalyst A substance that increases the velocity of a chemical reaction without being consumed by the process.
Catecholamines Any one of a group of biogenic amines having a sympathomimetic action and composed of a catechol molecule and the aliphatic portion of an amine.
Caudal Signifying an inferior position, toward the distal end of the spine.
Cellulitis An acute, diffuse, spreading, edematous inflammation of the deep subcutaneous tissues and sometimes muscle, characterized most commonly by an area of heat, redness, pain, and swelling, and occasionally by fever, malaise, chills, and headache.
Cephalic Of or pertaining to the head, or to the head end of the body.
Cerumen The waxlike secretion produced by vestigial apocrine sweat glands in the external ear canal.
Cheilosis A noninflammatory disorder of the lips and mouth characterized by chapping and fissuring.
Chelate A chemical compound composed of a central metal ion and an organic molecule with multiple bonds, arranged in ring formation, used especially in treatment of metal poisoning.
Chemoreceptor A sensory nerve cell activated by chemical stimuli, as a chemoreceptor in the carotid artery that is sensitive to changes in the oxygen content in the blood and reflexly increases or decreases respiration and blood pressure.
Chemotaxis A response involving cell orientation or cell movement that is either toward (positive chemotaxis) or away from (negative chemotaxis) a chemical stimulus.
Chimeric Relating to, derived from, or being an individual possessing one's own immunologic characteristics and that of another individual; a phenomenon that can occur as the result of procedures such as a bone marrow graft.
Chondrocyte Any one of the mature polymorphic cells that form the cartilage of the body.
Chromatid One of the paired threadlike chromosome filaments, joined at the centromere, that make up a metaphase chromosome.

Chromosome Any one of the structures in the nucleus of a cell containing a linear thread of DNA, which functions in the transmission of genetic information.
Chyme The creamy, viscous, semifluid material produced during digestion of a meal that is expelled by the stomach into the duodenum.
Cilia A minute, hairlike process projecting from a cell, composed of nine microtubules arrayed around a single pair. Cilia beat rhythmically to move the cell around in its environment or they move mucus or fluids over the surface.
Circadian Being, having, pertaining to, or occurring in a period or cycle of approximately 24 hours.
Circumduction The active or passive circular movement of a limb or of the eye.
Cisterna An enclosed space, such as a cavity, that serves as a reservoir for lymph or other body fluids.
Clone One or a group of genetically identical cells or organisms derived from a single parent.
Coagulation The process of transforming a liquid into a semisolid mass, especially of blood clot formation.
Coarctation A condition of stricture or contraction of the walls of a vessel.
Cofactor A substance that must unite with another substance in order to function.
Colic Sharp, intermittent abdominal pain localized in a hollow or tubular organ, resulting from torsion, obstruction, or smooth muscle spasm. (Adjective: colicky)
Collagen The protein substance of the white, glistening, inelastic fibers of the skin, tendons, bone, cartilage, and all other connective tissue.
Collateral Secondary or accessory rather than direct or immediate; or a small branch, as of a blood vessel or nerve.
Complement Any one of the complex, enzymatic serum proteins that are involved in physiologic reactions, including antigen–antibody reaction and anaphylaxis.
Confluent Flowing or coming together; not discrete.
Congenital Present at, and usually before, birth.
Conjugate To pair and fuse in conjugation; or a form of sexual reproduction seen in unicellular organisms in which genetic material is exchanged during the temporary fusion of two cells.
Contiguous In contact or nearly so in an unbroken sequence along a boundary or at a point.
Contralateral Affecting, pertaining to, or originating in the opposite side of a point or reference.
Contusion An injury of a part without a break in the skin, characterized by swelling, discoloration, and pain.
Convolution An elevation or tortuous winding, such as one of the irregular ridges on the surface of the brain, formed by a structure being infolded upon itself.
Corpuscle Any small mass, cell, or body, such as a red or white blood cell.
Costal Pertaining to a rib or ribs.
Crepitus A sound or sensation that resembles a crackling or grating noise.
Cutaneous Pertaining to the skin.
Cyanosis A bluish discoloration, especially of the skin and mucous membranes, caused by an excess of deoxygenated hemoglobin in the blood.
Cytokine Any of a class of polypeptide immunoregulatory substances that are secreted by cells, usually of the immune system, that affect other cells.
Cytology The study of cells, including their origin, structure, function, and pathology.
Cytosol Cytoplasm exclusive of membranous components (e.g., mitochondria, endoplasmic reticulum) and nonmembranous insoluble components.
Decibel A unit for expressing the relative power intensity of electric or acoustic signal power that is equal to one tenth of a bel.
Defecation The evacuation of feces from the digestive tract through the rectum.
Deformation The process of adapting in form or shape; also the product of such alteration.
Degeneration The deterioration of a normal cell, tissue, or organ to a less functionally active form. (Adjective: degenerative)
Deglutition The act or process of swallowing.
Degradation The reduction of a chemical compound to a compound less complex, usually by splitting off one or more groups.
Dehydration The condition that results from excessive loss of water from the body tissues.
Delirium An acute, reversible organic mental syndrome characterized by confusion, disorientation, restlessness, incoherence, fear, and often illusions.
Dendrite One of the branching processes that extends and transmits impulses toward a cell body of a neuron. (Adjective: dendritic)
Depolarization The reduction of a cell membrane potential to a less negative value than that of the potential outside the cell.
Dermatome The area of the skin supplied with afferent nerve fibers of a single dorsal root of a spinal nerve.
Desmosome A small, circular, dense area within the intercellular bridge that forms the site of adhesion between intermediate filaments and cell membranes.
Desquamation A normal process in which the cornified layer of the epidermis is shed in fine scales or sheets.
Dialysis The process of separating colloids and crystalline substances in solution, which involves the two distinct physical processes of diffusion and ultrafiltration; or a medical procedure for the removal of urea and other elements from the blood or lymph.
Diapedesis The outward passage of red or white blood corpuscles through the intact walls of the vessels.
Diaphoresis Perspiration, especially the profuse perspiration associated with an elevated body temperature, physical exertion, exposure to heat, and mental or emotional stress.
Diarthrosis A specialized articulation that permits, to some extent, free joint movement. (Adjective: diarthrodial)
Diastole The dilatation of the heart; or the period of dilatation, which is the interval between the second and the first heart sound and is the time during which blood enters the relaxed chambers of the heart from the systemic circulation and the lungs.
Differentiation The act or process in development in which unspecialized cells or tissues acquire more

specialized characteristics, including those of physical form, physiologic function, and chemical properties.

Diffusion The process of becoming widely spread, as in the spontaneous movement of molecules or other particles in solution from an area of higher concentration to an area of lower concentration, resulting in an even distribution of the particles in the fluid.

Dimer A compound or unit formed by the combination of two identical molecules or radicals of a simpler compound. (Adjective: dimeric)

Diopter A unit of measurement of the refractive power of lenses equal to the reciprocal of the focal length in meters.

Diploid Pertaining to an individual, organism, strain, or cell that has two full sets of homologous chromosomes.

Disseminate To scatter or distribute over a considerable area.

Distal Away from or being the farthest from a point of reference.

Diurnal Of, relating to, or occurring in the daytime.

Diverticulum A pouch or sac of variable size occurring naturally or through herniation of the muscular wall of a tubular organ.

Dorsum The back or posterior. (Adjective: dorsal)

Dysgenesis Defective or abnormal development of an organ or part, typically occurring during embryonic development. (Also called dysgenesia.)

Dyslexia A disturbance in the ability to read, spell, and write words.

Dyspepsia The impairment of the power or function of digestion, especially epigastric discomfort following eating.

Dysphagia A difficulty in swallowing.

Dysphonia Any impairment of the voice that is experienced as a difficulty in speaking.

Dysplasia The alteration in size, shape, and organization of adult cell types.

Eburnation The conversion of bone or cartilage, through thinning or loss, into a hard and dense mass with a worn, polished, ivorylike surface.

Ecchymosis A small hemorrhagic spot, larger than a petechia, in the skin or mucous membrane caused by the extravasation of blood into the subcutaneous tissues.

Ectoderm The outermost of the three primary germ layers of the embryo, and from which the epidermis and epidermal tissues, such as nails, hair, and glands of the skin, develop.

Ectopic Relating to or characterized by an object or organ being situated in an unusual place, away from its normal location.

Edema The presence of an abnormal accumulation of fluid in interstitial spaces of tissues. (Adjective: edematous)

Efferent Conveyed or directed away from a center.

Effusion The escape of fluid from blood vessels into a part or tissue, as an exudation or a transudation.

Embolus A mass of clotted blood or other formed elements, such as bubbles of air, calcium fragments, or a bit of tissue or tumor, that circulates in the bloodstream until it becomes lodged in a vessel, obstructing the circulation. (Plural: emboli)

Empyema An accumulation of pus in a cavity of the body, especially the pleural space.

Emulsify To disperse one liquid throughout the body of another liquid, making a colloidal suspension, or emulsion.

Endocytosis The uptake or incorporation of substances into a cell by invagination of its plasma membrane, as in the processes of phagocytosis and pinocytosis.

Endoderm The innermost of the three primary germ layers of the embryo, and from which epithelium arises.

Endogenous Growing within the body; or developing or originating from within the body or produced from internal causes.

Endoscopy The visualization of any cavity of the body with an endoscope.

Enteropathic Relating to any disease of the intestinal tract.

Enzyme A protein molecule produced by living cells that catalyzes chemical reactions of other organic substances without itself being destroyed or altered.

Epiphysis The expanded articular end of a long bone (head) that is separated from the shaft of the bone by the epiphyseal plate until the bone stops growing, the plate is obliterated, and the shaft and the head become united.

Epithelium The covering of the internal and the external surfaces of the body, including the lining of vessels and other small cavities.

Epitope The simplest form of an antigenic determinant that combines with an antibody or a T-cell receptor to cause a specific reaction by an immunoglobulin.

Erectile Capable of being erected or raised to an erect position.

Erythema The redness or inflammation of the skin or mucous membranes produced by the congestion of superficial capillaries. (Adjective: erythematous)

Etiology The study or theory of all factors that may be involved in the development of a disease, including susceptibility of an individual, the nature of the disease agent, and the way in which an individual's body is invaded by the agent; or the cause of a disease.

Eukaryotic Pertaining to an organism with cells having a true nucleus; that is, a highly complex, organized nucleus surrounded by a nuclear membrane containing organelles and exhibiting mitosis.

Euploid Pertaining to an individual, organism, strain, or cell with a balanced set or sets of chromosomes, in any number, that is an exact multiple of the normal, basic haploid number characteristic of the species; or such an individual, organism, strain, or cell.

Evisceration The removal of the viscera from the abdominal cavity, or disembowelment; or the extrusion of an internal organ through a wound or surgical incision.

Exacerbation An increase in the severity of a disease as marked by greater intensity in any of its signs and symptoms.

Exfoliation Peeling and sloughing off of tissue cells in scales or layers. (Adjective: exfoliative)

Exocytosis The discharge of cell particles, which are packaged in membrane-bound vesicles, by fusion of the vesicular membrane with the plasma membrane and subsequent release of the particles to the exterior of the cell.
Exogenous Developed or originating outside the body, as a disease caused by a bacterial or viral agent foreign to the body.
Exophthalmos A marked or abnormal protrusion of the eyeball.
Extension A movement that allows the two elements of any jointed part to be drawn apart, increasing the angle between them, as extending the leg increases the angle between the femur and the tibia.
Extrapyramidal Pertaining to motor systems supplied by fibers outside the corticospinal or pyramidal tracts.
Extravasation A discharge or escape, usually of blood, serum, or lymph, from a vessel into the tissues.
Extubation The process of withdrawing a previously inserted tube from an orifice or cavity of the body.
Exudate Fluid, cells, or other substances that have been slowly exuded or have escaped from blood vessels and have been deposited in tissues or on tissue surfaces.
Fascia A sheet or band of fibrous connective tissue that may be separated from other specifically organized structures, as the tendons, the aponeuroses, and the ligaments.
Febrile Pertaining to or characterized by an elevated body temperature, or fever.
Fibrillation A small, local, involuntary contraction of muscle, resulting from spontaneous activation of a single muscle fiber or of an isolated bundle of nerve fibers.
Fibrin A stringy, insoluble protein formed by the action of thrombin on fibrinogen during the clotting process.
Fibrosis The formation of fibrous connective tissue, as in the repair or replacement of parenchymatous elements.
Filtration The process of passing a liquid through or as if through a filter, which is accomplished by gravity, pressure, or vacuum.
Fimbria Any structure that forms a fringe, border, or edge or the processes that resemble such a structure.
Fissure A cleft or a groove, normal or otherwise, on the surface of an organ or a bony structure.
Fistula An abnormal passage or communication from an internal organ to the body surface or between two internal organs.
Flaccid Weak, soft, and lax; lacking normal muscle tone.
Flatus Air or gas in the intestinal tract that is expelled through the anus. (Adjective: flatulent)
Flexion A movement that allows the two elements of any jointed part to be brought together, decreasing the angle between them, as bending the elbow.
Flora The microorganisms, such as bacteria and fungi, both normally occurring and pathologic, found in or on an organ.
Focal Relating to, having, or occupying a focus.
Follicle A sac or pouchlike depression or cavity.
Fontanel A membrane-covered opening in bones or between bones, such as the soft spot covered by tough membranes between the bones of an infant's incompletely ossified skull.
Foramen A natural opening or aperture in a membranous structure or bone.
Fossa A hollow or depressed area, especially on the surface of the end of a bone.
Fovea A small pit or depression in the surface of a structure or an organ.
Fundus The base or bottom of an organ or the portion farthest from the mouth of an organ.
Ganglion One of the nerve cell bodies, chiefly collected in groups outside the central nervous system. (Plural: ganglia)
Genotype The entire genetic constitution of an individual, as determined by the particular combination and location of the genes on the chromosomes; or the alleles present at one or more sites on homologous chromosomes.
Glia The neuroglia, or supporting structure of nervous tissue.
Globulin One of a broad group of proteins classified by solubility, electrophoretic mobility, and size.
Gluconeogenesis The formation of glucose from any of the substances of glycolysis other than carbohydrates.
Glycolysis A series of enzymatically catalyzed reactions, occurring within cells, by which glucose is converted to adenosine triphosphate (ATP) and pyruvic acid during aerobic metabolism.
Gonad A gamete-producing gland, as an ovary or a testis.
Gradient The rate of increase or decrease of a measurable phenomenon expressed as a function of a second; or the visual representation of such a change.
Granuloma A small mass of nodular granulation tissue resulting from chronic inflammation, injury, or infection. (Adjective: granulomatous)
Hapten A small, nonproteinaceous substance that is not antigenic by itself but that can act as an antigen when combined with a larger molecule.
Haustrum A structure resembling a recess or sacculation. (Plural: haustra)
Hematoma A localized collection of extravasated blood trapped in an organ, space, or tissue, resulting from a break in the wall of a blood vessel.
Hematopoiesis The normal formation and development of blood cells.
Hemianopia Defective vision or blindness in half of the visual field of one or both eyes.
Heterogeneous Consisting of or composed of dissimilar elements or parts; or not having a uniform quality throughout. (Noun: heterogeneity)
Heterophagy The taking into the cell of an exogenous substance by phagocytosis or pinocytosis and the subsequent digestion of the newly formed vacuole by a lysosome.
Heterozygous Having two different alleles at corresponding loci on homologous chromosomes.
Histology The branch of anatomy that deals with the minute (microscopic) structure, composition, and function of cells and tissue. (Adjective: histologic)
Homolog Any organ or part corresponding in function, position, origin, and structure to another organ or part, as the flippers of a seal that correspond to human hands. (Adjective: homologous)

Homozygous Having two identical alleles at corresponding loci on homologous chromosomes.
Humoral Relating to elements dissolved in the blood or body fluids.
Hybridoma A tumor of hybrid cells produced by fusion of normal lymphocytes and tumor cells.
Hydrolysis The chemical alteration or decomposition of a compound into fragments by the addition of water.
Hypercapnia Excess amounts of carbon dioxide in the blood.
Hyperemia An excess or engorgement of blood in a part of the body.
Hyperesthesia An unusual or pathologic increase in sensitivity of a part, especially the skin, or of a particular sense.
Hyperplasia An abnormal multiplication or increase in the number of normal cells of a body part.
Hypertonic A solution having a greater concentration of solute than another solution with which it is compared, hence exerting more osmotic pressure than that solution.
Hypertrophy The enlargement or overgrowth of an organ that is due to an increase in the size of its cells rather than the number of its cells.
Hypesthesia An abnormal decrease of sensation in response to stimulation of the sensory nerves. (Also called hypoesthesia.)
Hypocapnia A deficiency of carbon dioxide in the blood.
Hypotonic A solution having a lesser concentration of solute than another solution with which it is compared, hence exerting less osmotic pressure than that solution.
Hypoxia An inadequate supply of oxygen to tissue that is below physiologic levels despite adequate perfusion of the tissue by blood.
Iatrogenic Induced inadvertently through the activity of a physician or by medical treatment or diagnostic procedures.
Idiopathic Arising spontaneously or from an unknown cause.
Idiosyncrasy A physical or behavioral characteristic or manner that is unique to an individual or to a group. (Adjective: idiosyncratic)
Incidence The rate at which a certain event occurs (e.g., the number of new cases of a specific disease during a particular period of time in a population at risk).
Inclusion The act of enclosing or the condition of being enclosed; or anything that is enclosed.
Indigenous Native, or natural, to the particular country or region where found.
Infarction Necrosis or death of tissues due to local ischemia resulting from obstruction of blood flow.
Inotropic Influencing the force or energy of muscular contractions.
In situ In the natural or normal place; or something, such as cancer, that is confined to its place of origin and has not invaded neighboring tissues.
Interferon Any one of a group of small glycoproteins (cytokines) produced in response to viral infection and which inhibit viral replication.
Interleukin Any of several multifunctional cytokines produced by a variety of lymphoid and nonlymphoid cells, including immune cells, that stimulate or otherwise affect the function of lymphopoietic and other cells and systems in the body.
Interstitial Relating to or situated between parts or in the interspaces of a tissue.
Intramural Situated or occurring within the wall of an organ.
Intrinsic Pertaining exclusively to a part or situated entirely within an organ or tissue.
In vitro A biologic reaction occurring in an artificial environment, such as a test tube.
In vivo A biologic reaction occurring within the living body.
Involution The act or instance of enfolding, entangling, or turning inward.
Ionize To separate or change into ions.
Ipsilateral Situated on, pertaining to, or affecting the same side of the body.
Ischemia Decreased blood supply to a body organ or part, usually due to functional constriction or actual obstruction of a blood vessel.
Juxta-articular Situated near a joint or in the region of a joint.
Juxtaglomerular Near to or adjoining a glomerulus of the kidney.
Karyotype The total chromosomal characteristics of a cell; or the micrograph of chromosomes arranged in pairs in descending order of size.
Keratin A fibrous, sulfur-containing protein that is the primary component of the epidermis, hair, and horny tissues. (Adjective: keratinous)
Keratosis Any skin condition in which there is overgrowth and thickening of the cornified epithelium.
Ketosis A condition characterized by the abnormal accumulation of ketones (organic compounds with a carboxyl group attached to two carbon atoms) in the body tissues and fluid.
Kinesthesia The sense of movement, weight, tension, and position of body parts mediated by input from joint and muscle receptors and hair cells. (Adjective: kinesthetic)
Kyphosis An abnormal condition of the vertebral column, characterized by increased convexity in the curvature of the thoracic spine as viewed from the side.
Lacuna A small pit or cavity within a structure, especially bony tissue; or a defect or gap, as in the field of vision.
Lateral A position farther from the median plane or midline of the body or a structure; or situated on, coming from, or directed towards the side.
Lesion Any wound, injury, or pathologic change in body tissue.
Lethargy The lowered level of consciousness characterized by listlessness, drowsiness, and apathy; or a state of indifference.
Ligament One of many predominantly white, shiny, flexible bands of fibrous tissue that binds joints together and connects bones or cartilages.
Ligand A group, ion, or molecule that binds to the central atom or molecule in a chemical complex.

Lipid Any of the group of fats and fatlike substances characterized by being insoluble in water and soluble in nonpolar organic solvents, such as chloroform and ether.
Lipoprotein Any one of the conjugated proteins that is a complex of protein and lipid.
Lobule A small lobe.
Lordosis The anterior concavity in the curvature of the lumbar and cervical spine as observed from the side.
Lumen A cavity or the channel within a tube or tubular organ of the body.
Luteal Of or pertaining to or having the properties of the corpus luteum.
Lysis Destruction or dissolution of a cell or molecule through the action of a specific agent.
Maceration Softening of tissue by soaking, especially in acidic solutions.
Macroscopic Large enough to be visible with the unaided eye or without the microscope.
Macula A small, flat blemish, thickening, or discoloration that is flush with the skin surface. (Adjective: macular)
Malaise A vague feeling of bodily fatigue and discomfort.
Manometry The measurement of tension or pressure of a liquid or gas using a device called a manometer.
Marasmus A condition of extreme protein-calorie malnutrition that is characterized by growth retardation and progressive wasting of subcutaneous tissue and muscle and occurs chiefly during the first year of life.
Matrix The intracellular substance of a tissue or the basic substance from which a specific organ or kind of tissue develops.
Meatus An opening or passage through any body part.
Medial Pertaining to the middle; or situated or oriented toward the midline of the body.
Mediastinum The mass of tissues and organs in the middle of the thorax, separating the pleural sacs containing the two lungs.
Meiosis The division of a sex cell as it matures, so that each daughter nucleus receives one half of the number of chromosomes characteristic of the somatic cells of the species.
Mesoderm The middle layer of the three primary germ layers of the developing embryo, lying between the ectoderm and the endoderm.
Metabolism The sum of all the physical and chemical processes by which living organisms are produced and maintained, and also the transformation by which energy is provided for vital processes and activities.
Metaplasia Change in type of adult cells in a tissue to a form that is not normal for that tissue.
Metastasis The transfer of disease (e.g., cancer) from one organ or part to another not directly connected with it. (Adjective: metastatic)
Miosis Contraction of the pupil of the eye.
Mitosis A type of indirect cell division that occurs in somatic cells and results in the formation of two daughter nuclei containing the identical complements of the number of chromosomes characteristic of the somatic cells of the species.
Molecule The smallest mass of matter that exhibits the properties of an element or compound.
Morbidity A diseased condition or state; the relative incidence of a disease or of all diseases in a population.
Morphology The study of the physical form and structure of an organism; or the form and structure of a particular organism. (Adjective: morphologic)
Mosaicism In genetics, the presence in an individual or in an organism of cell cultures having two or more cell lines that differ in genetic constitution but are derived from a single zygote.
Mutagen Any chemical or physical agent that induces a genetic mutation (an unusual change in form, quality, or some other characteristic) or increases the mutation rate by causing changes in DNA.
Mydriasis Physiologic dilatation of the pupil of the eye.
Myoclonus A spasm of a portion of a muscle, an entire muscle, or a group of muscles.
Myoglobin The oxygen-transporting pigment of muscle consisting of one heme molecule containing one iron molecule attached to a single globin chain.
Myopathy Any disease or abnormal condition of skeletal muscle, usually characterized by muscle weakness, wasting, and histologic changes within muscle tissue.
Myotome The muscle plate or portion of an embryonic somite that develops into a voluntary muscle; or a group of muscles innervated by a single spinal segment.
Necrosis Localized tissue death that occurs in groups of cells or part of a structure or an organ in response to disease or injury.
Neutropenia An abnormal decrease in the number of neutrophilic leukocytes in the blood.
Nidus The point where a morbid process originates, develops, or is located.
Nociception The reception of painful stimuli from the physical or mechanical injury to body tissues by nociceptors (receptors usually found in either the skin or the walls of the viscera).
Nosocomial Pertaining to or originating in a hospital, such as a nosocomial infection; an infection acquired during hospitalization.
Nystagmus Involuntary, rapid, rhythmic movements of the eyeball.
Oncogene A gene that is capable of causing the initial and continuing conversion of normal cells into cancer cells.
Oncotic Relating to, caused by, or marked by edema or any swelling.
Oocyte A primordial or incompletely developed ovum.
Oogenesis The process of the growth and maturation of the female gametes, or ova.
Opsonization The process of making cells, such as bacteria, more susceptible to the action of phagocytes.
Organelle Any one of the various membrane-bound particles of distinctive morphology and function present within most cells, as the mitochondria, the Golgi complex, and the lysosomes.
Orthopnea An abnormal condition in which a person must be in an upright position in order to breathe deeply or comfortably.

Orthosis An external orthopedic appliance or apparatus, as a brace or splint, used to support, align, prevent, or correct deformities, or to improve the function of movable parts of the body.
Osmolality The concentration of osmotically active particles in solution expressed in osmols or milliosmols per kilogram of solvent.
Osmolarity The concentration of osmotically active particles in solution expressed in osmols or milliosmols per liter of solution.
Osmosis The movement or passage of a pure solvent, such as water, through a semipermeable membrane from a solution that has a lower solute concentration to one that has a higher solute concentration.
Osteophyte A bony project or outgrowth.
Palpable Perceptible by touch.
Papilla A small nipple-shaped projection, elevation, or structure, as the conoid papillae of the tongue.
Papule A small, circumscribed, solid elevation of the skin less than one centimeter in diameter. (Adjective: papular)
Paracrine A mode of hormone action in which a chemical messenger that is synthesized and released from a cell acts on nearby cells of a different type and affects their function.
Paralysis An abnormal condition characterized by the impairment or loss of motor function due to a lesion of the neural or muscular mechanism.
Paraneoplastic Relating to alterations produced in tissue remote from a tumor or its metastases.
Parenchyma The basic tissue or elements of an organ as distinguished from supporting or connective tissue or elements. (Adjective: parenchymal)
Paresis Slight or partial paralysis.
Paresthesia Any abnormal touch sensation, which can be experienced as numbness, tingling, or a "pins and needles" feeling, often in the absence of external stimuli.
Parietal Pertaining to the outer wall of a cavity or organ; or pertaining to the parietal bone of the skull or the parietal lobe of the brain.
Parous Having borne one or more viable offspring.
Pathogen Any microorganism capable of producing disease.
Pedigree A systematic presentation, such as in a table, chart, or list, of an individual's ancestors that is used in human genetics in the analysis of inheritance.
Peptide Any of a class of molecular chain compounds composed of two or more amino acids joined by peptide bonds.
Perfusion The process or act of pouring over or through, especially the passage of a fluid through a specific organ or an area of the body.
Peripheral Pertaining to the outside, surface, or surrounding area of an organ or other structure; or located away from a center or central structure.
Permeable A condition of being pervious, or permitting passage, so that fluids and certain other substances can pass through, as a permeable membrane.
Pervasive Pertaining to something that becomes diffused throughout every part.
Petechia A tiny, perfectly round, purplish red spot that appears on the skin as a result of minute intradermal or submucous hemorrhage. (Plural: petechiae)
Phagocytosis The process by which certain cells engulf and consume foreign material and cell debris.
Phalanx Any one of the bones composing the fingers of each hand and the toes of each foot.
Phenotype The complete physical, biochemical, and physiologic makeup of an individual, as determined by the interaction of both genetic makeup and environmental factors.
Pheresis A procedure in which blood is withdrawn from a donor, a portion (plasma, leukocytes, etc.) is separated and retained, and the remainder is reperfused into the donor. It includes plasmapheresis and leukophoresis.
Pili Hair; or in microbiology, the minute filamentous appendages of certain bacteria. (Singular: pilus)
Plethoric Relating to an excess of any of the body fluids, especially blood; the term used to describe the beefy red coloration of a newborn.
Plexus A network of intersecting nerves, blood vessels, or lymphatic vessels.
Polygene Any of a group of nonallelic genes that interact to influence the same character in the same way so that the effect is cumulative, usually of a quantitative nature, as size, weight, or skin pigmentation. (Adjective: polygenic)
Polymorph One of several, or many, forms of an organism or cell. (Adjective: polymorphic)
Polyp A small, tumor-like growth that protrudes from a mucous membrane surface.
Polypeptide A molecular chain of more than two amino acids joined by peptide bonds.
Presbyopia A visual condition (farsightedness) that commonly develops with advancing years or old age in which the lens loses elasticity causing defective accommodation and inability to focus sharply for near vision.
Prevalence The number of new and old cases of a disease that are present in a population at a given time or occurrences of an event during a particular period of time.
Prodrome An early symptom indicating the onset of a condition or disease. (Adjective: prodromal)
Prokaryotic Pertaining to an organism, such as bacterium, with cells lacking a true nucleus and nuclear membrane that reproduces through simple fission.
Prolapse The falling down, sinking, or sliding of an organ from its normal position or location in the body.
Proliferation The reproduction or multiplication of similar forms, especially cells.
Pronation Assumption of a position in which the ventral, or front, surface of the body or part of the body faces downward. (Adjective: prone)
Propagation The act or action of reproduction.
Proprioception The reception of stimuli originating from within the body regarding body position and muscular activity by proprioceptors (sensory nerve endings found in muscles, tendons, joints).
Prosthesis An artificial replacement for a missing body part; or a device designed and applied to improve function, such as a hearing aid.

Proteoglycans Any one of a group of polysaccharide-protein conjugates occurring primarily in the matrix of connective tissue and cartilage.
Proto-oncogene A normal cellular gene that with alteration, such as by mutation, becomes an active oncogene.
Proximal Closer to a point of reference, usually the trunk of the body, than other parts of the body.
Pruritus The symptom of itching, an uncomfortable sensation leading to the urge to rub or scratch the skin to obtain relief. (Adjective: pruritic)
Purpura A small hemorrhage, up to about 1 cm in diameter, in the skin, mucous membrane, or serosal surface; or any of several bleeding disorders characterized by the presence of purpuric lesions.
Purulent Producing or containing pus.
Quiescent Quiet, causing no disturbance, activity, or symptoms.
Reflux An abnormal backward or return flow of a fluid, such as stomach contents, blood, or urine.
Regurgitation A flow of material that is in the opposite direction from normal, as in the return of swallowed food into the mouth or the backward flow of blood through a defective heart valve.
Remission The partial or complete disappearance of the symptoms of a chronic or malignant disease; or the period of time during which the abatement of symptoms occurs.
Resorption The loss of substance or bone by physiologic or pathologic means, for example, the loss of dentin and cementum of a tooth.
Retrograde Moving backward or against the usual direction of flow; reverting to an earlier state or worse condition (degenerating); catabolic.
Retroversion A condition in which an entire organ is tipped backward or in a posterior direction, usually without flexion or other distortion.
Rhabdomyolysis Destruction or degeneration of muscle, associated with myoglobinuria (excretion of myoglobin in the urine).
Rostral Situated near a beak (oral or nasal region).
Sacroiliitis Inflammation in the sacroiliac joint.
Sclerosis A condition characterized by induration or hardening of tissue resulting from any of several causes, including inflammation, diseases of the interstitial substance, and increased formation of connective tissues.
Scotopic vision Describes vision, especially night vision, when the eye is dark adapted.
Semipermeable Partially but not wholly permeable, especially a membrane that permits the passage of some (usually small) molecules but not of other (usually larger) particles.
Senescence The process or condition of aging or growing old.
Sepsis The presence in the blood or other tissues of pathogenic microorganisms or their toxins; or the condition resulting from the spread of microorganisms or their products. (Adjective: septic)
Serous Relating to or resembling serum; or containing or producing serum, such as a serous gland.
Shunt To divert or bypass bodily fluid from one channel, path, or part to another; a passage or anastomosis between two natural channels, especially between blood vessels, established by surgery or occurring as an abnormality.
Soma The body of an organism as distinguished from the mind; all of an organism, excluding germ cells; the body of a cell.
Spasticity The condition characterized by spasms or other uncontrolled contractions of the skeletal muscles. (Adjective: spastic)
Spatial Relating to, having the character of, or occupying space.
Sphincter A ringlike band of muscle fibers that constricts a passage or closes a natural orifice of the body.
Stenosis An abnormal condition characterized by the narrowing or stricture of a duct or canal.
Stochastic Involving a random process.
Stria A streak or a linear scarlike lesion that often results from rapidly developing tension in the skin; or a narrow bandlike structure, especially the longitudinal collections of nerve fibers in the brain.
Stricture An abnormal temporary or permanent narrowing of the lumen of a duct, canal, or other passage, as the esophagus, because of inflammation, external pressure, or scarring.
Stroma The supporting tissue or the matrix of an organ as distinguished from its functional element, or parenchyma.
Stupor A lowered level of consciousness characterized by lethargy and unresponsiveness in which a person seems unaware of his or her surroundings.
Subchondral Beneath a cartilage.
Subcutaneous Beneath the skin.
Subluxation An incomplete or partial dislocation in which the relationship between joint surfaces is altered, but contact remains.
Sulcus A shallow groove, depression, or furrow on the surface of an organ, as a sulcus on the surface of the brain, separating the gyri.
Supination Assuming the position of lying horizontally on the back, or with the face upward. (Adjective: supine)
Suppuration The formation of pus, or purulent matter.
Symbiosis Mode of living characterized by close association between organisms of different species, usually in a mutually beneficial relationship.
Sympathomimetic An agent or substance that produces stimulating effects on organs and structures similar to those produced by the sympathetic nervous system.
Syncope A brief lapse of consciousness due to generalized cerebral ischemia.
Syncytium A multinucleate mass of protoplasm produced by the merging of a group of cells.
Syndrome A complex of signs and symptoms that occur together to present a clinical picture of a disease or inherited abnormality.
Synergist An organ, agent, or substance that aids or cooperates with another organ, agent, or substance.
Synthesis An integration or combination of various parts or elements to create a unified whole.
Systemic Pertaining to the whole body rather than to a localized area or regional portion of the body.

Systole The contraction, or period of contraction, of the heart that drives the blood onward into the aorta and pulmonary arteries.
Tamponade Stoppage of the flow of blood to an organ or a part of the body by pathologic compression, such as the compression of the heart by an accumulation of pericardial fluid.
Teratogen Any agent or factor that induces or increases the incidence of developmental abnormalities in the fetus.
Thrombus A stationary mass of clotted blood or other formed elements that remains attached to its place of origin along the wall of a blood vessel, frequently obstructing the circulation. (Plural: thrombi)
Tinnitus A tinkling, buzzing, or ringing noise heard in one or both ears.
Tophus A chalky deposit containing sodium urate that most often develops in periarticular fibrous tissue, typically in individuals with gout. (Plural: tophi)
Torsion The act or process of twisting in either a positive (clockwise) or negative (counterclockwise) direction.
Trabecula A supporting or anchoring stand of connective tissue, such as the delicate fibrous threads connecting the inner surface of the arachnoid to the pia mater.
Transmural Situated or occurring through the wall of an organ.
Transudate A fluid substance passed through a membrane or extruded from the blood.
Tremor Involuntary quivering or trembling movements caused by the alternating contraction and relaxation of opposing groups of skeletal muscles.
Trigone A triangular-shaped area.
Ubiquitous The condition or state of existing or being everywhere at the same time.
Ulcer A circumscribed excavation of the surface of an organ or tissue, which results from necrosis that accompanies some inflammatory, infectious, or malignant processes. (Adjective: ulcerative)
Urticaria A pruritic skin eruption of the upper dermis, usually transient, characterized by wheals (hives) of various shapes and sizes.
Uveitis An inflammation of all or part of the uveal tract of the eye.
Vector An invertebrate animal (e.g., tick, mite, mosquito) that serves as a carrier, transferring an infective agent from one vertebrate host to another.
Ventral Pertaining to a position toward the belly of the body; or situated or oriented toward the front or anterior of the body.
Vertigo An illusory sensation that the environment or one's own body is revolving.
Vesicle A small bladder or sac, as a small, thin-walled, raised skin lesion, containing liquid.
Visceral Pertaining to the viscera, or internal organs of the body.
Viscosity Pertaining to the physical property of fluids, caused by the adhesion of adjacent molecules, that determines the internal resistance to shear forces.
Zoonosis A disease of animals that may be transmitted to humans from its primary animal host under natural conditions.

Appendix A

Lab Values

TABLE A-1 Prefixes Denoting Decimal Factors

Prefix	Symbol	Factor
mega	M	10^{6}
kilo	k	10^{3}
hecto	h	10^{2}
deci	d	10^{-1}
centi	c	10^{-2}
milli	m	10^{-3}
micro	μ	10^{-6}
nano	n	10^{-9}
pico	p	10^{-12}
femto	f	10^{-15}

TABLE A-2 Hematology

Test	Conventional Units	Conversion Factor	SI Units
Erythrocyte count (RBC count)	M. 4.2–5.4 × 10^{6}/μL F. 3.6–5.0 × 10^{6}/μL	1.0	M. 4.2–5.4 × 10^{12}/L F. 3.6–5.0 × 10^{12}/L
Hematocrit (Hct)	M. 40–50% F. 37–47%	0.01	M. 0.40–0.50 F. 0.37–0.47
Hemoglobin (Hb)	M. 14.0–16.5 g/dL F. 12.0–15.0 g/dL	10.0	M. 140–165 g/L F. 120–150 g/L
Mean corpuscular hemoglobin (MHC)	27–34 pg/cell		0.40–0.53 fmol/cell
Mean corpuscular hemoglobin concentration (MCHC)	31–35 g/dL	10.0	310–350 g/L
Mean corpuscular volume (MCV)	85–100 fL/cell		
Reticulocyte count	1.0–1.5% total RBC	1.0	
Platelet count	150–400 × 10^{3}/μL	1.0	150–400 × 10^{9}/L
Leukocyte count (WBC count)	4.8–10.8 × 10^{3}/μL	1.0	4.8–10.8 × 10^{9}/L
Basophils	0%–2%		
Eosinophils	0%–3%		
Lymphocytes	24%–40%		
Monocytes	4%–9%		
Neutrophils (segmented [Segs])	47%–63%		
Neutrophils (bands)	0%–4%		

TABLE A-3 Blood Chemistry*

Test	Conventional Units	Conversion Factor	SI Units
Alanine aminotransferase (ALT, SGPT, GPT)	7–56 units/L†	0.017	0.12–0.95 μkat/L†
Alkaline phosphatase	41–133 units/L†‡	0.017	0.7–2.3 μkat/L†‡
Ammonia	18–60 μg/dL	0.590	11–35 μmol/L
Amylase	20–110 units/L†	0.017	0.34–1.87 μkat/L†
Aspartase aminotransferase (AST, SGOT, GOT)	0–35 units/L†	0.017	0–0.59 μkat/L†
Bicarbonate	24–31 mEq/L	1.0	24–31 mmol/L
Bilirubin (total)	0.1–1.2 mg/dL	17.100	17.1–21 μmol/L
Direct	0.1–0.5 mg/dL		<8 μmol/L
Indirect	0.1–0.7 mg/dL		<12 μmol/L
Blood urea nitrogen (BUN)	8–20 mg/dL	0.360	2.9–7.1 mmol/L
Calcium (Ca^{2+})	8.5–10.5 mg/dL	0.250	2.1–2.6 mmol/L
Chloride	98–106 mEq/L	1.000	98–106 mmol/L
Creatine kinase (CK, CPK)	32–267 units/L†	0.017	0.54–4.53 μkat/L†
Creatinine (serum)	0.6–1.2 mg/dL‡	83.300	50–100 μmol/L‡
Gamma-glutamyl-transpeptidase (GGT)	9–85 units/L†	0.017	0.15–1.42 μkat/L†
Glucose (plasma, fasting)	<100 mg/dL	0.055	<5.6 mmol/L
Glycosylated hemoglobin (HbA_{1c})	3.9–6.9%		
Lactate dehydrogenase (LDH)	88–230 units/L†	0.017	1.46–3.82 μkat/L†
Lipids			
Cholesterol	<200 mg/dL (optimal) 200–239 mg/dL (borderline) ≥240 (high)	0.26	<5.2 mmol/L (optimal) 5.2–6.1 mmol/L (borderline) >6.2 mmol/L (high)
LDL cholesterol	<130 mg/dL	0.026	<3.37 mmol/L
HDL cholesterol	<40 low >60 high	0.026	1.04 mmol/L 1.56 mmol/L
Triglycerides	<165 mg/dL	0.01	<1.8 mmol/L (fasting)
Lipase	0–160 units/L†	0.017	0.272 μkat/L†
Magnesium	1.8–3.0 mg/dL	0.50	0.75–1.25 mmol/L
Osmolality	275–295 mOsm/kg H_2O		275–295 mmol/kg H_2O
pH (arterial)	7.35–7.45		
Phosphorus (inorganic)	2.5–4.5 mg/dL	0.32	0.80–1.45 mmol/L
Potassium	3.5–5.0 mEq/L	1.0	3.5–5.0 mmol/L
Prostate specific antigen (PSA)	0–4 ng/mL	1.0	0–4 μg/L
Protein total	6.0–8.0 g/dL	10.0	60–80 g/L
Albumin	3.4–4.7 g/dL	10.0	34–47 g/L
Globulin	2.3–3.5 g/dL	10.0	23–35 g/L
A/G ratio	1.0–2.2	10.0	10–22
Thyroid tests			
Thyroxine (T_4) total	5.0–11.0 μg/dL	12.80	64–142 nmol/L
Thyroxine, free (FT_4)	9–24 pmol/L†		
Triiodothyronine (T_3) total	95–190 ng/dL	0.015	1.5–2.9 nmol/L
Thyroid-stimulating hormone (TSH)	0.4–4.2 μU/mL	1.0	0.4–4.2 mU/L
Thyroglobin	3–42 ng/mL	1.0	3–42 μg/L
Sodium	135–145 mEq/L	1.0	135–145 mmol/L
Uric acid	Male: 2.4–7.4 mg/dL Female: 1.4–5.8 mg/dL	59.48	Male: 143–440 μmol/L Female: 83–345 μmol/L

*Values may vary with laboratory. The values supplied by the laboratory performing the test should always be used because the ranges may be method specific.
†Laboratory and/or method specific
‡Varies with age and muscle mass

Values obtained from Tierney L.M., McPhee S.J., Papadakis M.A. (2007). *Current medical diagnosis and treatment* (46th ed., pp. 1769–1777). Stamford, CT: Appleton & Lange; Fischbach F. (2004). *A manual of laboratory and diagnostic tests* (7th ed.). Philadelphia: Lippincott Williams & Wilkins; and other sources.

Index

Note: Page numbers followed by the letter f refer to figures; those followed by the letter t refer to tables, and those followed by the letter c refer to charts.

A

A band, 26, 26f
Abdominal aortic aneurysm, 420–421, 420f–421f
Absence seizures, 957
Absolute refractory periods, 390–391, 391f, 834
Absorption, 694–697, 694f
  of carbohydrates, 695–696, 695f, 695t
  disorders of, 722–723, 723t
  of fats, 696, 696f
  of protein, 696–697
Acanthamoeba keratitis, 971
Acceptable macronutrient distribution ranges (AMDRs), 226
Accommodation disorders, 972
ACE. *See* Angiotensin-converting enzyme
Acetylcholine
  in autonomic nervous system, 860–861, 860f
  in circulatory control, 403
Achalasia, 701
Acid-base balance, 192–205, 192b
  chemistry of, 192
  disorders of, 197–205, 199b
    metabolic, 198–203, 198t, 199b, 201t, 202f
    primary *v.* compensatory pH changes, 198–199, 198t
    respiratory, 198, 198t, 203–205, 203b, 204t
    single *v.* mixed, 198t, 199
  laboratory tests for, 197, 198f
  pH regulation, 193–197, 193f
  production of, 192–193, 193f
Acid-fast stain, 304
Acidosis, 197–198
Acne conglobata, 1180–1181
Acne vulgaris, 1179–1180, 1180f
Acoustic neuromas, 997
Acquired immunodeficiency syndrome (AIDS), 364–374, 364b. *See also* Human immunodeficiency virus
  malignancies with, 370–371, 371f
  opportunistic infections with, 369–370, 369f
  wasting syndrome and metabolic disorders, 371–372
Acral lentiginous melanoma, 1196
Acromegaly, 780, 781f
ACSs. *See* Acute coronary syndromes
ACTH. *See* Adrenocorticotropic hormone
Actin filaments, 25–27, 26f–27f, 31b
Actinic keratosis, 1202–1203, 1203f
Action potentials, 19b, 20, 833–834, 834f
  of cardiac muscles, 389–390, 390f
Active immunity, 341
Active transport, 15–17
Acute adrenal crisis, 795
Acute chest syndrome, 287
Acute coronary syndromes (ACSs), 454–460
  electrocardiographic changes in, 454, 455f
  myocardial infarction, 455f, 456–460, 458f–459f
  non-ST elevation myocardial infarction, 456
  serum biomarkers, 454–456
Acute heart failure syndromes (AHFSs), 495–496
Acute inflammation, 52
Acute laryngotracheobronchitis. *See* Viral croup
Acute lung injury (ALI), 507, 593–595, 594c, 594f
Acute lymphocytic leukemia (ALL), 253–254
Acute myeloid leukemia (AML), 253–254
Acute-phase proteins, 64
Acute-phase response, 55, 64–65
Acute rejection, 354
Acute renal failure (ARF), 507, 641–645, 642b
  diagnosis and treatment of, 644–645
  intrinsic failure, 642c, 642f, 643–644
  postrenal failure, 642c, 642f, 644
  prerenal failure, 642c, 642–643, 642f
Acute respiratory distress syndrome (ARDS), 507, 593–595, 594c, 594f
Acute stage, of infection, 311, 311f
Acute stress disorder (ASD), 219
Acute tubular necrosis (ATN), 642c, 643–644, 643f
Acute vestibular neuronitis, 1003
ADA. *See* Adenine deaminase
Adaptation
  cellular, 33–36, 34b, 34f
  factors affecting ability of, 216, 216f, 218
  to stress, 215–218, 215b, 216f
Adaptive hypertrophy, 35
Adaptive immunity, 319–321, 320f, 332–342, 333b
  antigens, 332–333, 333f
  cells of, 333–336
  innate immunity in stimulating, 331–332
Addison disease. *See* Adrenal cortical insufficiency
Adenine, in DNA, 90
Adenine deaminase (ADA), deficiency of, 363
Adenocarcinoma, 132–133, 133t
  lungs, 555, 555f
Adenomas, 132–133, 133t
  of pituitary gland, 776
Adenomatous polyps, 724, 724f
Adenomyosis, 1048
Adenosine diphosphate (ADP), 265
  in energy metabolism, 9, 9f, 12
Adenosine monophosphate (AMP), in energy metabolism, 9, 9f, 12
Adenosine triphosphate (ATP)
  in energy metabolism, 9, 9f, 10b–11b, 12
  synthesis of, 7
Adenylyl cyclase, 14, 20b
Adequate intake (AI), 226
ADH. *See* Alcohol dehydrogenase; Antidiuretic hormone
Adhering junctions, 29–30, 31b
Adhesion factors, 309t, 310
Adipose tissue, 25, 225–226
  obesity and, 232–233
Adjuvant analgesics, 879
Adjuvants, 332
Adolescents, hypertension in, 434–436, 435t
ADP. *See* Adenosine diphosphate
Adrenal cortical insufficiency, 793–795, 794f, 794t
Adrenal gland
  disorders of, 793–796
    adrenal cortical insufficiency, 793–795, 794f, 794t
    congenital adrenal hyperplasia, 793, 793f
    glucocorticoid hormone excess, 795–796, 796f

Adrenal gland (*continued*)
function of, 790–792, 790f–791f, 791b, 792t
cortical, 790–792, 790f–791f, 792t
pharmacologic suppression of, 792
tests of, 792–793
hormones of, 790–792, 790f–791f, 792t
androgens, 790–791, 790f
glucocorticoids, 791–792, 791f, 792t
mineralcorticoids, 791
incidental adrenal mass, 796
β-Adrenergic receptor blockers, for heart failure, 498
Adrenergic receptors, in autonomic nervous system, 860f, 861
Adrenocortical hormone, disorders of, 430
Adrenocorticotropic hormone (ACTH), stress response of, 214
Adults
growth hormone deficiency in, 780
growth hormone excess in, 780–782, 781f
Adult hemoglobin (HbA), 280
Adult polycystic disease, 631–632, 631f
Adult respiratory distress syndrome, 524
Advanced glycation end products (AGEs), 48
Adynamic osteodystrophy, 649
Aerobes, 304
Aerobic metabolism, 6–7, 10b–11b, 12
Afferent neurons, 28
Affinity
of hemoglobin, 533–534
of hormone receptors, 765
AFP. *See* α-Fetoprotein
Afterload, 395, 487
Agammaglobulinemia, X-linked, 360–361
Age (aging)
adaptation and, 216–217
cellular, 47–49
menstrual cycle and, 1058
orthostatic hypotension and, 437–438
premature, 48–49, 48f
skin disorders and, 1198–1203, 1199f–1203f
AGEs. *See* Advanced glycation end products
Agranulocytes, 244f, 246–247, 246f
Agranulocytosis, 248–250, 249c
AHFSs. *See* Acute heart failure syndromes
AI. *See* Adequate intake
AIDS. *See* Acquired immunodeficiency syndrome
Airflow
during breathing, 524–525, 525f
laminar and turbulent, 525
Airways
conducting, 513–518, 514b, 514f–515f
forced expiration compression of, 525, 526f
laryngotracheal, 515–516, 515f
lower, infection of, 562–563
nasopharyngeal, 515
obstructive disorders of, 573–586, 573b
bronchial asthma, 573–579, 574f–575f, 577t
bronchiectasis, 583–584, 583f
chronic obstructive pulmonary disease, 579–583, 579f–582f
cystic fibrosis, 584–586, 585f
physiology of, 573
parasympathetic nervous system and, 520
resistance of, 524–525, 525f
in children and neonates, 558
respiratory, 514b, 518–520, 518f
upper, infection of, 561–562, 561f, 561t
Alanine aminotransferase (ALT), 736
Alarm stage, in GAS, 211
Albinism, 1168
Albumin, 616
Alcohol. *See also* Fetal alcohol syndrome
cancer and, 144
fetal development and, 125
liver metabolism of, 743–744
Alcohol dehydrogenase (ADH), 743
Alcoholic cirrhosis, 744, 745f
Alcoholic hepatitis, 744
Alcohol-induced liver disease, 744, 744f–745f
Aldosterone, in potassium regulation, 179, 182
Aldosterone receptor antagonists, for heart failure, 498
Algesia, endogenous, 874
ALI. *See* Acute lung injury
Alimentary canal. *See* Gastrointestinal system
Alkaline phosphatase, 736
Alkalosis, 197–198
ALL. *See* Acute lymphocytic leukemia
Alleles, 100
Allergens, 345–346
Allergic conjunctivitis, 969
Allergic contact dermatitis, 352
Allergic dermatoses, 1181–1184, 1182f–1184f
Allergic reactions, 345–346, 346b
Allergic rhinitis, 348
Allergies, food, 348–349
Allogeneic graft, 353
Allografts, immune recognition of, 353–354
Allostasis, 212
Alport syndrome, 625–626
ALS. *See* Amyotrophic lateral sclerosis
ALT. *See* Alanine aminotransferase
Alveolar dead space, 529
Alveolar macrophages, 519, 519f
Alveolar pressure, 521, 521f
Alveolar ventilation, 528, 566–567
Alveoli
oxygen transport, 532, 532f
structures, 518–519, 518f–519f
Alzheimer disease, 959–961, 960f
Amblyopia, 987–988
AMDRs. *See* Acceptable macronutrient distribution ranges
Amenorrhea, 1056
Amino acids, excitatory, in brain injury, 929, 929f
Aminotransferases, 733
AML. *See* Acute myeloid leukemia
Ammonia, urea conversion of, 732t, 733–734, 733f
Ammonia buffers, 197
Amniocentesis, 127f, 128
AMP. *See* Adenosine monophosphate
Ampulla of Vater. *See* Hepatopancreatic ampulla
Amyloid precursor protein (APP), 960
Amyotrophic lateral sclerosis (ALS), 913–914
Anaerobes, 304
Anaerobic metabolism, 10b, 12
Anagen follicles, 1166
Analgesics, 878–879
Anaphylactic shock, 500c, 501f, 505
Anaphylaxis, 348
Anaplasia, 134, 135f
Anaplasmataceae, 305–306
Anasarca, 163
Anatomic dead space, 529
Anatomic reserve, for adaptation, 216
Anatomic shunt, 530
ANCAs. *See* Antineutrophil cytoplasmic antibodies
Anchorage independence, 135

Androgens, 1039
adrenal, 790–791, 790f
Andropause, 1030
Anemia, 284–293, 285b, 285f, 749
aplastic, 292
blood loss, 285, 285f
of chronic disease, 292
with CKD, 649–650
folic acid-deficiency, 291–292
hemolytic, 285–286
iron-deficiency, 290
megaloblastic, 290–292, 291f
sickle cell, 286–288, 286f–287f
thalassemias, 288–290
vitamin B_{12}-deficiency, 291, 291f
Anergy, 356–357, 552
Aneuploidy, 119, 134–135
Aneurysm(s), 419–421, 420f
aortic, 420–421, 420f–421f
aortic dissection, 420f, 421
dissecting, 419–420, 420f
subarachnoid hemorrhage, 948–950, 949f
ventricular, 459–460, 459f
Angelman syndrome, 102, 115
Angiitis, 414–415, 415f, 415t
Angina
stable, 460, 460f
variant, 460–461
Angiogenesis, 80–81, 81f, 138
Angiotensin-converting enzyme (ACE) inhibitor, 426
for heart failure, 497–498, 510
for myocardial infarction, 457
Angiotensin I, 426, 426f
Angiotensin II
in circulatory control, 401–402, 426–427, 426f
stress response of, 214
Angiotensinogen, 426, 426f
Angle-closure glaucoma, 981f, 982
Angular deformities, of limbs, 1117–1119, 1118f–1119f
Anion gap, 197, 198f
Ankylosing spondylitis, 1145–1146, 1146f
Ankyrin, 279, 280f
Anopia, 984
Anorexia, 697
in cancer, 146–147
Anorexia nervosa, 237b, 238
ANP. *See* Atrial natriuretic peptide
ANS. *See* Autonomic nervous system
Anterior cord syndrome, 919, 919f
Anterolateral pathway, 866–867, 866f
Anthrax, 316–317
Antibiotics, 315
for cystic fibrosis, 586
Antibodies, 320–321, 320f, 332. *See also* Immunoglobulins
Antibody-mediated hypersensitivity disorders, 349–350, 349f
Antibody titer, 312
Antidiuretic hormone (ADH), 426–427, 426f
disorders of, 170–172
stress response of, 214
in urine concentration, 609–611, 610f–611f
Antifungal agents, 315
Antigenic determinants. *See* Epitopes
Antigenic drift, 543–544
Antigenic shift, 544
Antigen-presenting cells, 322
Antigens, 320, 332–333, 333f
superantigens, 358
Antiglobulin test, 290
Antihormone therapy, for cancer, 153
Antimicrobial agents, 315
Antineutrophil cytoplasmic antibodies (ANCAs), 414
Antioxidants, 43
Antiphospholipid syndrome, 270–271
Antiporters, 15, 15f
Antipyretic drugs, 70
α_1-Antitrypsin, in emphysema, 579–581
Antiviral agents, 315
for influenza, 545
Aorta, coarctation of, 430–431, 477f, 480–481
Aortic aneurysm, 420–421, 420f–421f
Aortic balloon pump, for cardiogenic shock, 502, 502f
Aortic dissection, 420f, 421
Aortic valve, 387–388, 387f–388f, 471–472
regurgitation of, 470f, 472–473
stenosis of, 470f, 472
Apex, of lung, 514
Aphasia, from stroke, 948
Aplastic anemia, 248–250, 249c, 292
Apneustic center, 536–537, 536f
Apocrine sweat glands, 1164
Apoproteins, 407
Apoptosis, 44–46, 44f–45f, 74b, 74f
mitochondria in, 7
neoplasms and, 132
Apoptosis activating factor-1, 7
Apotransferrin, 281, 281f
APP. *See* Amyloid precursor protein
Appendicitis, 717
Appendicular skeleton, 1081
Appetite, 228–229, 229f
Aquaporin-2 channel, 609, 611, 611f
Aquaporins, 160, 171
Arachidonic acid metabolites, in inflammation, 60, 60f
Arachnodactyly, 112, 112f
Arachnoid, 852, 852f
Arachnoid villi, 853f, 854
Archilayer, of white matter, 843f, 844
ARDS. *See* Acute respiratory distress syndrome
Areola, 1059, 1059f
Areolar tissue. *See* Loose connective tissue
ARF. *See* Acute renal failure
Arginine vasopressin (AVP), 170–171
Arrhythmias, 391, 495
Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), 463
Arterial blood gases, 197
Arterial blood pressure, 424, 424f
disorders of, 422–439, 422f
Arterial chemoreceptors, 425, 426f
Arterial system, 397–398, 397f
disorders of, 407–422, 407b. *See also specific disorder*
Arteries, coronary, 450–453, 450f, 452f–453f
Arteriovenous malformations, 950, 950f
Arteriovenous (AV) shunts, 399
in heat loss, 66, 66t
Arteritis, 414–415, 415f, 415t
Arthritis, 1138
juvenile idiopathic, 1153
polyarthritis, 468
psoriatic, 1147
reactive, 1146–1147, 1147f
rheumatoid, 1138–1142, 1139f–1140f, 1141c

Arthus reaction, 351
ARVC/D. *See* Arrhythmogenic right ventricular cardiomyopathy/dysplasia
Aschoff bodies, 467
Ascites, 167, 747, 747f
ASD. *See* Acute stress disorder
Aspartate aminotransferase (AST), 736
Aspiration pneumonia, 516
AST. *See* Aspartate aminotransferase
Astereognosis, 866
Asthma
  bronchial, 573–579
  cardiac, 495
  in children, 578–579
  clinical features of, 576–578, 577t
  diagnosis and treatment of, 576–578, 577t
  etiology and pathogenesis of, 573–576, 574f–575f
  extrinsic, 574–575, 574f–575f
  intrinsic, 574f–575f, 575–576
  manifestations of, 576
  severe, 578
Astrocytes, 28, 832–833, 833f
Astrocytoma, 953
Asymmetric replication, 75, 78
Asymptomatic hematuria, 622t, 625–626, 626f
Ataxia, 899
Atelectasis, 572, 572f
Atherosclerosis, 411–414, 412f
  clinical manifestations of, 414
  in coronary artery disease, 451
  development of, 413–414, 413f, 416–417, 416f–417f
  epidemiology of, 411–413, 412c
  risk factors for, 411–413, 412c
Atherosclerotic plaque
  stable *v.* unstable, 451, 453f, 454
  thrombosis and vessel occlusion, 454
Atmospheric pressure, 520–521
ATN. *See* Acute tubular necrosis
Atonic seizures, 957
Atopic dermatitis, 1182, 1182f
Atopic reactions, 348–349
ATP. *See* Adenosine triphosphate
Atrial natriuretic peptide (ANP), 613–614
Atrial septal defects, 477f–478f, 478
Atrioventricular (AV) node, 388–389, 389f
Atrioventricular (AV) valves, 386–388, 387f–388f
Atrium, filling and contraction of, 393f, 394
Atrophy, 34, 34f
  of muscles, 900
Atypical pneumonia, 546, 546f, 549
Auscultatory gap, 436
Auspitz sign, 1185
Autocrine action, of hormones, 762, 762f
Autograft, for thermal injury, 1191–1192
Autoimmune diseases, 355c, 355–358, 355b
  diagnosis and treatment of, 358
  gastritis, 707
  immunologic tolerance, 355–357, 356f
  mechanisms of, 357–358
Autoimmune hepatitis, 741
Autologous graft, 353
Autonomic dysreflexia, 922–923, 922f
Autonomic hyperreflexia, with spastic bladder, 666
Autonomic nervous system (ANS), 855–861
  in bladder control, 661f, 662
  in blood pressure regulation, 423, 425–426, 426f
  central integrative pathways of, 857, 859
  circulatory system control by, 403
  craniosacral division of, 857. *See also* Parasympathetic nervous system
  disorders of, orthostatic hypotension and, 438
  efferent pathways of, 856–857, 857t
  in gastrointestinal system, 684–686, 685f–686f
  neurotransmission in, 859–861
  spinal cord injury and disruption in, 921–923, 922f
  in stress response, 212, 213f
  thoracolumbar division of, 856. *See also* Sympathetic nervous system
Autonomic neurotransmitters, 403
Autophagolysosome, 6, 6f
Autophagosome, 6, 6f
Autoregulation, of renal blood flow, 611–612
Autosomal dominant disorders, 110–113, 110f, 111t
  polycystic kidney diseases, 631–632, 631f
Autosomal recessive disorders, 113–114, 113f
  polycystic kidney diseases, 632
Autosomes, 97. *See also* Chromosomes
AV node. *See* Atrioventricular node
Avoidance, in PTSD, 219
AVP. *See* Arginine vasopressin
AV shunts. *See* Arteriovenous shunts
AV valves. *See* Atrioventricular valves
Axial skeleton, 1081
Axon hillock, 830f, 831
Axons, 830f, 831
  degeneration of, 903–904, 904f
Azotemia, 641
  with chronic kidney disease, 648f, 650–651

B

Bacillus anthracis, 317
Back pain, 905–908
Bacteria, 302–305, 302f–303f, 304, 305f
  in intestines, 693
  pneumonia, 547–549, 548t
Bacterial conjunctivitis, 968
Bacterial infections
  in intestines, 714–715
  of skin, 1176–1177, 1176f–1177f
Bacterial meningitis, 951–952
Bacterial prostatitis, 1023
Bacterial vaginosis, 1073
Bactericidal, 315
Bacteriostatic, 315
Balanitis, 1016
Balanoposthitis, 1016
Baroreceptor reflexes, 425
Baroreceptors, 169, 425, 426f
Barr body, 98
Barrel chest, 581, 582f
Barrett esophagus, 703
Bartholin gland cyst, 1041
Basal cell carcinoma, 1197, 1197f
Basal ganglia
  disorders of, 909–913
  in motor function, 893
  movement disorders, 910, 910t
Base, of lung, 514
Basement membrane, 21
Basement membrane zone, 1164, 1164f–1165f
Basolateral membrane, 606
Basophils, 244f, 245–246, 246f
  in inflammation, 54
B-cell lymphomas, 256c, 256–257
BCR. *See* Breakpoint cluster
Becker muscular dystrophy (BMD), 900–901

Bed rest, orthostatic hypotension and, 438
Bedsores. *See* Pressure ulcers
Bence Jones proteins, 259–260
Benign paroxysmal positional vertigo (BPPV), 1001f, 1003
Berry aneurysm, 419, 420f, 948–950
Beta oxidation, 10b
Bicarbonate
  in acid-base balance, 200
  buffer system, 193, 195
  carbon dioxide and, 192–194, 194f
  reabsorption of, 196, 202, 202f
Bile, formation of, 734
Bile canaliculi, 731, 731f
Biliary cirrhosis, 742
Biliary disorders, intrahepatic, 742
Bilirubin
  formation of, 734–735, 734f
  heme conversion to, 283, 283f
Bilirubinuria, 754
Binge eating, 237b, 239
Biochemical analyses, prenatal, 128–129
Bioelectrical impedance, body fat measurement, 230
Biofeedback, for stress, 221
Biofilms, 303–304, 304f
Biologic agents, cellular injury from, 41
Biologic response modifiers, for cancer, 153–154
Biopsy
  for cancer diagnosis, 150
  fetal, 128
  liver, 736
Bioterrorism agents, 316–317
Biotherapy, for cancer, 153–154
Biotransformations, 742
Birth defects. *See* Congenital disorders
Birthmarks, 1199–1200
Blackheads, 1179–1180
Bladder
  cancer of, 675–676
  flaccid, 661f, 666–667, 666b
  function of, 660b
    disorders of, 663–670, 664f, 665c, 665t, 666b, 668b, 668t
    evaluation of, 663
    neural control of, 660–663, 661f, 662t
  infection of. *See* Urinary tract infection
  neurogenic disorders, 665–667, 665t, 666b
  overactive, 668–669, 668b, 668t
  spastic, 661f, 665–666, 665t, 666f
  structure of, 659–660, 660f
    disorders of, 663–670, 664f, 665c, 665t, 666b, 668b, 668t
Blast cells, 247, 247f
Blastomycosis, 553
Bleeding
  disorders of, 271–277, 271b
    with CKD, 650
  with vascular disorders, 275
Blisters, 1167, 1167f
Blood-brain barrier, 854, 854f
Blood flow
  control of, 396–402, 397b
    autoregulation, 400
    endothelial, 400–401, 401f
    humoral, 401–402
  coronary, 450–453, 451f–453f
  distribution of, 529, 529f
  hemodynamics of, 382–383, 382f–383f
  laminar, 380–381, 383, 383f
  myocardial, 452–453, 452f–453f
  principles of, 380–384, 382f–383f
  renal, regulation of, 611–613
  turbulent, 380–381, 383, 383f
  velocity of, 380–382, 382f
  for wound healing, 85–86
Blood loss anemia, 285, 285f
Blood pressure
  aortic, 452, 452f
  arterial, 424, 424f
    disorders of, 422–439, 422f
  determinants of, 424–425, 424f–425f
  high. *See* Hypertension
  low. *See* Hypotension
  measurement of, 427
  RAAS in, 615
  regulation of, 423, 423f, 425–427, 426f
Blood supply
  to bones, 1084
  to joints, 1093
  to retina, 974–976, 975f
    disorders of, 975b, 976–978, 976f–977f
Blood tests, 617–618, 617t
  for endocrine function, 771
Blood urea nitrogen (BUN), 614–615, 617t, 618
Blood vessels
  anatomy of, 396–397, 396f
  arterial, 397–398, 397f
  compliance of, 381
  in dermis, 1163
  distensibility of, 381
  structure of, 405–407, 406f
  venous, 398, 398f
  wall tension of, 381–382, 381f–382f
Blount disease. *See* Tibia vara
Blue bloaters, 581
B lymphocytes, 246, 246f
  in adaptive immunity, 334, 334f–335f
  differentiation of, 244, 244f, 337, 337f
  humoral immunity and, 336–339, 337f
  immunodeficiency disorders, 360–361, 360f, 363
  in innate immunity, 320–323, 320f
  tolerance to, 351f, 356
BMD. *See* Becker muscular dystrophy
BMI. *See* Body mass index
Body circumferences, 230
Body mass index (BMI), calculation of, 230, 230t
Body-self neuromatrix, 870
Body weight. *See* Weight
Bone(s)
  blood supply to, 1084
  buffer activity of, 195
  cells of, 1085–1086, 1086t
  disease of, with CKD, 648–649
  formation of, 1089, 1089f
    hormonal control of, 1087–1091, 1088f–1091f, 1090t
  growth of, 1086–1087
  healing of, 1104–1107, 1106f–1107f
  infections of, 1109–1111
  metabolism of, 1089, 1089f
    disorders of, 1130–1137, 1131b
    hormonal control of, 1087–1091, 1088f–1091f, 1090t
  metastatic disease of, 1116
  remodeling of, 1087–1088, 1088f, 1107, 1107f
  resorption of, 1088, 1088f
  tumors of, 1113b
    benign, 1113–1114
    malignant, 1114–1116, 1114f–1115f
  types of, 1083–1084, 1083f–1084f
Bone marrow, 244–245, 244f, 245b, 1084

Bone tissue, 1084–1086, 1085f, 1086t
Bony callus formation, 1107, 1107f
Boosting, 552
Bovine spongiform encephalopathy (BSE), 301
Bowen disease, 1018
Bowlegs. *See* Genu varum
Bowman space, 603f, 604, 605f
BPD. *See* Bronchopulmonary dysplasia
BPPV. *See* Benign paroxysmal positional vertigo
Brachytherapy, 151
Bradykinesia, 899
Bradykinin, in circulatory control, 402
Brain, 848–855, 848f, 850f–854f
  infections of, 951–952
  meninges of, 852, 852f–853f
  pain and, 874
  tumors of, 952–955
  ventricular system of, 852–854, 853f
Brain attack. *See* Stroke
Brain injury
  diffuse, 938–940, 938b, 938t–940t, 939f–940f
  edema, 929–930
  excitatory amino acids in, 929, 929f
  hematomas, 936–938, 936f–937f
  herniation, 931, 931f, 933–934, 934f
  hydrocephalus, 934–935
  hypoxic, 927–929, 928f
  increased intracranial pressure in, 930–931
  ischemic, 927–929, 928f
  mechanisms of, 927–930
  traumatic, 935–938
Brain stem, 842t–843t, 848f, 849
  in bladder control, 661–662, 661f, 662t
  in motor function, 892
Breakpoint cluster (BCR), 252–253, 252f
Breast
  cancer of, 1061–1064, 1063f
  disorders of, 1060–1061
  fibrocystic changes of, 1060–1061
  inflammation of, 1060
  proliferative lesions of, 1061
  structures of, 1059–1060, 1059f
Breathing. *See also* Ventilation
  airflow during, 524–525, 525f
  alterations in, 558–559, 558f
  control of, 536–539, 536f
  efficiency of, 527–528
  mechanics of, 521–525, 521b
  regulation of, 537–538
  work of, 527–528
Breathlessness. *See* Dyspnea
Bronchi, 516–518, 517f
Bronchial asthma, 573–579
  in children, 578–579
  clinical features of, 576–578, 577t
  diagnosis and treatment of, 576–578, 577t
  etiology and pathogenesis of, 573–576, 574f–575f
  extrinsic, 574–575, 574f–575f
  intrinsic, 574f–575f, 575–576
  manifestations of, 576
  severe, 578
Bronchial circulation, 518f, 519–520
Bronchiectasis, 583–584, 583f
Bronchiolitis, acute, 561f, 561t, 562–563
Bronchitis, chronic, 581
Bronchopulmonary dysplasia (BPD), 560
Bronchospasm, 518
Brown fat, 225–226
Brown pigmentation, with chronic venous insufficiency, 441
Brown-Séquard syndrome, 919, 920f
Bruch membrane, 973
Bruise, 1097
Brush border enzymes, 695
BSE. *See* Bovine spongiform encephalopathy
Buerger disease. *See* Thromboangiitis obliterans
Buffer system, 193
Bulbourethral glands, 1013
Bulimia nervosa, 237b, 238–239
Bullae, 1167, 1167f
BUN. *See* Blood urea nitrogen
Bundle of His, 389, 389f
Buphthalmos, 983
Burkitt lymphomas, 256, 256c
Burn. *See* Thermal injury
Bursae, 1093–1094, 1094f

C

CABG. *See* Coronary artery bypass grafting
Cachexia
  in cancer, 146–147
  with heart failure, 495
CAD. *See* Coronary artery disease
Cadherins, 30, 31b
CAH. *See* Congenital adrenal hyperplasia
Calcarine sulcus, 851–852
Calcifications, pathologic, 37, 37f
Calcipotriene ointment, for psoriasis, 1186
Calcitonin, in bone formation and metabolism, 1090, 1090t
Calcium
  absorption of, 722, 723t
  imbalance of
    cellular injury from, 44
    with CKD, 648–649
Calcium antagonists, 461
Calcium balance, 183–191, 184f, 186b
  disorders of, 185–189, 186f
  regulation of, 186
Calcium stones, in kidneys, 635–636, 635t
Callus, 1167
Calor, in inflammation, 55
Caloric testing, 1004
Calories, 224
  energy requirements for, 226, 227t
cAMP. *See* Cyclic adenosine monophosphate
CAMs. *See* Cell adhesion molecules
Cancer. *See also specific anatomic site*
  anorexia and cachexia in, 146–147
  childhood, 154–156, 154f
  clinical manifestations of, 146–148
  diagnosis of, 149–151, 149t, 155
  etiology of, 139–146, 155
  fatigue and sleep disorders in, 147
  genetic basis of, 139–142
  host and environmental factors of, 142–143
  invasion of, 137
  metastasis. *See* Metastasis
  molecular basis of, 139–142
  screening for, 148
  survivors of childhood and adolescent, 155–156
  treatment of, 151–155
Cancer-associated genes, 139–140, 140f
Candida albicans, 307
  in vagina, 1072, 1072f
Candidiasis

skin, 1176
vaginal, 1072, 1072f
CAPD. *See* Continuous ambulatory peritoneal dialysis
Capillaries
colloidal osmotic pressure in, 163–164, 164f
filtration of, 163, 165
hydrostatic pressure in, 163–164, 164f
lymphatic drainage by, 163, 165, 165f
obstruction of, 165
oxygen transport to, 532, 532f
peritubular, 603f, 604
permeability of, in edema, 165
structure of, 399, 399f
Capillary pores, 399, 399f
Caput medusae, 748
Carbaminohemoglobin, 535
Carbohydrates
digestion and absorption of, 695–696, 695f, 695t, 722, 723t
liver in, 732, 732t, 733f
energy requirements for, 226–228
renal blood flow and, 613
for wound healing, 83, 85
Carbon, cellular accumulation of, 37
Carbon dioxide
bicarbonate production and, 192–193
increased production of, 204
transport of, 194–195, 194f–195f, 535
Carbonic acid, 535
Carbonic anhydrase, 192, 194, 535
Carcinogenesis, apoptosis and, 45
Carcinoma, 132–133, 133t. *See also specific types*
Cardiac asthma, 495
Cardiac conduction system, 388–392, 389f
action potentials in, 389–390, 390f
disorders of, 391
electrocardiography of, 391–392, 391f–392f
refractory periods in, 390–391, 391f
Cardiac contractility, 395, 395f
Cardiac cycle, 392–394, 393f
atrial filling and contraction, 393f, 394
diastole, 393–394, 393f
systole, 392–393, 393f
Cardiac glycosides, for heart failure, 498
Cardiac muscle, 25, 31b
Cardiac orifice, 681
Cardiac output (CO), 394
control of, 487
Cardiac region, 681
Cardiac reserve, 394
Cardiac resynchronization, for heart failure, 498
Cardiac tamponade, 448–449, 449f
Cardiogenic embolic stroke, 945
Cardiogenic shock, 500c, 500–502, 501f–502f
Cardioinhibitory center, 402
Cardiomyopathies, 461–465
arrhythmogenic right ventricular, 463
dilated, 463, 463f
hypertrophic, 462, 462f
myocarditis, 464
peripartum, 464
primary restrictive, 463–464
secondary, 465, 465c
takotsubo, 464–465
Cardiovascular center, of brain, 425
Cardiovascular system
disorders of, in chronic kidney disease, 648f, 650
thyroid hormone and, 785
Carditis, rheumatic, 467–468
Carina, 516–517, 517f
Carpal tunnel syndrome, 904–905, 904f
Carrier, in genetics, 102, 104
Carrier state, of hepatitis, 738
Cartilage
repair of, 1083
types of, 1082–1083
Caseous necrosis, 46
Catagen follicles, 1166
Cataracts, 972–973
Catastrophic antiphospholipid syndrome, 271
Catecholamine, in autonomic nervous system, 860f, 861
Catheter-induced infection, urinary tract infection, 672
Cauda equina, 845
Caveolae, 17
CCK. *See* Cholecystokinin
CCPD. *See* Continuous cyclic peritoneal dialysis
$CD4^+$. *See* Helper T cells
$CD8^+$. *See* Cytotoxic T lymphocytes
CDH. *See* Chronic daily headache
CDKs. *See* Cyclin-dependent kinases
CD molecules. *See* Cluster of differentiation molecules
Celiac disease, 722–723
Celiac sprue. *See* Celiac disease
Cell(s)
communication among, 13–14, 13f
differentiation of, 73–74, 74b, 74f
adaptations of, 33–36, 34f
division. *See* Meiosis; Mitosis
function of
components of, 1–9, 2f, 3b, 3f–8f
genetic control of, 89–97, 90b
integration of, 12–20
growth of, adaptations of, 33–36, 34f
in inflammation, 52–55, 52f
metabolism of, 9–12, 9f
aerobic, 10b–11b, 12
anaerobic, 10b, 12
proliferation of, 73–74, 74b, 74f
tumor transformation of, 142, 142f
Cell adhesion molecules (CAMs), 30–31, 31b
in inflammation, 54
Cell body, of neuron, 830
Cell coat, 3, 9b
Cell columns, 840–841, 841f, 842t–843t, 843
dorsal horn, 841, 841f
ventral horn, 841, 841f, 843
Cell cycle, 74–77, 76f–77f
Cell death, 44–46, 44f–45f
Cell density-dependent inhibition, 135
Cell-derived mediators, 58–62, 59f
Cell differentiation, 21
Cell injury, 38–49, 38b
biologic agents, 41
causes of, 38–42
chemical, 40–41
free radicals, 42–43
hypoxic, 43–44
mechanisms of, 42–44, 42f
nutritional imbalances, 42
physical, 38–39, 39f
radiation, 39–40
reversible, 44, 44f
Cell junctions, 29–30, 29f, 31b
Cell-matrix, extracellular matrix interactions with, 78–79, 79f

Cell-mediated hypersensitivity disorders, 351–352, 351f
Cell-mediated immunity, 320f, 321, 332, 335f, 341
  T lymphocytes and, 339–341, 340f
Cell membrane, 2–3, 3b, 3f, 9b
  potentials of, 17–20, 18b–19b
  receptors of, 13–14, 13f
  transport mechanisms of, 14–17, 14f–15f
Cell surface receptors, 766–768, 766f
Cellular aging, 47–49
Cellular immunity. *See* Cell-mediated immunity
Cellular response, to stress, 33–38, 34b, 34f–35f, 37f
Cellular swelling, 44
Cellules, 664
Cellulitis, 1177, 1177f
Cement lines, 1136, 1137f
Central auditory pathways, 994–995, 995f
  disorders of, 996
Central chemoreceptors, 537
Central circulation, 377–378, 378f
Central cord syndrome, 919, 919f
Central cyanosis, 567
Central integrative pathways, of autonomic nervous system, 857, 859
Central nervous system (CNS), 28
  circulatory system response of, 403
  CKD and, 651
  demyelinating disorders of, 914–916, 915f
  longitudinal tracts of, 843–845, 843f–844f, 844t
  lymphomas of, 953
  segmental organization of, 840–845, 840f–841f, 842t–844t, 843f–844f
  in stress response, 212, 213f
  supporting cells of, 832–833, 832f
Central tolerance, 355–356
Central venous pressure, 398
Centriacinar emphysema, 581, 581f
Centric fusion, in chromosome, 118, 118f
Centrioles, 8
Cerebellum
  disorders of, 908–909
  in motor function, 893
Cerebral circulation, 941–943, 942f
Cerebral edema, 929
Cerebral hemispheres, 848f, 850, 851f
Cerebral vasospasm, 949–950
Cerebrospinal fluid (CSF), 852–854, 853f
Cerebrospinal fluid–brain barrier, 854–855
Cerebrovascular disease, 941–950
  circulation and, 941–943, 942f
  stroke. *See* Stroke
Cervicitis, 1043–1044
Cervix, 1035, 1035f
  cancer of, 1044–1046, 1044b
  disorders of, 1043–1046, 1044b, 1044f
CF. *See* Cystic fibrosis
CFTR. *See* Cystic fibrosis transmembrane regulator
CFUs. *See* Colony-forming units
Chancroid, 1071
Channelopathies, 15
Channel proteins, 14
Checkpoints, of cell cycle, 74–75, 77, 77f
Chemical(s)
  cancer and, 144c, 144–145
  cellular injury from, 40–41
  as teratogenic agent, 124
Chemical gastropathy, 707
Chemical synapses, 834–835
Chemokines, 324–325
  in inflammation, 61, 61f
  in metastasis, 138
Chemoreceptor reflexes, 425
Chemoreceptors, for breathing regulation, 537
Chemotaxis, inflammatory response, 57–58
Chemotherapy
  for cancer, 151–153, 152f
  side effects of, 152–153
Cherry angiomas, 1203
Chest wall, in neonate, 557–558, 558f
Cheyne-Stokes respiration, 495
Chickenpox. *See* Varicella
Childhood, cancer, 154f
Childhood, male reproductive system disorders of, 1028–1030, 1028f–1029f
Children
  bronchial asthma in, 578–579
  cancer in, 154–156, 154f
  chronic kidney disease in, 655
  fever in, 70
  gastroesophageal reflux disease in, 703–704
  GH and IGF deficiency in, 779–780, 779f
  GH excess in, 780, 781f
  hearing loss in, 998–999
  heart disease in, 474–483
  heart failure in, 508–510, 509c
  HIV in, 373
  hypertension in, 434–436, 435t
  obesity in, 234–235
  pain in, 886–887
  respiratory tract infections in, 560–563, 561f, 561t, 563c
  rheumatic disorders in, 1153–1154
  short stature in, 778c, 778–779
  skeletal disorders in, 1116–1127
  skin disorders in, 1198–1202, 1199f–1201f
  urinary tract infections in, 674
Chill, 68–69, 68f
Chlamydiaceae, 305–306
Chlamydial conjunctivitis, 968
Chlamydial infections, 1074–1075, 1075f
Chloride/bicarbonate exchange, 196
Cholangiocarcinoma, 751
Cholangitis, 754–755
Cholecystitis, 753–754
Cholecystokinin (CCK), 229, 229f, 690–691, 690t, 753
Choledocholithiasis, 754–755
Cholelithiasis, 753, 753f
Cholestasis, 735–736
Cholestatic drug reactions, 743
Cholesterol
  bad. *See* Low-density lipoprotein
  good. *See* High-density lipoprotein
Cholinergic receptors, in autonomic nervous system, 860–861, 860f
Chondrocytes, 1082
Chondromas, 1114
Chondrosarcoma, 1114f, 1115
Chorea, 468, 899
Chorionic villus sampling, 127f, 128
Choroid plexus, 832f, 833, 853–854, 853f
Chromatin, 3–4, 91–92, 91f
Chromosomes, 91, 91f, 97–100, 98b, 98f. *See also* Sex chromosomes
  abnormalities of, 134–135
  disorders of, 117–122
  numeric disorders of, 119–120, 119f
  structure of, 98f, 99–100, 100f
    abnormalities in, 118–119, 118f

Chronic daily headache (CDH), 885–886
Chronic hypertension, 433t, 434
Chronic inflammation, 52
Chronic ischemic heart disease, 460–461, 460f
Chronic kidney disease (CKD), 645–656, 646b
  bone disorders of, 648–649, 648f
  cardiovascular disorders with, 648f, 650
  in children, 655
  clinical manifestations of, 647–652, 648f
  definition and classification of, 645–647, 646f, 646t
  dietary management of, 654
  drug elimination disorders with, 648f, 651–652
  in elderly, 655–656
  glomerular filtration rate and, 645–647, 646f, 646t
  hematologic disorders with, 648f, 649–650
  management of, 652–654, 653f
  mineral disorders of, 648–649, 648f
  nitrogenous waste accumulation with, 648f, 650–651
Chronic lymphocytic leukemia (CLL), 254
Chronic myelogenous leukemia (CML), 254–255, 255f
Chronic obstructive pulmonary disease (COPD), 579–583
  chronic bronchitis, 581
  diagnosis and treatment of, 582–583
  emphysema, 579–581, 580f–581f
  manifestations of, 581–582, 582f
Chronic rejection, 354
Chronic wasting disease, 301
Chvostek sign, 188, 188f
Chylothorax, 570
Chyme, 685
Cigarette smoking. *See* Smoking
Cilia, 8, 8f, 21–22
Cingulate herniation, of brain, 931, 931f
Circadian rhythms, 217
Circulation. *See also* Blood flow
  arterial system, 397–398, 397f
  bronchial, 518f, 519–520
  cerebral, 941–9943, 942f
  collateral, 402
  coronary, 450–451, 450f
  disorders of
    arterial, 407–422, 407b
    venous, 439–443, 439b
  fetal and perinatal, 474–475, 474f
  microcirculation. *See* Microcirculation
  neural control of, 402–403
  organization of, 377–380, 378b, 378f–379f
  pulmonary. *See* Pulmonary circulation
  systemic, 396–402, 397b
  venous, 398, 398f
    of lower extremities, 439–440, 440f
Circulatory failure. *See* Shock
Circulatory overload, 174
Cirrhosis, 745–746, 746f
  alcoholic, 744, 745f
  biliary, 742
Citric acid cycle, 10b, 12
CJD. *See* Creutzfeldt-Jakob disease
CKD. *See* Chronic kidney disease
Clathrin, 17
Clathrin-coated pits, 17
Cleft lip, 117, 117f
Cleft palate, 117, 117f
Climacteric, 1058
Clitoris, 1033, 1034f
CLL. *See* Chronic lymphocytic leukemia
Cloning, of genes, 105, 105f
Clostridium difficile colitis, 715
Clot
  dissolution of, 267, 267f, 269
  increase in activity of, 270–271
  retraction of, 267, 267f, 269
Clubfoot, congenital, 1123, 1123f
Cluster headache, 884–885
Cluster of differentiation (CD) molecules, 322
CML. *See* Chronic myelogenous leukemia
CNS. *See* Central nervous system
CO. *See* Cardiac output
Coagulase, 310
Coagulation. *See also* Hypercoagulability
  defects of, 749
  disorders of, 274–275
  in hemostasis, 267–269, 267f–268f
  system components of, 264–265
Coagulation necrosis, 46
Coccidioidomycosis, 553
Codons, 92, 92t, 94
Cognitive deficits, from stroke, 948
Colchicine, 99
Colitis, *Clostridium difficile*, 715
Collagen, 30, 31b
Collateral circulation, 402
Collecting tubule, 603f, 605
  in urine formation, 608–610, 609f–610f
Colloid, 783
Colloidal osmotic pressure, 163–164, 164f
  in edema, 165
Colon, motility in, 689
Colonic diverticula, 716, 716f
Colonization, 300
Colonoscopy, for colorectal cancer, 725
Colony-forming units (CFUs), 244
Colony-stimulating factors (CSFs), 245, 325–326, 325t
Colorectal cancer, 724–725
Columnar epithelium, 21, 24f
Comedones, 1179
Commensal flora, 300
Commensalism, 300
Comminuted fracture, 1103, 1103f
Common cold, 541
Common variable immunodeficiency (CVID), 361
Community acquired, 309
Community-acquired pneumonia, 546–547
Compartment syndrome, 1105, 1108, 1108f
Compensatory hyperplasia, 35
Compensatory hypertrophy, 35
Complement-mediated hypersensitivity disorders, 349–350, 349f
Complement system, 329–331, 330f–331f
Complex regional pain syndrome (CRPS), 881–882
Compliance
  of blood vessels, 381
  of lungs, 523–524, 524f
Compound fracture, 1102–1103, 1103f
Compound nevi, 1194
Compression therapy, for chronic venous insufficiency, 441
Computed tomography (CT)
  of body fat, 230
  for endocrine function, 772
Conditioning factors, 211
Conducting airways, 513–518, 514b, 514f–515f
Conduction, in heat loss, 66t, 67
Conductive hearing loss, 996–997, 997c
Condylomata acuminata. *See* Genital warts
Congenital, scoliosis, 1125

Congenital adrenal hyperplasia (CAH), 793, 793f
Congenital disorders, 109–129, 110b
  with atypical patterns of inheritance, 114–116
  autosomal dominant, 110–113, 110f, 111t
  autosomal recessive, 113–114, 113f
  chromosomal, 117–122
  environmental influences in, 123–126, 123f, 124c, 124b
  glaucoma, 983
  hypothyroidism, 786–787, 786f
  mitochondrial, 115–116, 116t
  multifactorial inheritance disorders, 116–117
  single-gene, 110–116, 111t
  skeletal deformities, 1120–1123
  X-linked, 114, 115f
Congenital heart disease, 475–481
  aorta, coarctation of, 477f, 480–481
  atrial septal defects, 477f, 478, 478f
  endocardial cushion defects, 477f, 479
  functional single-ventricle anatomy, 481, 481f
  great arteries, transposition of, 477f, 480
  manifestations and treatment of, 476
  patent ductus arteriosus, 476–478, 477f
  pulmonary blood flow in, 475–476
  pulmonary stenosis, 477f, 479–480
  shunting and cyanotic disorders, 475
  tetralogy of Fallot, 477f, 480
  ventricular septal defects, 477f, 478–479
Congenital infection, 308
Conidia, 306
Conjunctiva, 967–968
Conjunctivitis, 968–969, 968f
Connective tissue, 21b, 22t, 24–25, 25f, 31b
  adipose, 25
  healing and, 80–87, 80b, 81f
    cutaneous, 82–85, 82f, 83f
    factors affecting, 83–87
    phases of, 80–82, 81f
  loose, 24–25
  reticular and dense, 25
Consanguineous mating, 113
Consciousness
  deteriorating, 939–940, 940f
  diffuse brain injury and, 938–939, 938b, 939f
  levels of, 939, 939t
Constipation, 719
Constrictive pericarditis, 449–450
Contact, with infectious agents, 308
Contact dermatitis, allergic, 352
Continence, maintenance of, 663
Continuous ambulatory peritoneal dialysis (CAPD), for CKD, 653
Continuous cyclic peritoneal dialysis (CCPD), for CKD, 653
Continuous fever, 68, 69f
Continuous renal replacement therapy (CRRT), for acute renal failure, 645
Contraction
  of skeletal muscle, 26–27, 27f
  of smooth muscle, 28
Contrast venography, for pulmonary embolism, 590–591
Control systems, for homeostasis, 210–211, 210f
Conus medullaris syndrome, 919–920
Convalescent stage, of infection, 311–312, 311f
Convection, in heat loss, 66t, 67
Cooley anemia. *See* β-Thalassemias
Coombs test, 290
Cooper ligaments, 1059, 1059f
COPD. *See* Chronic obstructive pulmonary disease
Cornea, 969, 970f
Corns, 1167
Coronary artery bypass grafting (CABG), for myocardial infarction, 458, 458f
Coronary artery disease (CAD), 450–461, 454b
  acute coronary syndrome. *See* Acute coronary syndromes
  chronic ischemic heart disease, 460–461, 460f
  pathogenesis of, 451, 454
Corpora cavernosa, 1014
Cor pulmonale, 490, 593
Corpus callosum, 848f
Corpus luteum, 1040
Corpus spongiosum, 1014
Cortical brain centers, in bladder control, 661f, 662
Cortical collecting tubule, 605
Cortical nephrons, 603f, 604
Corticosteroids, for COPD, 583
Corticotropin-releasing factor (CRF), in stress response, 212, 213f, 214
Cortisol, 792, 792t
  stress response of, 214
Costimulators, 332
Cotransport. *See* Secondary active transport
Cough reflex, 538
Countercurrent, 609
Coxiella, 305–306
Cradle cap, 1199
Cranial nerves, organization of, 840
C-reactive protein (CRP), in inflammation, 64
Creatine kinase, 456
Creatinine, serum, 617–618, 617f, 617t
Creutzfeldt-Jakob disease, 301
Creutzfeldt-Jakob disease (CJD), 962
CRF. *See* Corticotropin-releasing factor
Cristae, 7, 7f
Crohn disease, 711f, 711t, 712–713
Crossing over, 98, 99f
Croup, 561–562, 561f, 561t
CRP. *See* C-reactive protein
CRPS. *See* Complex regional pain syndrome
CRRT. *See* Continuous renal replacement therapy
Cryptorchidism, 1029–1030, 1029f
Crystal-induced arthropathies, 1151–1152, 1152f, 1154–1155
CSF. *See* Cerebrospinal fluid
CSFs. *See* Colony-stimulating factors
CT. *See* Computed tomography
CTLs. *See* Cytotoxic T lymphocytes
Cuboidal epithelium, 21, 24f
Culture, for infection diagnosis, 312, 313f
Curling ulcer, 709
Cushing disease, 275, 795
Cushing reflex, 403
Cushing syndrome, 795–796, 796f
Cushing ulcer, 709
Cutaneous pain, 874–875
Cuticle. *See* Eponychium
CVID. *See* Common variable immunodeficiency
Cyanosis, 567
  with heart failure, 495
Cyclic adenosine monophosphate (cAMP), 14, 20b
Cyclin-dependent kinases (CDKs), in cell cycle, 75, 77, 77f
Cyclins, in cell cycle, 75, 77, 77f
Cycloplegia, 972
Cystatin C, 618
Cystic diseases, of kidneys, 630–632, 631f
Cystic fibrosis (CF), 584–586, 585f
Cystic fibrosis transmembrane regulator (CFTR), 584–586
Cystine stones, 635–636, 635t

Cystocele, 1050, 1051f
Cysts, renal, 632
Cytogenetics, 99
  prenatal analyses, 128–129
Cytokines, 324–326, 325t
  blood cell regulation, 244–245
  in inflammation, 57–58, 61, 61f, 329
  in stress response, 215
Cytopathic effect, 312
Cytoplasm, 2, 2f, 4–7, 5f–7f, 9b, 302
Cytoplasmic membrane, 302
Cytosine, in DNA, 90
Cytoskeleton, 2, 7–9, 8f, 9b
Cytosol, 2
Cytotoxic edema, 930
Cytotoxic T lymphocytes (CTLs), 322, 335f, 336, 340–341, 340f, 351, 351f

D

Daily values (DVs), 226
Damage theories, of cellular aging, 47–48
Dane particle, 738
DCM. *See* Dilated cardiomyopathy
DDAVP. *See* Desmopressin acetate
DDH. *See* Developmental dysplasia of the hip
Dead air space, 529
Death receptors, 46
Decerebrate posturing, 933, 934f, 940
Decorticate posturing, 933, 934f, 940
Decubitus ulcers. *See* Pressure ulcers
Deep somatic pain, 874–875
Deep tendon reflex (DTR), 894–895, 897–899, 897f
Deep venous thrombosis (DVT), 442c, 442–443
  pulmonary embolism and, 590–591
  with spinal cord injury, 924
Defecation, control of, 689
Defervescence, 68f, 69
Defibrillator, for heart failure, 498
Dehisce, 86
Delayed hemodynamic response, 58
Delayed-type hypersensitivity (DTH) disorders, 352
Delayed union, 1105, 1105t
Dementia, 959–963
  Alzheimer type, 959–961, 960f
  in Creutzfeldt-Jakob disease, 962
  frontotemporal, 962
  in Huntington disease, 962–963
  vascular, 961–962
  in Wernicke-Korsakoff syndrome, 962
Demyelinating disorders, of central nervous system, 914–916, 915f
Dendritic cells, 830f, 831
  in adaptive immunity, 333–334
  in innate immunity, 321
Dendrocytes, dermal, 1163
Denervation atrophy, 34
Dennie-Morgan folds, 1182
Dense connective tissue, 25
Deoxyribonucleic acid. *See* DNA
Deoxyribose, in DNA, 90
Depolarization, 834, 834f
Dermal dendrocytes, 1163
Dermatitis
  allergic contact, 352
  atopic, 1182, 1182f
Dermatomes, 864–865, 865f
Dermatomyositis, juvenile, 1153–1154
Dermatophytes, 307
Dermatophytid reaction, 1175, 1176f
Dermatoses
  allergic and hypersensitive, 1181–1184, 1182f–1184f
  papulosquamous, 1184–1187, 1185f–1187f
Dermis, 1160f, 1162–1164
Desmopressin acetate (DDAVP), for coagulation disorders, 274
Desmosomes, 29–30
Detrusor muscle, 659–660, 660f
Detrusor–sphincter dyssynergia, 662, 666
Detumescence, 1014
Developmental dysplasia of the hip (DDH), 1121–1122, 1121f
DEXA. *See* Dual electron x-ray absorptiometry
Dexamethasone suppression test, for Cushing syndrome, 796
DI. *See* Diabetes insipidus
Diabetes insipidus (DI), 171
Diabetic glomerulosclerosis, 626–627
Diabetic retinopathy, 976–978, 977f
Dialysis. *See* Hemodialysis; Peritoneal dialysis
Diaper dermatitis, 1198–1199
Diaphragm, 522, 522f
Diaphysis, 1083–1084, 1084f
Diarrhea, 717–718, 718c
  inflammatory, 718
  osmotic, 718
  secretory, 718
Diastole, 393–394, 393f
Diastolic heart failure, 489
Diastolic pressure, 422, 422f, 425, 425f
DIC. *See* Disseminated intravascular coagulation
Diencephalon, 849–850, 850f
Dietary Reference Intakes (DRIs), 226
Differentiation, cellular
  adaptations of, 33–36, 34b, 34f
  neoplasms and, 132, 134, 135f
Diffuse brain injury, 938–940, 938b, 938t–940t, 939f–940f
Diffuse large B-cell lymphomas, 256, 256c
Diffuse lymphoid tissue, 248
Diffuse parenchymal lung diseases. *See* Interstitial lung disease
Diffusion, 15–16, 20b, 160–161, 161f
  of gases, 531, 531f
  impaired, 596
  in respiration, 566–567
Diffusion potentials, 18b, 20
DiGeorge syndrome. *See* Thymic hypoplasia
Digestion, 694–697, 694f
  of carbohydrates, 695–696, 695f, 695t
  of fats, 696, 696f
  of protein, 696–697
Digestive tract. *See* Gastrointestinal system
Digitalis, for heart failure, 498
Dilated cardiomyopathy (DCM), 463, 463f
Diluting segment, 605, 608
Dimorphic, 553
Direct antigen detection, 313
Disease-modifying antirheumatic drugs (DMARDs), 1142
Dislocation, 1098
  of hip, 1101
Dissecting aneurysm, 419–420, 420f
Disseminated intravascular coagulation (DIC), 275–277, 276c, 276f
  with shock, 507
Distensibility, of blood vessels, 381
Distributive shock, 500c, 501f, 504–506
Disuse atrophy, 34
Diuretics, for heart failure, 497
Diverticular disease, 716–717, 716f
Diverticulosis, 716, 716f

DMARDs. *See* Disease-modifying antirheumatic drugs
DMD. *See* Duchenne muscular dystrophy
DNA
  genetic code, 92, 92t
  genetic variability in, 93
  mitochondrial, 7, 93
  in nucleus, 4, 4f
  packaging of, 91–92, 91f
  recombinant, 104–106
  repair of, 92–93
  structure of, 90–91, 90f
DNA fingerprinting, 105, 106f
DNA probe hybridization, 313–314
DNA sequencing, for infection diagnosis, 313–314, 314f
Dolor, in inflammation, 55
Dominant trait, 102
Dorsal column–medial lemniscal pathway, 865–866, 866f
Dorsal root ganglia, 838, 839f
Doubling time, 136
Down-regulation, 765
Down syndrome, 119–120, 120f
Dressler syndrome, 459
DRIs. *See* Dietary Reference Intakes
Drug-induced liver disease, 743
Drug-induced neuromuscular junction disorder, 901–903, 901f
Drug-induced photosensitivity, 1189
Drug-induced skin eruptions, 1183–1184, 1184f
Drug-induced thrombocytopenia, 273
Drug-related nephropathies, 629–630
Drugs
  bladder control and, 662, 662t
  cellular injury from, 40
  elimination of, 615
    with CKD, 651
  liver metabolism of, 742–743
  for pain, 878–879
  as teratogenic agent, 124
DTH disorders. *See* Delayed-type hypersensitivity disorders
DTR. *See* Deep tendon reflex
Dual electron x-ray absorptiometry (DEXA), for endocrine function, 772
Duchenne muscular dystrophy (DMD), 900–901, 900f
Ductus venosus, 474
Dumping syndrome, 688
Dural cisterna spinalis, 847
Dura mater, 852, 852f
DVs. *See* Daily values
DVT. *See* Deep venous thrombosis
Dwarfism, psychosocial, 779
Dysarthria, from stroke, 948
Dysdiadochokinesia, 899
Dysfunctional bleeding, 1055–1056
Dysmenorrhea, 1056–1057
Dysmetria, 899
Dysphagia, 701
Dysplasia, 34f, 36
Dysplastic nevi, 1194, 1195f
Dyspnea, 495, 538–539
Dystrophic calcifications, 37, 37f

E

Ear
  external, 988–989, 989f
  inner, 994–996, 994f–995f
  middle, 989f, 990
Ear disorders. *See also* Hearing loss
  external, 989
  inner, 995–996
  middle, 990b, 991–994
Eating disorders, 237–239, 237b
EBV. *See* Epstein-Barr virus
Eccrine sweat glands, 1164
ECF compartment. *See* Extracellular fluid compartment
ECG. *See* Electrocardiography
Eclampsia, 433–434, 433t
ECM. *See* Extracellular matrix
Ectoderm, 21, 23f
Ectopic pacemaker, 391
Edema, 163–167, 166c, 166f
  capillary filtration in, 163, 165
  causes of, 163, 166c
  cerebral, 929
  colloidal osmotic pressure in, 165
  with heart failure, 494–495
  with spinal cord injury, 924
EER. *See* Estimated energy requirements
Effector, 13–14
Efferent neurons, 28
Efferent pathways, in autonomic nervous system, 856–857, 857t
Effusion, 167
  pericardial, 448–449, 449f
  pleural, 520, 569–570
EIA. *See* Enzyme immunoassay
Eicosanoids, 762–763
Eisenmenger syndrome, 479
Ejaculation, 1014
Ejection fraction, in cardiac cycle, 394
Ejection period, in cardiac cycle, 392
Elastic recoil, 523
Elastin, 30, 31b
Elderly
  chronic kidney disease in, 655–656
  fever in, 70–71
  hearing loss in, 999
  heart failure in, 510
  hypertension in, 436
  immune response in, 343
  pain in, 887–888
  red blood cell changes in, 295–296
  rheumatic disorders in, 1154–1156
  skin disorders in, 1202–1203, 1202f–1203f
  urinary incontinence in, 670
  urinary tract infection in, 674–675
  wound healing in, 86–87
Electrical burns, cellular injury from, 39, 39f
Electrical synapses, 834
Electrocardiographic changes in, acute coronary syndromes (ACSs), 455f
Electrocardiography (ECG), 391–392, 391f, 392f
  of acute coronary syndromes, 454, 455f
Electrolytes, dissociation of, 160
Electron transport chain, 11b, 12
Electronystagmography (ENG), 1004
Elementary body, 305
Elimination
  of drugs, 615, 651
  of hormones, 765
  of minerals, 613–614
  of organic ions, 614
  of urea, 614–615
  of urine, 659–663, 660b, 660f–661f, 662t
Emphysema, 579–581, 580f, 581f
Empyema, 569
Emulsification, 696

Encephalitis, 952
Endocardial cushion defects, 477f, 479
Endocardium, 386
  disorders affecting, 466–468, 466f
Endochondromas, 1114
Endocrine stimulation, atrophy and, 34
Endocrine system, 761–772
  diagnostic tests for, 771–772
  disorders of, 749, 774–797
    hyperfunction, 775
    hypofunction, 774–775
    primary, secondary, and tertiary, 775
  hormones of. *See* Hormone(s)
Endocytosis, 15, 17
Endoderm, 21, 23f
Endogenous algesia, 874
Endolymph, 994
Endometrial cancer, 1044b, 1048–1049
Endometrioid carcinomas, 1044b, 1049
Endometriosis, 1047–1048, 1047f–1048f
Endometritis, 1046
Endomysium, 26, 26f
Endoneurium, 831, 903
Endonucleases, in DNA repair, 92–93
Endoplasmic reticulum (ER), 4–5, 5f, 9b
  nuclear membrane and, 4
Endosomes, 5, 6f
Endosteum, 1083f, 1084
Endothelial cells, 406, 406t
  in inflammation, 52–53
Endothelial dysfunction, 406
Endothelial relaxing factor. *See* Nitric oxide
Endothelins, 493
Endothelium, 21, 406
  blood flow control, 400–401, 401f
  in coagulation, 265
Endotoxins, 309, 309t
Energy, storage of, 225–226
  assessment of, 229–230, 230t
  regulation of, 228–229, 229f
Energy metabolism, 9, 9f, 224–226, 225b
ENG. *See* Electronystagmography
Enteric nervous system, 684, 686, 686f
Enterocolitis, infectious, 714–715
Enterocytes, 694–695
Enterohepatic circulation, 734, 734f
Enterotoxins, 310
Environment, internal, constancy of, 209–210, 210b
Environmental influences
  autoimmune disease and, 357–358
  on cancer, 142–143
  in congenital disorders, 123–126, 123f, 124c, 124b
Enzyme immunoassay (EIA), for HIV, 372
Enzyme-linked immunosorbent assay, for HIV, 372
Enzyme-linked receptors, 14, 20b
Enzymes
  for carbohydrate digestion, 695, 695t
  in infection diagnosis, 313
  inherited defects of, 289
  in lysosomes, 5
Eosinophils, 244f, 245, 246f
  in inflammation, 53–54
Ependymal cells, 28–29, 31b, 832f, 833
Ependymomas, 953
Epicardium, 385, 386f
Epidermis, 1160–1162, 1160f–1162f
Epididymitis, 1021
Epidural hematomas, 936–937, 936f
Epigenetic mechanisms, in cancer, 140
Epiglottitis, 561f, 561t, 562
Epimysium, 25–26, 26f
Epinephrine, in circulatory control, 401, 403
Epineurial sheath, 831
Epineurium, 903
Epiphyseal growth plate, 1086
Epiphyses, 1083–1084, 1084f
Epiphysis, femoral, slipped capital, 1125
Epispadias, 1028–1029, 1028f
Epistasis, 101
Epithelial barriers, in innate immunity, 326–327
Epithelial hyperplasia, 1061
Epithelial tissue, 21–24, 21b, 22t, 23f–24f, 31b
  glandular, 23–24
  renewal of, 24
  simple, 21–22
  stratified and pseudostratified, 22–23
  transitional, 23
Epithelioid cells, 63–64, 64f
Epitopes, 332–333, 333f
Eponychium, 1166, 1166f
Epstein-Barr virus (EBV)
  cancer and, 145
  in infectious mononucleosis, 250
Equilibrium potentials, 18b, 20
ER. *See* Endoplasmic reticulum
Erectile dysfunction. *See* Penile erection, dysfunction
Erosion, 1167
Error theories, of cellular aging, 47–48
Erythema marginatum, 468
Erythema multiforme minor, 1184, 1184f
Erythroblastosis fetalis, 295
Erythrocytes. *See* Red blood cell(s)
Erythrocyte sedimentation rate (ESR), in inflammation, 64
Erythroplasia of Queyrat, 1018
Erythropoiesis, 281–282, 282f
Erythropoietin, 282
  in renal failure, 649–650
  synthesis of, 615
Escherichia coli O157:H7, 715
Esophageal diverticula, 701
Esophageal lacerations, 701
Esophageal motility, 685, 688f
Esophageal phase, of swallowing, 685, 688f
Esophageal varices, 747f, 748
Esophagus, 680–681, 680f
  cancer of, 704
  disorders of, 700–704, 702f–703f. *See also* Gastroesophageal reflux disease
ESR. *See* Erythrocyte sedimentation rate
Estimated Average Requirement, 226
Estimated energy requirements (EER), 227t
Estrogens, 1037–1038, 1038t
Euchromatin, 4
Eumelanin, 1162
Eustachian tube, 989f, 990
  disorders of, 990, 990b, 991f
Euvolemic hypotonic hyponatremia, 175
Evaporation, in heat loss, 66t, 67
Evasive factors, 309t, 310
Ewing sarcoma, 1114f, 1115–1116
Exercise, for heart failure, 497
Exhaustion stage, in GAS, 211
Exocytosis, 15, 17
Exons, 95, 96f

Exotoxins, 309–310, 309t
Expiration, 522–523, 522f–523f
Expressivity, 100
  in congenital disorders, 111
Extracellular fluid (ECF) compartment, 160, 161t
  body fluid distribution, 162–163, 162f
Extracellular matrix (ECM), 30, 31b
  cell-matrix interactions with, 78–79, 79f
  in healing, 81
Extracorporeal shock-wave lithotripsy, 637
Extremities
  arterial disease of, 415, 418–419
  torsional and angular deformities of, 1117–1119, 1118f–1119f
  venous circulation of, 439–440, 440f
Extrinsic apoptosis, 45–46, 45f
Extrinsic reflexes, 425
Exudate, 569
Exudative retinal detachment, 978, 978f
Eye, 966–967, 967f
  muscles of, 984–985, 985f, 985t
Eye disorders, 966–988
  conjunctival, 967–969, 968f
  corneal, 969–971, 970f
  lens, 971–973, 972f
  movement, 984–988, 985f–986f, 985t
  neural, 983–984, 983f–984f
  retinal, 973–980, 974f–978f, 975b, 980f

F

Facilitated diffusion, 15, 20b
Factor VIII replacement therapy, 275
FAD. *See* Flavin adenine dinucleotide
Fallopian tubes, 1035, 1036f
Falx cerebri, 852, 853f
Farsightedness. *See* Hyperopia
FAS. *See* Fetal alcohol syndrome
Fascicles, 26, 26f, 831
Fast response, cardiac action potential, 390, 390f
Fat embolism syndrome (FES), 1109
Fatigue
  in cancer, 147
  with heart failure, 495
Fatigue stress fracture, 1102
Fat necrosis, 1060
Fats
  digestion and absorption of, 696, 696f, 722, 723t
    liver in, 732, 732t, 733f
  energy requirements for, 226–228
  for wound healing, 83, 85
Fatty liver disease, 744, 744f
  nonalcoholic, 744–745
Fatty streaks, 413, 413f
Feedback regulation, of hormones, 769–771, 770f
Feedback systems, for homeostasis, 210–211, 210f
Female athlete triad, 1132
Female reproductive system, 1033–1064, 1034b.
    See also specific components
Femoral epiphysis, slipped capital, 1125
Femoral torsion, 1118–1119, 1118f–1119f
Fenestrations, 399, 604, 605f
Ferritin, 281, 281f
FES. *See* Fat embolism syndrome
Fetal alcohol syndrome (FAS), 125, 125f
Fetal biopsy, 128
Fetal hemoglobin (HbF), 280
α-Fetoprotein (AFP), for prenatal screening and diagnosis, 127–128
Fetor hepaticus, 749, 749f
FEV. *See* Forced expiratory volume
Fever, 65–71
  causes of, 67, 68f
  in children, 70
  in elderly, 70–71
  febrile response and, 67–71, 67b
  management of, 69–70
  manifestations of, 68–69f, 68f
  patterns of, 68, 69f
  purpose of, 67–68
Fever of unknown origin (FUO), 69
Fiber, requirements of, 228
Fibrillation, 391
Fibrinolytic drugs, for myocardial infarction, 457–458
Fibrinous exudates, 62
Fibroblasts, 31b
  in healing, 81, 82, 84, 84f
Fibrocartilaginous callus formation, 1106, 1106f
Fibroma, 132–133, 133t
Fibrosarcoma, 132–133, 133t
Fibrosis, 80
Fibrous atheromatous plaque, 413, 413f
Fibrous proteins, 30
Fibrous skeleton, of heart, 386–388, 387f–388f
Fick law of diffusion, 531
Fight-or-flight response, 214
Filtrate, 604, 605f
Filtration slits, 604, 605f
Fimbriae, 303
Fingernails, 1166, 1166f
First-degree burn, 1189
Flaccid bladder, 661f, 666–667, 666b
Flagella, 8, 8f, 303
Flavin adenine dinucleotide (FAD), in fuel metabolism, 10b–11b, 12
Floppy mitral valve syndrome, 471, 471f
Fluid(s), 159–167, 160f, 161t
  capillary/interstitial exchange of, 163–167, 164f–165f
  compartmental distribution of, 162–163, 162f
  diffusion of, 160–161, 161f
  osmosis of, 161–162, 161f
  retention of, with heart failure, 494–495
  third-space accumulation of, 167
  water balance, 167–169
    disorders of, 172–177, 172f, 173b
Flush, 68f, 69
Focal segmental glomerulosclerosis, 625
Folic acid, deficiency in, 125–126
Folic acid-deficiency anemia, 291–292
Follicles
  hair, 1165–1166, 1165f
  in lymph system, 247–248, 248f
  in ovaries, 1039–1040, 1039f
  in thyroid, 783, 783f
Follicular lymphomas, 256, 256c
Fomites, 309
Food
  allergies to, 348–349
  intake of, regulation of, 228–229, 229f
Foramen ovale, 478, 478f
Forced expiratory volume (FEV), 527, 527t
Forced vital capacity (FVC), 527, 527t
  in asthma, 576
Forebrain, 842t–843t, 848f, 849–850, 850f–852f
Foreign body, wound healing and, 86
Foreign body giant cell, 63–64, 64f
Fracture(s), 1102–1109
  bone healing, 1104–1107, 1106f–1107f

classification of, 1102–1103, 1103f
complications of, 1105, 1105t, 1108–1109, 1108f
diagnosis and treatment of, 1103–1104
of hip, 1101f, 1102
manifestations of, 1103, 1103f
Fracture blisters, 1105
Fragile X syndrome, 115
Frank-Starling mechanism, 394–395, 395f, 491, 492f
FRC. *See* Functional residual capacity
Free nerve endings, 868
Free radicals
cellular injury and, 42–43
in inflammation, 62
Frontal lobe, 850, 851f
Frontotemporal dementia (FTD), 962
Fructose, digestion and absorption of, 695, 695f, 695t
FTD. *See* Frontotemporal dementia
Full-thickness skin graft, for thermal injury, 1192
Fulminant hepatitis, 741–742
Functio laesa, in inflammation, 55
Functional residual capacity (FRC), 526
Fundus, 681, 681f
Fungal infections
of respiratory tract, 553–554
of skin, 1172–1176, 1174f–1176f
Fungi, 306–307, 306f
FUO. *See* Fever of unknown origin
Fusiform aneurysm, 419, 420f
FVC. *See* Forced vital capacity

G

GAGs. *See* Glycosaminoglycans
Galactose, digestion and absorption of, 695, 695f, 695t
Gallbladder
cancer of, 755
disorders of, 752–755, 752f
Gamma motor neurons, 895, 897, 897f
Gangliosidoses, 114
Gangrene, 46–47, 47f
Gap junctions, 30, 31b, 834, 859–860
Gap phases, of cell cycle, 74–77, 76f–77f
GAS. *See* General adaptation syndrome
Gas(es)
basic properties of, 520–521
diffusion of, 531, 531f
exchange and transport of, 528–536
in neonates and children, 528–536
Gas gangrene, 47
Gastric acid, secretion of, 692–693, 692f
Gastric inhibitory peptide, 687
Gastric mucosal barrier, 682, 682f, 705–706
Gastric secretion, 691–693, 691t, 692f
Gastrin, 690, 690t
Gastritis, 706–707, 706f
Gastroesophageal reflux disease (GERD), 702–703, 702f–703f
in children, 703–704
Gastroesophageal sphincter, 681
reflux, 702f
Gastrointestinal system
CKD and, 651
digestion and absorption in, 694–697, 694f
carbohydrates, 695–696, 695f, 695t
fats, 696, 696f
protein, 696–697
disorders of, 700–726
with spinal cord injury, 923
hormones of, 690–691, 690t
intestinal flora, 693
lower, organization of, 680f, 681–682
middle, organization of, 680f, 681
motility in, 684–690
colon, 689
control of, 684–685, 685f
disorders of, 717–721, 717b, 718c, 720f–721f
gastric, 685, 688
small intestine, 686–689, 686f–687f, 689f
swallowing and esophageal, 685, 686f
organization of, 680–684, 680f–683f, 681b
secretions of, 691–693, 691t, 692f
shock and, 507
thyroid hormone and, 785
upper, organization of, 680–681, 680f–681f
wall structure of, 682–683, 682f–683f
Gastrointestinal tract infections, with HIV, 370
Gate control theory, of pain, 870
G-CSF. *See* Granulocyte colony-stimulating factors
Gender, adaptation and, 217
Gene(s)
in cancer, 139–142
expression of, regulation of, 97
isolation and cloning of, 105, 105f
proteins from, 93–97
Gene dosage studies, for genetic mapping, 104
General adaptation syndrome (GAS), 211
Generalized bronchiectasis, 584
Generalized seizures, 956c, 957–958
Generalized vulvodynia, 1042
General somatic afferent (GSA) neurons, 841, 863
General somatic efferent (GSE) neurons, 843
General visceral afferent (GVA) neurons, 841, 863
General visceral efferent (GVE) neurons, 841, 843
Gene technology, 103–107
Gene therapy, 106
Genetic(s)
adaptation and, 216–217
autoimmune disease and, 357
in cell function, 89–97, 90b
in cellular aging, 48
Mendel laws, 102, 102f
in patterns of inheritance, 100–103, 101b
Genetic imprinting, 101–102, 101f
Genetic instability, 134–135
Genetic maps, 103–104
Genetic tests, for endocrine function, 772
Genital herpes, 1069–1071, 1070f
Genitalia
female
disorders of, 1041–1042
external, 1033–1035, 1034f–1035f
internal, 1035–1036, 1036f
male. *See* Male reproductive system
sexually transmitted infections of, 1068–1071
Genital warts, 1068–1069, 1069f
Genomic imprinting, 101–102, 101f, 115
Genotype, 100
Genu valgum, 1119–1120, 1120f
Genu varum, 1119–1120, 1120f
GERD. *See* Gastroesophageal reflux disease
German measles. *See* Rubella
Gestational hypertension, 433t, 434
GFR. *See* Glomerular filtration rate
GGT. *See* γ-Glutamyltransferase
GH. *See* Growth hormone
Ghon complex, 550, 551f

Ghon focus, 550
Ghrelin, 690, 690t
Giant cell arteritis, 1155
Giant cell tumor, 1114, 1114f
Gigantism, 780, 781f
GIP. *See* Glucose-dependent insulinotropic polypeptide
Glandular epithelium, 23–24
Glasgow coma scale, 940t
Glaucoma, 981–983, 981f
Gliosis, 832–833
Glisson capsule, 729–730
Global infectious diseases, 316
Glomerular filtration rate (GFR), 606, 617
  chronic kidney disease and, 645–647, 646f, 646t
  juxtaglomerular complex, 612–613, 612f
Glomerulonephritis, 620–621
  chronic, 626
  membranous, 625
  post infection, 622–623, 622t, 623f
  rapidly progressive, 622t, 623, 624f
  systemic lupus erythematosus with, 626
Glomerulosclerosis
  diabetic, 626–627
  focal segmental, 625
Glomerulus, 603f, 604–605, 605f, 620
  disorders of, 620–627, 621f, 622b
    asymptomatic hematuria or proteinuria, 622t, 625–626, 626f
    etiology of, 621–622, 621f
    nephritic, 622–623, 622t, 623f
    nephrotic syndrome, 623–625, 624f
    pathogenesis of, 621–622, 621f
    rapidly progressive glomerulonephritis, 622t, 623, 624f
    with systemic disease, 622t, 626–627
  urine formation in, 605–606
Glottis, 515f, 516
GLP-1. *See* Glucagon-like peptide-
Glucagon-like peptide-1 (GLP-1), 229, 229f, 690, 690t
Glucocorticoids, 791–792, 791f, 792t
  excess of, 795–796, 796f
Glucose
  digestion and absorption of, 695, 695f, 695t
  for nervous tissue, 833
  renal blood flow and, 613
Glucose-dependent insulinotropic polypeptide (GIP), 690, 690t
γ-Glutamyltransferase (GGT), 736
Gluten-sensitive enteropathy. *See* Celiac disease
Glycocalyx, 3, 9b
Glycogen, in energy storage, 225
Glycolysis, 10b, 12
Glycosaminoglycans (GAGs), 30
GM-CSF. *See* Granulocyte-monocyte colony-stimulating factors
Goblet cells, 22
Golgi apparatus, 5, 5f, 9b
Golgi tendon organs, 894–895
Gompertzian model, 136
Gonadotropin hormones, 1036
Gonorrhea, 1075–1077, 1076f
Goodpasture syndrome, 350, 623, 624f
"Goose bumps," 1164
Gout, 1151–1152, 1152f, 1155
G-protein–linked receptors, 13–14, 13f, 20b
G proteins, 13–14, 13f
Graft, 353
Graft-*versus*-host-disease (GVHD), 354
Gram calorie. *See* Calories
Gram stain, 304
Grand mal seizures. *See* Tonic-clonic seizures
Granulation tissue, 80–82, 81f
Granulocyte colony-stimulating factors (G-CSF), 245, 325, 325t
Granulocyte-monocyte colony-stimulating factors (GM-CSF), 245, 325, 325t
Granulocytes, 244f, 245–246, 246f, 321
Granuloma, 63
Granulomatous inflammation, 63–64, 64f
Granulosa cells, 1039
Graves disease, 350, 788
Gray matter, intermediate, 845–846, 846f
Great arteries, transposition of, 477f, 480
Greenstick fracture, 1102–1103
Ground substance, 30
Growth and development
  of cells, adaptations of, 33–36, 34b, 34f
  of neoplasms, 135–136
  normal, variations of, 1117–1120, 1117b, 1117f
Growth factors, 74
  influence of, 78, 79t
Growth fraction, 136
Growth hormone (GH), 776–778, 777f, 778b
  deficiency
    in adults, 780
    in children, 779–780, 779f
  excess
    in adults, 780–782, 781f
    in children, 780, 781f
  stress response of, 214
Grunting, 559
GSA neurons. *See* General somatic afferent neurons
GSE neurons. *See* General somatic efferent neurons
GTPase cycle. *See* Guanosine triphosphatase
Guanine, in DNA, 90
Guanosine triphosphatase (GTPase) cycle, 13–14
Guided imagery, for stress, 221
Guillain-Barré syndrome, 905
Gut. *See* Gastrointestinal system
GVA neurons. *See* General visceral afferent neurons
GVE neurons. *See* General visceral efferent neurons
GVHD. *See* Graft-*versus*-host-disease

H

Hair follicles, 1165–1166, 1165f
HANDs. *See* HIV-associated neurocognitive disorders
Haplotype, 93, 336
  mapping, 104
Haptens, 333
Haptoglobin, 283
Hardiness, adaptation and, 217
Hashimoto thyroiditis, 787
Haustra, 689, 716
Haustrations, 689
HAV. *See* Hepatitis A virus
HbA. *See* Adult hemoglobin
HbF. *See* Fetal hemoglobin
HbH. *See* Hemoglobin H
HBV. *See* Hepatitis B virus
HC. *See* Hypertrophic cardiomyopathy
HCV. *See* Hepatitis C virus
HD. *See* Huntington disease
HDL. *See* High-density lipoprotein
HDV. *See* Hepatitis D virus
Headache, 883–886
  chronic daily, 885–886
  cluster, 884–885
  migraine, 883–884
  tension-type, 885

Health status, adaptation and, 217
Hearing loss, 996–999, 996b, 997c
  conductive, 996–997, 997c
  diagnosis and treatment of, 998
  in elderly, 999
  in infants and children, 998–999
  sensorineural, 997c, 997–998
Heart
  conduction system of, 388–392, 389f
  functional anatomy of, 384–388, 384b, 385f–386f
  performance regulation, 394–395
  transplantation, 498–499
Heart attack. *See* Myocardial infarction
Heart block, 391
Heart disease
  cardiomyopathies, 461–465
  congenital. *See* Congenital heart disease
  coronary artery disease, 450–461, 454b
  endocardium disorders, 466–468, 466f
  in infants and children, 474–483
  pericardium disorders, 447–450, 448c
  rheumatic, 467–468
  valvular, 468–473, 469b
Heart failure, 486–499, 489b
  AHFSs, 495–496
  compensatory mechanisms of, 491–494, 492f
  diagnosis of, 496–497, 496t
  in elderly, 510
  high-output *v.* low-output, 490–491
  in infants and children, 508–510, 509c
  left ventricular dysfunction, 489, 491f
  manifestations of, 494–495
  pathophysiology of, 486–487
  right ventricular dysfunction, 489–490, 490f
  systolic *v.* diastolic, 487–489
  treatment of, 497–499
  types of, 487–491
Heart rate, 395
Heart valves. *See also specific valves*
  anatomy of, 386–388, 387f–388f
Heat
  loss of, mechanisms of, 66–67, 66t
  production of, mechanisms of, 65–66, 66t
Heinz bodies, 288
Helicobacter pylori
  cancer and, 145, 709
  gastritis, 706–707, 706f
  peptic ulcer and, 708
Helminths, 307
Helper T cells, 322, 335–336, 335f, 339–340
Hemagglutinins, 310
Hemangiomas of infancy, 1199
Hematocele, 1020
Hematocrit, 283, 283t, 284f
Hematogenous osteomyelitis, 1110–1111
Hematogenous spread, of cancer, 137–138, 138f
Hematologic system, disorders of, in chronic kidney disease, 648f, 649–650
Hematomas, 936–938, 936f–937f, 1097, 1106, 1106f
Hematopoiesis, 244–245, 244f, 245b
  neoplastic disorders of, 251–260, 251b
Hematopoietic cells, transplantation of, 354
Hematopoietic growth factors, 244–245
Hematuria, asymptomatic, 622t, 625–626, 626f
Hemianopia, 984
Hemidesmosomes, 30
Hemiplegia, 898, 898f
Hemodialysis
  for acute renal failure, 645
  for CKD, 652–653, 653f
Hemodynamic instability, with thermal injury, 1190–1191
Hemoglobin, 279–280, 280f
  carbon dioxide transport, 195, 195f, 535
  laboratory tests for, 283, 283t
  oxygen binding to, 532–534, 532f
  oxygen dissociation curve, 534–535, 534f
  synthesis of, 281, 281f
Hemoglobin H (HbH), 289
Hemolytic anemia, 283, 285–286
  acquired, 289–290
Hemolytic disease of newborn, 295
Hemolytic uremic syndrome (HUS), 273, 310
Hemophilia A, 274–275
Hemorrhage, aneurysmal subarachnoid, 948–950, 949f
Hemorrhagic exudates, 62
Hemorrhagic measles. *See* Rubeola
Hemorrhagic stroke, 945–946
Hemorrhagic telangiectasia, 275
Hemostasis, 263, 264b
  mechanism of, 264f, 265–269
    clot dissolution, 267, 267f, 269
    clot retraction, 267, 267f, 269
    coagulation cascade, 267–269, 267f–268f
    platelet plug formation, 265–268, 266f
    vessel spasm, 265–266, 266f
Hemothorax, 570
Henson disease, 310
Hepatic encephalopathy, 750
Hepatic sinusoids, 731, 731f
Hepatic syndromes, 745–750
  cirrhosis, 745–746, 746f
  portal hypertension, 746–748, 746b, 747f–748f
Hepatitis, 737–741
  acute fulminant, 741–742
  alcoholic, 744
  alcohol-induced, 744f–745f
  autoimmune, 741
  drug-induced, 743
  viral, 737–741
    chronic, 740–741
Hepatitis A virus (HAV), 738, 738f
Hepatitis B virus (HBV), 738–739, 739f
  cancer and, 145
Hepatitis C virus (HCV), 739–740, 740f
  cancer and, 145
Hepatitis D virus (HDV), 740
Hepatitis E virus (HEV), 740
Hepatobiliary tree, 731, 731f
Hepatocellular carcinoma, 750–751
Hepatocytes, 730
Hepatopancreatic ampulla, 731
Hepatorenal syndrome, 749–750
Hepatotropic viruses, 737
Herald patch, 1186
Hereditary angioneurotic edema, 1183
Heredity, cancer and, 142–143
Hernia
  brain, 931, 931f, 933–934, 934f
  hiatal, 701–702, 702f
  in intestinal obstruction, 720f
Herniated disk, 906–907, 906f–907f
Herpes simplex keratitis, 970–971

Herpes simplex virus (HSV)
in genital herpes, 1069–1070
in skin, 1178, 1178f
Herpes zoster, in skin, 1178–1179, 1179f
Heterochromatin, 4
Heterozygotes, 102, 140
HEV. *See* Hepatitis E virus
HHV-6. *See* Human herpes virus 6
HHV-8. *See* Human herpes virus 8
Hiatal hernia, 701–702, 702f
Hiatus, 681, 701
Hierarchy of control, 837
HIFs. *See* Hypoxia-inducible factors
High–bone-turnover osteodystrophy, 649
High-density lipoprotein (HDL), 407–408, 408f, 409t
High-output heart failure, 490–491
Hilus
of kidneys, 602
of lungs, 517, 517f
Hindbrain, 842t–843t, 848–849, 848f
Hinge joints, 1092
Hip
developmental dysplasia of, 1121–1122, 1121f
injuries to, 1101–1102, 1101f
Histamine
in circulatory control, 402
in hypersensitivity disorders, 347
in inflammation, 59–60
Histone, 91, 91f
Histoplasmosis, 553
HIV. *See* Human immunodeficiency virus
HIV-associated neurocognitive disorders (HANDs), 370
HLAs. *See* Human leukocyte antigens
Hodgkin lymphoma, 257–258, 257f
Homeostasis, 209–211, 210b, 210f
Homograft, for thermal injury, 1191–1192
Homonymous, 984
Homozygotes, 102
Hormonal hyperplasia, 35
Hormone(s), 761–768, 762b, 763t. *See also specific hormones*
action of, 763t
of adrenal gland, 790–792, 790f–791f, 792t
in bone formation and metabolism, 1087–1091, 1088f–1091f, 1090t
for cancer, 153
in cancer development, 143
elimination of, 765
of gastrointestinal system, 690–691, 690t
in male reproductive system, 1011, 1011c
mechanisms of action, 765, 767–768, 768c
metabolism of, 765
ovary production of, 1037–1039
of pituitary gland, 769, 770f
receptors for, 765–768, 766f–767f, 768c
regulation of, 768–771, 769f–770f
feedback, 769–771, 770f
hypothalamic-pituitary axis, 768–769, 769f–770f
source of, 763t
structural classification of, 763–764, 764t
synthesis and transport of, 764–765, 765f
of thyroid gland, 784–785, 784b
Hormone response element (HRE), 767
Hospital-acquired pneumonia, 547
Host, 299–300
Host defenses, in UTI, 672
HPV. *See* Human papilloma virus
HRE. *See* Hormone response element
HSV. *See* Herpes simplex virus
5-HT. *See* 5-Hydroxytryptamine
HTLV-1. *See* Human T-cell leukemia virus-1
Human Genome Project, 103
Human granulocytic ehrlichiosis, 305
Human herpes virus 6 (HHV-6), 1200
Human herpes virus 8 (HHV-8), cancer and, 145
Human immunodeficiency virus (HIV)
in children, 373
classification and phases of, 367c, 367–368, 367f
diagnosis of, 372
malignancies with, 370–371, 371f
molecular and biologic features of, 365–367, 365b, 366f
opportunistic infections with, 369–370, 369f
in pregnancy, 373
respiratory tract infections with, 369f
transmission of, 364–365, 364b
treatment of, 372–373
Human leukocyte antigens (HLAs), 336
in transplantation, 353
Human monocytic ehrlichiosis, 305
Human papilloma virus (HPV)
with AIDS, 371
cancer and, 145
in genital warts, 1068–1069, 1069f
Human T-cell leukemia virus-1 (HTLV-1), cancer and, 145–146
Humoral control
of blood flow, 401–402
of blood pressure, 426, 426f
of renal blood flow, 611
Humoral immunity, 320–321, 320f, 332, 339, 339f
B lymphocytes and, 336–339, 337f
immunodeficiency disorders, 360–361, 360f
Humoral rejection, 353
Hunger, 228–229, 229f
Huntington disease (HD), 962–963
HUS. *See* Hemolytic uremic syndrome
Hutchinson-Gilford progeria syndrome, 48
Hyaline cartilage, 1082
repair of, 1083
Hyaline casts, 616
Hybridization studies, for genetic mapping, 104
Hybridomas, 313
Hydrocele, 1019–1020, 1019f
Hydrocephalus, 934–935
Hydrogen/bicarbonate exchange, 195–196, 197f
Hydronephrosis, 634, 634f
Hydrops fetalis, 295
Hydrostatic pressure, 163–164, 164f
Hydrothorax, 569
5-Hydroxytryptamine (5-HT)
in circulatory control, 402
in inflammation, 59–60
in stress response, 214
Hydroxyurea, for sickle cell anemia, 288
Hyperacute rejection, 353–354
Hyperarousal, in PTSD, 219
Hyperbilirubinemia, in neonates, 294–295
Hypercalcemia, 187t, 188–189
Hypercalcemic crisis, 189
Hypercapnia, 203, 568, 596
Hypercapnic/hypoxemic respiratory failure, 596
Hyperchloremic acidosis, 200
Hyperchloremic alkalosis, 196
Hypercholesteremia, 409–411, 409t, 410f
Hypercoagulability, 269–271, 270c, 270b
Hyperemia, 400

Hyper-IgM syndrome, 362–363
Hyperkalemia, 180f, 181t, 182–183, 182f
Hyperkeratosis, 1185
Hyperlipidemia, 407–411, 408f–409f
  with nephrosis, 624
Hypermagnesemia, 190t, 191
Hypermetabolic response, to thermal injury, 1191
Hypernatremia, 176t, 177
Hyperopia, 971–972, 972f
Hyperparathyroidism, 185
Hyperphosphatemia, 649
Hyperpituitarism, 776
Hyperplasia, 34f, 35–36
  prostate, 1024–1026, 1024b, 1024f–1025f
Hyperpolarization, 834
Hypersensitive dermatoses, 1181–1184, 1182f–1184f
Hypersensitivity disorders, 345–353, 346b, 346t
  type I, immediate, 345–349, 346t, 347f
  type II, antibody-mediated, 349–350, 349f
  type III, immune complex-mediated, 350–351, 350f
  type IV, cell-mediated, 351–352, 351f
Hypersensitivity pneumonitis, 352
Hypersplenism, 747–748
Hypertension, 427–433, 428b, 428t
  in children and adolescents, 434–436, 435t
  with CKD, 650
  diagnosis and treatment of, 432
  in elderly, 436
  hypertensive crisis, 432–433
  portal, 746–748, 746b, 747f–748f
  in pregnancy, 433–434, 433t
  primary, 428–429
  pulmonary, 591–593, 592f
  pulmonary arterial, 592–593, 592f
  secondary, 429–431
Hypertensive emergency, 433
Hypertensive glomerular disease, 627
Hypertensive retinopathy, 978
Hypertensive urgency, 432–433
Hyperthyroidism, 786t, 788, 789f
Hypertonic hyponatremia, 175
Hypertrophic cardiomyopathy (HC), 462, 462f
Hypertrophic pyloric stenosis, 687
Hypertrophy, 34–35, 34f–35f
Hyperuricemia, 253
Hypervolemic hypotonic hyponatremia, 175
Hyphae, 306, 306f, 553
Hypocalcemia, 186–188, 187t, 188f, 649
Hypocapnia, 204–205
Hypochloremic alkalosis, 196
Hypochromic, 284
Hypodipsia, 170
Hypogammaglobulinemia, 254
  transient, of infancy, 360
Hypokalemia, 180, 180f, 181t, 182, 182f
Hypokalemic familial periodic paralysis, 181
Hypomagnesemia, 190–191, 190t
Hyponatremia, 175–177, 176t
Hypoparathyroidism, 184–185
Hypopituitarism, 776
Hypopolarization, 834
Hypospadias, 1028–1029, 1028f
Hypotension
  drug-induced, 437
  orthostatic, 436–438, 437f
Hypothalamic-pituitary axis
  assessment of, 775–776
  hormone regulation by, 768–769, 769f
  in menstrual cycle, 1036–1037, 1037f
Hypothalamus
  hormones of, 768–769, 769f–770f
  hunger regulation in, 228, 229f
  male reproductive system and, 1013, 1013f
Hypothyroidism, 786–788, 786t
  acquired, 786t, 787–788, 788f
  congenital, 786–787, 786f
Hypotonic hyponatremia, 175
Hypoventilation, 596
Hypovolemia, 173
Hypovolemic hypotonic hyponatremia, 175
Hypovolemic shock, 500c, 501f, 502–504, 503f
Hypoxemia, 567–568
  with COPD, 582
  pneumothorax and, 571
  with respiratory failure, 595–596
Hypoxemic respiratory failure, 595c, 595–596
Hypoxia
  brain injury, 927–929, 928f
  cellular injury from, 43–44
Hypoxia-induced vasoconstriction, 530
Hypoxia-inducible factors (HIFs), 43
H zone, 26, 26f

I

IA neuron. *See* Input association neuron
I band, 26, 26f
IBD. *See* Inflammatory bowel disease
IC. *See* Inspiratory capacity
ICF compartment. *See* Intracellular fluid compartment
ICP. *See* Intracranial pressure
Icterus. *See* Jaundice
Idiopathic pulmonary fibrosis (IPF), 588
IDL. *See* Intermediate-density lipoprotein
IE. *See* Infective endocarditis
IFNs. *See* Interferons
IgA, 338, 338f
  selective deficiency of, 361
IGF-binding proteins (IGFBPs), 777–778
IGFBPs. *See* IGF-binding proteins
IGFs. *See* Insulin-like growth factors
IgG, 337f–338f, 338
  subclass deficiency of, 361
IgM, 338–339, 338f
  hyper-IgM syndrome, 362–363
Ig superfamily. *See* Immunoglobulin superfamily
IL-1. *See* Interleukin-1
Illness, malnutrition in, 236–237
ILs. *See* Interleukins
Immediate sustained response, 58
Immediate transient response, 55
Immobility, orthostatic hypotension and, 438
Immune cells, in dermis, 1163
Immune complex-mediated hypersensitivity disorders, 350–351, 350f
Immune response
  to allografts, 353–354
  in elderly, 343
  hypersensitivity disorders of, 345–353, 346b, 346t
    type I, 345–349, 346t, 347f
    type II, 349–350, 349f
    type III, 350–351, 350f
    type IV, 351–352, 351f
  impaired, in wound healing, 86
  regulation of, 341–342
  to stress, 215

Immune surveillance hypothesis, 143
Immune system
  cells of, 321–322
  developmental aspects of, 342–343
  disorders of, with CKD, 651
  tissues of, 322–324, 322f
Immune thrombocytopenic purpura (ITP), 271–273
Immunity, 319
  adaptive. *See* Adaptive immunity
  innate. *See* Innate immunity
  transfer from mother to infant, 342–343, 343f
Immunization, 341
  for influenza, 545
Immunocompromised hosts, pneumonia in, 547
Immunodeficiency disorders, 359–374
  AIDS, 364b. *See* Acquired immunodeficiency syndrome
  primary, 359c, 359–363, 359b
Immunogens. *See* Antigens
Immunoglobulin A nephropathy, 625, 626f
Immunoglobulins, 332, 337–339, 337f, 338t
Immunoglobulin (Ig) superfamily, 31, 31b
Immunohistochemistry, for cancer diagnosis, 150
Immunologic mechanisms, cancer and, 143
Immunologic tolerance, 355–357, 356f
Immunotherapy, for cancer, 143, 153
Impacted cerumen, 989
Impedance plethysmography, for pulmonary embolism, 590–591
Impetigo, 1176–1177, 1176f
Impotence, with CKD, 651
Incretin, 690t, 691
Incubation period, of infection, 311, 311f
Incus, 989f, 990
Induction, in gene expression, 97
Infant respiratory distress syndrome, 524, 559–560, 559f
Infants. *See also* Neonates
  glaucoma, 983
  hearing loss in, 998–999
  heart disease in, 474–483
  heart failure in, 508–510, 509c
  HIV in, 373
  skin disorders of, 1198–1199, 1199f
  transient hypogammaglobulinemia of, 360
Infarction, 46
Infection(s)
  agents of, 300–307, 300b, 300t
  bacteria, 302–305, 302f–303f, 305f
  bioterrorism agents, 316–317
  bones, 1109–1111
  CKD and, 651
  course of, 311–312, 311f
  diagnosis of, 312–314, 313f–314f
  epidemiology of, 307–312
  fungi, 306–307, 306f
  global infectious diseases, 316
  parasites, 307
  of penis, 1016–1017
  portal of entry of, 308
  prions, 301
  site of, 311
  of skin, 1172–1179, 1173b
    fungal, 1172–1177, 1174f–1177f
  skin manifestations of, 1200–1202, 1200f–1201f
  source of, 308–309
  terminology for, 299–300
  treatment for, 314–315
  virulence factors, 309–310, 309t
  viruses, 301–302, 301f–302f
  in wounds, 86
Infectious agents, as teratogenic agent, 126
Infectious mononucleosis, 250–251, 250f
Infective endocarditis (IE), 466–467, 466f
Inflammation, 51–55, 52b
  acute, 55–63
  acute-phase response, 64–65
  adipose tissue and, 233
  of breast, 1060
  cells of, 52–55, 52f
  cellular stage of, 57–58
  chronic, 63–64
  fever, 65–71
  granulomatous, 63–64, 64f
  impaired response to, in wound healing, 86
  local manifestations of, 62
  mediators of, 58–62, 59f
  of penis, 1016–1017
  resolution of, 62
  systemic manifestations of, 64–71
  vascular stage of, 55–56, 58
  in would healing, 82, 84, 84f
Inflammatory bowel disease (IBD), 711–714, 711f, 711t
  etiology and pathogenesis of, 711–712
Inflammatory diarrhea, 718
Inflammatory response, 326
Influenza, 543–545, 544f
Infratentorial herniation, of brain, 931f, 933–934
Ingestion, of infectious agents, 308
Inhalation, of infectious agents, 308
Inheritance, patterns of, 100–103, 101b
Inhibin A, for prenatal screening and diagnosis, 128
Injury, cellular, 38–49, 38b
Innate immunity, 319–321, 320f, 326–332, 326b
  cells of, 327–328, 328f
  pathogen recognition, 328–329, 328t
  soluble mediators of, 329–331, 330f–331f
  in stimulating adaptive immunity, 331–332
Inner medullary collecting tubule, 605
Innervation
  of dermis, 1163–1164
  of lungs, 520
Inotropic influence, in cardiac contractility, 395
Inotropy, 487, 488f
Input association (IA) neuron, 840–841
Insensible perspiration, 67
Insensible water losses, 168
Inspiration, 522, 522f–523f
Inspiratory capacity (IC), 526
  in asthma, 576
Inspiratory retractions, 558f, 559
Insulin-like growth factors (IGFs), 777–778
  deficiency, in children, 779–780, 779f
Insulin resistance syndrome. *See* Metabolic syndrome
Integral proteins, 3, 3f
Integrase inhibitors, for HIV infection, 373
Integrins, 30–31, 31b
  in inflammation, 54
Integumentum. *See* Skin
Intercalated cells, 609
Intercalated disks, 386, 386f
Intercostal muscles, 522, 523f
Interferons (IFNs), 324
  for cancer, 153–154

Interleukin-1 (IL-1), in inflammation, 61, 61f
Interleukins (ILs), 324
  for cancer, 154
Intermediate-density lipoprotein (IDL), 407–408, 408f
Intermediate gray matter, 845
Intermembrane space, 7, 7f
Intermittent fever, 68, 69f
Intermittent pneumatic compression (IPC), for pulmonary embolism, 591
International HapMap Project, 104
Interstitial cells of Cajal, 684, 687, 687f
Interstitial lung disease, 586–589, 587b
  causes of, 587, 587c
  clinical features of, 587–588
  idiopathic pulmonary fibrosis, 588
  pathogenesis of, 587
  sarcoidosis, 588–589
Intervertebral disk, disorders of, 906–907, 906f–907f
Intestinal flora, 693
Intestinal obstruction, 720–721, 720f–721f
Intestinal secretions, 691t, 693
Intestinal smooth muscle, 687, 687f
Intestines. *See* Colon; Large intestine; Small intestine
Intoeing, 1117–1118, 1118f
Intra-articular menisci, 1094
Intracellular accumulations, 36–37, 37f
Intracellular fluid (ICF) compartment, 159–160, 161t
Intracellular receptors, 14
Intracerebral hematomas, 937–938, 937f
Intracranial pressure (ICP), 932–933, 932f–933f
  increased, 930–931
Intraductal papillomas, 1061
Intraepidermal squamous cell carcinoma, 1197
Intraocular pressure, 980–981, 981f
Intrapleural pressure, 521–522, 521f
Intrapulmonary pressure. *See* Alveolar pressure
Intrathoracic pressure, 521f, 522
Intrinsic apoptosis, 45–46, 45f
Intrinsic reflexes, 425
Intrinsic renal failure, 642c, 642f, 643–644
Introitus, 1034–1035, 1034f
Introns, 95, 96f
Intrusion, in PTSD, 219
Intussusception, 720, 720f
Invasive factors, 309t, 310
Invasive squamous cell carcinoma, 1197
Involuntary muscle. *See* Smooth muscle
Ion channels, 15–16, 16f
Ion channel-linked receptors, 14, 20b
Ion gates, 15–16, 16f
Ionizing radiation. *See* Radiation
IPC. *See* Intermittent pneumatic compression
IPF. *See* Idiopathic pulmonary fibrosis
Iron-deficiency anemia, 290
Irritable bowel syndrome, 710–711
Irritant receptors, 537–538
Ischemia, brain injury, 927–929, 928f, 936
Ischemic stroke, 944–945, 944f
Isochromosome formation, 118, 118f
Isotonic fluid volume
  deficit of, 173–174, 173t
  excess of, 173t, 174–175
Isovolumetric contraction period, 392
Isovolumetric relaxation period, 393
ITP. *See* Immune thrombocytopenic purpura

J

Jaundice, 36–37, 283, 734–735, 735c, 735f
JDMS. *See* Juvenile dermatomyositis
JIA. *See* Juvenile idiopathic arthritis
Joints, 1092–1094, 1092b
  injuries to, 1097–1102, 1097b
  synovial, 1092–1094, 1093f–1094f
  vasculature and innervation, 1093
Junctional nevi, 1194, 1194f
Juvenile dermatomyositis (JDMS), 1153–1154
Juvenile idiopathic arthritis (JIA), 1153
Juvenile osteochondroses, 1123–1125, 1124f
Juvenile spondyloarthropathies, 1154
Juxtacapillary receptors, 538
Juxtaglomerular complex, 612–613, 612f
Juxtamedullary nephrons, 603f, 604

K

Kaposi sarcoma (KS), with AIDS, 370–371, 371f
Karyotype, 98f, 99
Kawasaki disease, 481–482
Keloid, 83, 83f
Keratin, 22, 1160
Keratinocytes, 1160–1161, 1161f
Keratitis, 969–971
Keratohyalin, 1161, 1161f
Kerion, 1174
Kernicterus, 295
Ketoacids, formation of, 193, 200
Kidneys. *See also* Renal *entries*
  in acid-base balance, 195–197, 200, 202, 202f
  blood flow in, regulation of, 611–613
  cystic diseases of, 630–632, 631f
  disease, chronic. *See* Chronic kidney disease
  function of, 613b
    elimination, 613–615
    endocrine, 615
    tests of, 616–618, 616t–617t, 617f
  hypertension, 429–430
  location of, 601–603, 602f–603f
  malignant tumors of, 637–639
  nephron in, 603–605, 603f, 604b, 605f
  obstructive disorders of. *See* Urinary tract obstruction
  in potassium regulation, 178–179
  stones, 634–637, 635b, 635t, 636f
  structure of, 601–603, 602f–603f
  transplantation of, for CKD, 654
  urine formation in, 605–611, 606f–611f
Kilocalorie, 224
Kimmelstiel-Wilson syndrome, 626–627
Klinefelter syndrome, 121–122, 122f
Knee, injuries to, 1100–1101, 1100f
Knee-jerk reflex, 897, 897f
Knock-knees. *See* Genu valgum
Köbner phenomenon, 1185
Koplik spots, 1201
Krause end bulbs, 1163–1164
Krebs cycle. *See* Citric acid cycle
KS. *See* Kaposi sarcoma
Kupffer cells, 731, 731f
Kussmaul breathing, 200–201
Kwashiorkor, 236, 236f

L

Labia, 1033, 1034f
Labile tissues, 75

Laboratory response network (LRN), 317
Lactate dehydrogenase (LDH), 569
Lactic acid
  in energy metabolism, 10b, 12
  formation of, 193
Lactic acidosis, 200
Lacunar infarct, 945
LAD. *See* Leukocyte adhesion deficiency
Laennec cirrhosis. *See* Alcoholic cirrhosis
LAIV. *See* Live, attenuated influenza vaccine
Lamellar bone, 1084–1085
Lamina propria, 682, 682f
Laminar airflow, 525
Laminar blood flow, 380–381, 383, 383f
Langerhans cells, 333–334, 1162, 1162f
Large calorie. *See* Kilocalorie
Large cell carcinomas, lungs, 555
Large intestine, disorders of, 710–725
Laryngotracheal airways, 515–516, 515f
Late distal tubule, 605
  in urine formation, 608–609, 609f
Latent tuberculosis infection, 550, 551f
Lateral geniculate nucleus (LGN), 983–984
Lateral sacs, 26, 26f
Law of Laplace, 381–382, 381f–382f
LDH. *See* Lactate dehydrogenase
LDL. *See* Low-density lipoprotein
Lead-pipe rigidity, 898
Lead poisoning, 37
  cellular injury from, 40–41
Lectins, 3, 310
Left ventricular heart failure, 489, 491f
Legg-Calvé-Perthes disease, 1124, 1124f
Legionnaire disease, 548–549
Leiden mutation, 270
Leiomyomas, uterine, 1049–1050, 1050f
Lens, 971, 972f
Lentiform nucleus, 909, 909f
Lentigo maligna, 1203
Lentigo maligna melanomas, 1196
Leptin, 229, 232
Lesions, 1166–1167, 1167f
Leukemias, 251–255, 251b, 252f
  acute, 253–254
  chronic, 254–255, 255f
Leukocyte adhesion deficiency (LAD), 54
Leukocytes, 244f, 245–247, 246f
  developmental stages of, 247, 247f
  in inflammation, 53–54, 53f, 57–58, 64–65
  nonneoplastic disorders of, 248–251
  recruitment of, 54
Leukocytosis, 64–65
Leukopenia, 749
Leukostasis, 253
Leukotriene pathway inhibitors, 578
LGN. *See* Lateral geniculate nucleus
LGV. *See* Lymphogranuloma venereum
Lhermitte sign, 915
Lichenification, 1167
Lichen planus, 1187, 1187f
Lichen sclerosus, 1041
Lichen simplex, 1187, 1187f
Ligaments, 1092–1093, 1097
  injuries to, 1100
Ligand, 310
Limbic system, 852, 852f
Limbs. *See* Extremities
  torsional deformities of, 1118f–1119f
Linkage studies, for genetic mapping, 99f, 103–104
Lipid bilayer, in cell membrane, 2–3
Lipids. *See* Fats
Lipodystrophy, 372
Lipofuscin, 37, 37f
Lipoid nephrosis. *See* Minimal-change disease
Lipoproteins, 407–408, 408f
Liquefaction necrosis, 46
Live, attenuated influenza vaccine (LAIV), 545
Liver
  cancer of, 750–751
  disease
    alcohol-induced, 744, 744f–745f
    drug-induced, 743
  failure of, 748–750, 749f
  function
    bile formation, 734, 734f
    disorders of, 737–751, 737b
    metabolic, 732–734, 732t, 733f
    tests of, 736
  metabolism and, 732–734, 732t, 733f
  physiologic functions of, 732–736, 732t, 733f–735f, 735c
  structure of, 729–731, 730f–731f
  transplantation
    for hepatitis, 741
    for liver failure, 750
LMNs. *See* Lower motor neurons
Lobules, 731, 731f
Local immune complex disorders, 351
Localized bronchiectasis, 584
Localized vulvodynia, 1042
Locus, of genes, 100
Locus ceruleus, 212, 213f, 214
Longevity genes, 48
Longitudinal tracts, 843–845, 843f–844f, 844t
Long-term medications, for asthma, 577–578
Loop of Henle, 603f, 605
  urine formation in, 608, 608f, 610, 610f
Loose connective tissue, 24–25
Low–bone-turnover osteodystrophy, 649
Low-density lipoprotein (LDL), 407–408, 408f, 409t
Lower limb compression ultrasonography, for pulmonary embolism, 590–591
Lower motor neurons (LMNs), 843, 893
  of detrusor muscle, 660–661
Low-output heart failure, 490–491
LRN. *See* Laboratory response network
Luminal membrane, 606, 607f
Lungs, 514b, 518–520, 518f
  cancer of, 554–557, 555f
  compliance of, 523–524, 524f
  development of, 557–558, 557f
  inflation, disorders of, 569–572, 571f–572f
  interstitial disease, 586–589, 587c, 587b
  transplantation of, 593
  volume of, 526, 526f, 527t
    in neonates and children, 558
Lung receptors, for breathing regulation, 537–538
Lyme disease, 304–305
Lymphatic spread, of cancer, 137, 137f
Lymphatic system, 399–400, 400f, 401f
Lymph drainage, 163, 165, 165f
  obstruction of, 165
Lymph nodes, 323, 323f

Lymphoblasts, 247f, 253
Lymphocytes, 246, 246f, 334, 334f–335f
  in inflammation, 53f, 54
Lymphocytic leukemias, 252
Lymphogranuloma venereum (LGV), 1071
Lymphoid organs, 322f–323f, 323–324
Lymphoid tissues, 247–248, 248f, 323
  neoplastic disorders of, 251–260, 251b
Lymphomas, non-Hodgkin, 255–257, 256c
Lyon principle, 98
Lysosomal storage diseases, 6
Lysosomes, 5–6, 6f, 9b

M

Macrophage colony-stimulating factors (M-CSF), 245, 325, 325t
Macrophages, 246–247, 246f, 321
  in adaptive immunity, 333
  alveolar, 519, 519f
  in inflammation, 54
  in innate immunity, 327–328, 328f
Macula densa, 612
Macular degeneration, 979–980, 980f
Macule, 1167, 1167f
Magnesium ammonium phosphate stones, 635–636, 635t, 636f
Magnesium balance, 183–191, 184f, 189b
  disorders of, 189–191
  regulation of, 189–190
Magnetic resonance imaging (MRI)
  of body fat, 230
  for endocrine function, 772
Major histocompatibility complex (MHC), 322, 334–336, 336f–337f, 336t
  in transplantation, 353
Malabsorption syndrome, 722, 723t
Male reproductive system. *See also specific components*
  aging and, 1030
  disorders of
    of childhood, 1028–1030, 1028f–1029f
    penile, 1016–1018, 1017f
    prostatic, 1023–1027
    scrotal and testicular, 1018–1023, 1018f–1020f
  hormonal control of, 1013, 1013f
  hormone production, 1011, 1011c
  neural control of, 1014–1015, 1014f
  physiology of, 1009–1016, 1010b, 1010f
  spermatogenesis in, 1011–1013, 1011f–1012f
Male-specific region (MSY), 97
Malignant melanoma, 1195–1197, 1196f
Malleus, 989f, 990
Mallory-Weiss syndrome, 701
Malnutrition, 235–237, 236f
  with heart failure, 495
  protein-energy, 235–236, 236f
  in trauma and illness, 236–237
MALT. *See* Mucosa-associated lymphoid tissue
MALT lymphomas, 256c, 257
Malunion, 1105, 1105t
Mammary duct ectasia, 1060
Mantle cell lymphomas, 256c, 256–257
Marasmus, 236
Marasmus-kwashiorkor, 236
Marfan syndrome, 111–112, 112f
Marginal zone lymphomas, 256c, 257
Margination, inflammatory response, 57–58
Massage therapy, for stress, 221
Mast cells
  in hypersensitivity disorders, 346
  in inflammation, 54
Mastitis, 1060
Maternal serum markers, for prenatal screening and diagnosis, 127–128, 127f
Matrix, 5, 5f
Matrix space, 7, 7f
Maximum voluntary ventilation (MVV), 527, 527t
MCH. *See* Mean cell hemoglobin
MCHC. *See* Mean corpuscular hemoglobin concentration
M-CSF. *See* Macrophage colony-stimulating factors
MCV. *See* Mean corpuscular volume
Mean arterial pressure, 422, 422f
Mean cell hemoglobin (MCH), 283t, 284
Mean corpuscular hemoglobin concentration (MCHC), 283t, 284
Mean corpuscular volume (MCV), 283t, 284
Measles. *See* Rubeola
Mechanical forces, cellular injury from, 38
Medial lemniscus, 866
Mediastinum, 513–514, 514f
Medications
  cellular injury from, 40
  elimination of, 615
Mediterranean anemia. *See* β-Thalassemias
Medulloblastoma, 953
Megakaryocytes, 263
Megaloblastic anemia, 290–292, 291f
Meiosis, 98, 99f
Meissner corpuscles, 868, 1163
Melanin, 909, 1160–1161
Melanocytes, 1161–1162, 1161f
  malignant melanoma, 1195–1197, 1196f
Melanocytic nevi, 1199
Melanosomes, 1161–1162
Melasma, 1168
Membrane potentials, 17–20, 20b
  action potentials, 19b, 20, 20b
  diffusion potentials, 18b, 20, 20b
  equilibrium potentials, 18b, 20, 20b
  resting membrane potential, 19b, 20, 20b
Membrane transport proteins, 14
Membranous exudates, 62
Membranous glomerulonephritis, 625
Mendel laws, 102, 102f
Ménière disease, 1003
Meninges, of brain, 852, 852f–853f
Meningiomas, 953
Meningitis, 951–952
Meniscus
  injuries to, 1100, 1100f
  intra-articular, 1094
Menopause, 1058
Menstrual cycle, 1036–1040, 1037f
  amenorrhea, 1056
  disorders of, 1055–1058, 1056b
  dysfunctional bleeding, 1055–1056
  dysmenorrhea, 1056–1057
Mental confusion, with heart failure, 495
MEOS. *See* Microsomal ethanol-oxidizing system
Mercury toxicity, cellular injury from, 41
Merkel cells, 1162
Merkel disks, 868
Mesangium, 605, 605f
Mesentery, 682–683, 682f–683f
Mesoderm, 21, 23f, 838, 839f
Mesothelium, 21

Messenger RNA (mRNA), 4
  structure and function of, 93
Metabolic acidosis, 199c, 199–202, 201t
Metabolic alkalosis, 201t, 202–203, 202f
Metabolic syndrome, 233, 429
Metabolism
  of bones, 1089, 1089f
    disorders of, 1130–1137, 1131b
    hormonal control of, 1087–1091, 1088f–1091f, 1090t
  of drugs, 742–743
  energy, 9, 9f, 224–226, 225b
  for heat production, 65
  of hormones, 765
  liver and, 732–734, 732t, 733f
  thyroid hormone and, 785
Metaphysis, 1084, 1084f
Metaplasia, 34f, 36
Metastasis, 137–138
  hematogenous spread, 137–138, 138f
  lymphatic spread, 137, 137f
Metastatic calcifications, 37
Metatarsus adductus, 1117–1118, 1118f
Methotrexate, for psoriasis, 1186
MGUS. *See* Monoclonal gammopathy of undetermined significance
MHC. *See* Major histocompatibility complex
MI. *See* Myocardial infarction
Microalbuminuria, 616, 627
Microarray technology, for cancer diagnosis, 150
Microbial agents, cancer and, 145–146
Microcirculation, 399–400, 399f
Microfilaments, 8–9, 9b
Microflora, 300
Microglia, 28, 832f, 833
Micronodular cirrhosis. *See* Alcoholic cirrhosis
MicroRNA genes, 140
Microsomal ethanol-oxidizing system (MEOS), 743–744
Microtubules, 7–8, 8f, 9b
Micturition, 663
  pontine center for, 661–662, 661f
Midbrain, 842t–843t, 848f, 849
Migraine headache, 883–884
Miliary tuberculosis, 551
Milk-alkali syndrome, 188, 202
Mineralcorticoids, 791
Minerals
  requirements of, 228
  for wound healing, 85
Minimal-change disease, 624–625
Minute volume, 527
Mitochondria, 6–7, 7f, 9b
  citric acid cycle, 10b, 12
  electron transport chain, 11b
  gene disorders of, 115–116, 116t
Mitochondrial DNA, 7, 93
Mitochondrion-induced apoptosis. *See* Intrinsic apoptosis
Mitosis, 90–, 91, 91f, 98, 99f
Mitral valve, 469–470
  prolapse of, 471, 471f
  regurgitation, 470–471, 470f
  stenosis, 470, 470f
M line, 26, 26f
MoAbs. *See* Monoclonal antibodies
MODS. *See* Multiple organ dysfunction syndrome
Molds, 306, 306f
Molecular chaperones, 96
Molecular mimicry, 467
Moles. *See* Nevi
Mongolian spots, 1199
Monkeypox, 316
Monoclonal antibodies (MoAbs), 313
  for cancer, 154
Monoclonal gammopathy of undetermined significance (MGUS), 258
Monocytes, 246–247, 246f, 321
  in inflammation, 54
Mononeuropathy, 904–905, 904f
Mononucleosis, infectious, 250–251, 250f
Monoplegia, 898, 898f
Monosomy, 119
Monro-Kellie hypothesis, 932, 932f
Mons pubis, 1033, 1034f
Morulae, 305
Motion sickness, 698, 1002
Motor cortex, 892–893, 892f–893f
Motor deficits, from stroke, 947–948
Motor function
  assessment of, 895, 898–899, 898f
  organization of, 891–899, 892b
  pathways for, 895, 897, 897f
  with spinal cord injury, 920–921
Motor neurons, 893. *See also* Lower motor neurons; Upper motor neurons
Motor unit, 893–895
  disorders of, 899–908
Movement, coordination of, 899
M phase, of cell cycle, 74, 76, 76f
M protein, 259, 259f
MRI. *See* Magnetic resonance imaging
mRNA. *See* Messenger RNA
MSY. *See* Male-specific region
Mucociliary blanket, 514
Mucosa-associated lymphoid tissue (MALT), 248, 322f, 324
Mucosal layer, gastric, 682, 682f, 705–706
Mucous layer, 310
Multifactorial inheritance, 101
  disorders of, 116–117
Multiple myeloma, 258–260, 259f
Multiple organ dysfunction syndrome (MODS), with shock, 507–508
Multiple sclerosis, 914–916, 915f
Multipotent stem cells, 78
Mumps, 691
Muscle(s)
  atrophy of, 900
  of eye, 984–985, 985f, 985t
  intercostal, 522, 523f
  respiratory, 522–523, 522f–523f
Muscle compartment, 1108, 1108f
Muscle fibers, 26, 26f
Muscle pump, 440
Muscle spasm, 876
Muscle spindles, 894
Muscle tissue, 21b, 22t, 25–28, 31b
  cardiac. *See* Cardiac muscle
  skeletal, 26f. *See* Skeletal muscle
  smooth, 27–28, 28f. *See* Smooth muscle
Muscular dystrophy, 900–901, 900f
Muscularis externa, 682, 682f
Music therapy, for stress, 221
Mutations, in DNA, 92
Mutualism, 300
MVV. *See* Maximum voluntary ventilation
Myasthenia gravis, 902–903

Mycelium, 306
Mycoplasmas, 305
Myeloblasts, 247, 247f
Myelogenous leukemias, 252
Myeloma nephrosis, 259
Myenteric plexus, 684, 686, 686f
Myocardial infarction (MI), 455f, 456–460, 458f–459f
  diagnosis and treatment for, 457–458, 458f
  non-ST elevation, 456
  pathologic changes in, 456–457
  recovery period, 458–460, 459f
  silent, 460
Myocarditis, 464
Myocardium, 385–386, 386f
  blood flow of, 452–453, 452f–453f
  contractility of, 487, 488f
  hypertrophy of, 493–494, 494f
  remodeling of, 493–494, 494f
Myoclonic seizures, 957–958
Myofibrils, 26, 26f
Myopia, 971–972, 972f
Myosin filaments, 25–27, 26f–27f, 31b
Myxedematous coma, 788

N

Nabothian cysts, 1043
NAD. *See* Nicotinamide adenine dinucleotide
NAFLD. *See* Nonalcoholic fatty liver disease
Nail bed, 1166, 1166f
Nail groove, 1166, 1166f
Nail matrix, 1166, 1166f
Nails, 1166, 1166f
  tinea of, 1175, 1175f
Naive lymphocyte, 322
Nasal flaring, 559
Nasopharyngeal airways, 515
Natriuretic peptides (NPs), 493
Natural immunity. *See* Innate immunity
Natural killer (NK) cells, 246, 246f, 321–322
  differentiation of, 244, 244f
  receptors, 327–328, 327f
Nausea, 697
Nearsightedness. *See* Myopia
Necrosis, 46–47, 47f
Neisseria gonorrhoeae, 1075–1076
Neolayer, of white matter, 843f, 845
Neonates
  hemolytic disease of, 295
  hyperbilirubinemia in, 294–295
  immunity transfer to, 342–343, 343f
  red blood cell changes in, 293–295, 294t
  respiratory tract infections in, 559–560, 559f, 561t, 563c
  ventilation in, 557–558, 558f
Neoplasm, 131–157, 132f. *See also* Cancer; Tumor(s)
Neospinothalamic tract, 867
Nephritic syndrome, 622–623, 622t, 623f
Nephrolithiasis. *See* Renal calculi
Nephron, 603–605, 603f, 604b
  glomerulus, 603f, 604–605, 605f
  tubular components of, 605
  urine formation in, 606–609, 606f–609f
Nephronophthisis-medullary cystic disease complex, 632
Nephropathies, drug-related, 629–630
Nephrosclerosis, benign, 627
Nephrosis, lipoid. *See* Minimal-change disease
Nephrotic syndrome, 622t, 623–625, 624f
Nernst potential, 20
Nervous system
  cell columns of, 840–841, 841f, 842t–843t, 843
  cells of, 829–833, 830b, 830f, 832f
    supporting, 831–833, 832f
  embryonic developmental of, 837–839, 838b, 839f–840f
  HIV manifestations in, 370
  longitudinal tracts of, 843–845, 843f–844f, 844t
Nervous tissue, 21b, 22t, 28–29, 31b
  metabolic requirements of, 833
Neural control
  of bladder function, 660–663, 661f, 662t
  of blood pressure, 423, 425–426, 426f
  of circulatory function, 402–403
  of male reproductive system, 1014–1015, 1014f
  of renal blood flow, 611
  thyroid hormone and, 785
Neural crest cells, 838, 839f
Neuralgia, 881
Neural pathways
  ascending, 865–867, 866f
    spinal cord circuitry and, 873–874, 873f
  in vision, 983–984, 983f–984f
Neural plate, 838, 839f
Neural tube, 838, 839f
  defects of, 838–839, 840f
Neuritic plaques, 959, 960f
Neuroendocrine response, to stress, 210–215, 212t, 213f
Neurofibrillary tangle, 9, 959–960, 960f
Neurofibromatosis, 112–113f, 113f
Neurogenic bladder disorders, 665–667, 665t, 666b
Neurogenic fever, 67
Neurogenic inflammation, 872
Neurogenic shock, 500c, 501f, 505
Neuroglia, 28–29, 31b
Neuromatrix theory, of pain, 870
Neuromodulators, 835
Neuromuscular junction, 901, 901f
  disorders of, 901–903, 901f
Neuromuscular scoliosis, 1125
Neurons, 28–29, 31b, 830–831, 830f
  communication of, 833–835, 834f
  spinal, 846f–847f, 847
Neuropathic pain, 880–881
Neurotransmission, in autonomic nervous system, 859–861
Neurotransmitters, 834–835
  autonomic, 403
  removal of, 837, 837f
  synthesis and release of, 836, 836f
Neurotrophic factors, 835
Neutropenia, 248–250, 249c
Neutrophils, 244f, 245, 246f, 327–328, 328f
  in inflammation, 53, 53f
Nevi, 1194–1195, 1194f–1195f
  melanocytic, 1199
  nevocellular, 1199
Nevocellular nevi, 1194, 1194f, 1199
Newborn. *See* Neonates
Newborn screening, for cystic fibrosis, 585
Nexus junctions, 30
NHL. *See* Non-Hodgkin lymphoma
Nicotinamide adenine dinucleotide (NAD), in fuel metabolism, 10b–11b, 12
Nikolsky sign, 1184
NIPD. *See* Nocturnal intermittent peritoneal dialysis
Nitric oxide (NO)
  in inflammation, 61–62
  in smooth muscle control, 397, 592

Nitric oxide synthase, 400, 401f
Nitrogenous waste accumulation. *See* Azotemia
Nitroglycerin, for myocardial infarction, 457
NK cells. *See* Natural killer cells
NO. *See* Nitric oxide
Nociceptors, 871–873
  stimulation of, 872
Nocturia, 494
Nocturnal asthma, 576
Nocturnal intermittent peritoneal dialysis (NIPD), for CKD, 653
Nodes of Ranvier, 831
Nodular basal cell carcinoma, 1197, 1197f
Nodular melanomas, 1196
Nodules, 1167, 1167f
Nonalcoholic fatty liver disease (NAFLD), 744–745
Nondisjunction, 119, 119f
Nonenzymatic glycation, 48
Non-Hodgkin lymphoma (NHL), 255–257, 256c
  with AIDS, 371
Nonionizing radiation, cellular injury from, 40
Nonneoplastic epithelial disorders, 1041
Nonnutrient flow, 399
Nonparalytic strabismus, 986
Non-small cell lung cancers (NSCLCs), 555, 555f
Non-ST elevation myocardial infarction (NSTEMI), 456
Nonthrombocytopenic purpura, 275
Nonunion, 1105, 1105t
Norepinephrine, in circulatory control, 401
Normochromic, 284
Normovolemic shock. *See* Distributive shock
Nosocomial, 309
Notochord, 838, 839f
NPs. *See* Natriuretic peptides
NRM. *See* Nucleus raphe magnus
NSCLCs. *See* Non-small cell lung cancers
NSTEMI. *See* Non-ST elevation myocardial infarction
Nuclear envelope, 3–4, 4f
Nuclear lamina, 4, 4f
Nuclear receptors, 767–768, 767f
Nuclear scintigraphy, 636
Nucleolus, 3–4, 93
Nucleoplasm, 2
Nucleoproteins, 4
Nucleosome, 91, 91f
Nucleus, 2f, 3–4, 3b, 4f, 9b
Nucleus raphe magnus (NRM), 874
Nutrient flow, 399
Nutrition. *See also* Food; Malnutrition
  adaptation and, 217
  assessment of, 229–230, 230t
  atrophy and, 34
  imbalance of, cellular injury and, 42
  wound healing and, 83, 85
Nystagmus, 908–909, 1001–1002, 1002f

O

OA. *See* Osteoarthritis
OA neuron. *See* Output association neuron
Obesity, 231–235, 231b, 232f
  adipose tissue and, 232–233
  cancer and, 143
  causes of, 231–232
  childhood, 234–235
  chronic inflammation and, 63
  treatment and prevention of, 233–234
  types of, 230t, 232f–233f, 233
Obligatory urine output, 168
Obstructive shock, 500c, 501f, 504
Occipital lobe, 851–852
Occluding junctions, 29, 31b
Oligodendrocytes, 28, 832, 833f
Oligodendrogliomas, 953
Oliguria, 494
OM. *See* Otitis media
Omega-3 polyunsaturated fatty acids, in inflammation, 60–61
Omentum, 683, 683f
Oncogenes, 139
Open-angle glaucoma, 981–982, 981f
OPG. *See* Osteoprotegerin
Opioid analgesics, 879
Opportunistic pathogens, 300
Opsonins, 329
Opsonization, inflammatory response, 57–58, 329
Optic nerves, 983–984, 983f–984f
  disorders of, 984
  organization of, 840
Oral contraceptives, hypertension and, 431
Oral phase, of swallowing, 685, 688f
Oral replacement therapy (ORT), for diarrhea, 719
Orchitis, 1021–1022
Organelles, 3b, 4–7, 5f–7f
Organic ions, elimination of, 614
Organogenesis, 123, 123f
ORT. *See* Oral replacement therapy
Orthopnea, 495
Orthostatic hypotension, 436–438, 437f
Osgood-Schlatter disease, 1124–1125
Osmolality, 162
  of urine, 617
Osmolarity, 162
  in urine concentration, 610, 610f
Osmole, 162
Osmoreceptors, 169, 170f
Osmosis, 161–162, 161f
Osmotic diarrhea, 718
Osteitis fibrosa, 649
Osteoarthritis (OA), 1147–1151, 1148b, 1148f–1149f, 1150t, 1154
Osteoblasts, 1085–1086, 1086t
Osteochondroma, 1114
Osteochondroses, juvenile, 1123–1125, 1124f
Osteoclastoma, 1114
Osteoclasts, 1086, 1086t
Osteocytes, 1086, 1086t
Osteodystrophy, 648f, 649
Osteogenesis imperfecta, 1121, 1121t
Osteomalacia, 1134–1135
Osteomyelitis, 1109–1111
Osteonecrosis, 1104c, 1104–1105, 1111–1112, 1112f
Osteopenia, 1131
Osteophytes, 1149, 1149f
Osteoporosis, 1131c, 1131–1134, 1133f
Osteoprogenitor cells, 1085, 1086t
Osteoprotegerin (OPG), 1087
Osteosarcoma, 1114–1115, 1114f–1115f
Ostiomeatal complex, 541, 542f
Otic fluid. *See* Endolymph
Otitis externa, 989
Otitis media (OM), 991–994, 991f
Otoliths, 1000, 1003
Otosclerosis, 991f, 994
Outflow obstruction, 664–665, 665c
Output association (OA) neuron, 840–841
Outtoeing, 1117–1118, 1118f

Ovaries, 1035–1036, 1036f
cancer of, 1044b, 1054
cystic lesions of, 1051–1052, 1052f
disorders of, 1051–1054, 1052f–1053f
follicle development and ovulation, 1039–1040, 1039f
hormone production, 1037–1039
neoplasms of, 1044b, 1053–1054, 1053f
polycystic ovary syndrome, 1052–1053
Overactive bladder, 668–669, 668b, 668t
Overflow incontinence, 668b, 668t, 669
Overweight. *See* Obesity
Oxidative damage, 43
Oxygen
delivery of, for wound healing, 85–86
dissolved, 533
transport of, 531–535, 532f–534f
Oxygen free radicals, in inflammation, 62
Oxygen-hemoglobin dissociation curve, 534–535, 534f
Oxygen therapy
for COPD, 583
for heart failure, 498
hyperbaric, for wound healing, 86
Oxyhemoglobin, 533

P

p35 tumor-suppressor gene, activation of, 7
Pacinian corpuscle, 868, 1163
PAD. *See* Peripheral arterial disease
PAF. *See* Platelet-activating factor
PAG. *See* Periaqueductal gray
Paget disease, 1064, 1136–1137, 1137f
PAH. *See* Pulmonary arterial hypertension
Pain, 870–879, 871b
acute, 876–877, 877t
back, 905–908
brain centers and, 874
in children, 886–887
chronic, 876–878, 877t
cutaneous, 874–875
deep somatic, 874–875
in elderly, 887–888
head. *See* Headache
management of, 878–879
mechanisms of, 871, 872f
modulation of, 874
neuropathic, 880–881
pathways of, 871–874, 873f
phantom limb, 882
referred, 875–876, 876f
sensitivity to, alterations in, 880
temporomandibular joint, 886
theories of, 870–871
types of, 874–878, 875b
visceral, 875
Pain fibers, 872–873
Paleolayer, of white matter, 843f, 845
Paleospinothalamic tract, 867
PAMPs. *See* Pathogen-associated molecular patterns
Panacinar emphysema, 581, 581f
Pancreas
cancer of, 756–757
disorders of, 752, 752f, 755–757
Pancreatitis, 755–756
Pannus, 1139
Papanicolaou test, 150
Papillary dermis, 1163
Papillary necrosis, 629
Papilledema, 976, 976f
Papilloma, 133, 133t
Papillomatosis, 166
PAPP-A. *See* Pregnancy-associated plasma protein A
Papule, 1167, 1167f, 1180
Papulosquamous dermatoses, 1184–1187, 1185f–1187f
Paracrine action, of hormones, 762, 762f
Paradoxical movement, 522
Paralytic strabismus, 986–987, 986f
Paraneoplastic syndromes, 136, 147–148, 147t
Paraphimosis, 1029
Paraplegia, 898, 898f
Parasites, 307
Parasitic relationship, 300
Parasympathetic nervous system, 857, 857t, 858f
airways and, 520
in gastrointestinal system, 684, 685f–686f, 686
neurotransmission in, 859–861, 860f
Parathyroid hormone (PTH)
in bone formation and metabolism, 1087, 1090, 1090f, 1090t
in calcium balance regulation, 183–184, 184f, 187
disorders of, 184–185, 184f
in magnesium balance regulation, 191
Parenchymal tissues, 73
in neoplasms, 132
Parietal layer, 569
Parietal lobe, 850–851, 851f
parietal peritoneum, 682
Parkinson disease, 910–913, 911f
Parotitis. *See* Mumps
Paroxysmal nocturnal dyspnea, 495
Partial pressure, 521
Partial seizures, 956c, 956–957
Passive immunity, 341
Passive transport, 15
Patella, subluxation and dislocations of, 1100–1101
Patellofemoral pain syndrome, 1100f, 1101
Patent ductus arteriosus, 476–478, 477f
Pathogen-associated molecular patterns (PAMPs), 328
Pathogens, 300
Pathogen virulence, in UTI, 672
Pathologic calcifications, 37, 37f
Pathologic stress fractures, 1102
Pattern recognition receptors (PRRs), 328
Pattern theory, of pain, 870
PCI. *See* Percutaneous coronary intervention
PCOS. *See* Polycystic ovary syndrome
PCR. *See* Polymerase chain reaction
Pedigree, 102
Pelvic inflammatory disease (PID), 1046–1047, 1046f
Pelvic nerve, 660
Pelvic pain syndrome, chronic, 1023–1024
Pemphigus, 29–30
Pendrin, 783
Penetrance, 100
in congenital disorders, 111
Penetration, of infectious agents, 308
PE neurons. *See* Pharyngeal efferent neurons
Penile erection, 1014–1015
dysfunction of, 1014b, 1015–1016
Penis
infection/inflammation of, 1016–1017
neoplasms of, 1018
Penumbra, ischemic, 944–945
Pepsin, 696–697
Pepsinogen, 696–697
Peptic ulcer disease, 707–709, 707f

Peptidoglycan, 302
Percutaneous coronary intervention (PCI), for myocardial infarction, 458, 458f
Percutaneous umbilical cord blood sampling, 128
Perfusion, 518f, 529–530
  in respiration, 566–567
  ventilation matching with, 530, 530b, 530f, 595–596
Periaqueductal gray (PAG) region, 874
Pericardial effusion, 448–449, 449f
Pericardial sac, 447
Pericarditis
  acute, 448
  with CKD, 650
  constrictive, 449–450
  myocardial infarction and, 459
Pericardium, 384–385, 385f–386f
  disorders of, 447–450, 448c
Perichondrium, 1082
Perilymph, 994
Perimenopause, 1058
Perimysium, 26, 26f
Perineurium, 831, 903
Perinuclear cisternal space, 4, 4f
Periosteum, 1083f, 1084
Periotic fluid. *See* Perilymph
Peripartum cardiomyopathy, 464
Peripheral arterial disease (PAD), 418
Peripheral chemoreceptors, 537
Peripheral circulation, 377–378, 378f
Peripheral cyanosis, 567
Peripheral nervous system (PNS), 28
  longitudinal tracts of, 843–845, 843f–844f, 844t
  segmental organization of, 840–845, 840f–841f, 842t–844t, 843f–844f
  supporting cells of, 831–832, 832f
Peripheral neuropathies, 903–908. *See also specific neuropathy*
  flaccid bladder and, 667
Peripheral proteins, 3, 3f
Peripheral tolerance, 355–356
Peripheral vascular disorders, 415, 418–419
Peripheral vascular resistance (PVR), 380
Peristaltic movements, in small intestine, 688, 689f
Peritoneal cavity, 682
Peritoneal dialysis, for CKD, 653–654, 653f
Peritonitis, 721–722
Peritubular capillaries, 603f, 604
Permanent tissues, 75
Peroxisomes, 6
PET. *See* Positron emission tomography
Petit mal seizures. *See* Absence seizures
Peyronie disease, 1017, 1017f
pH
  calculation of, 193, 196f
  primary *v.* compensatory changes in, 198–199, 198t
  regulation of, 193–197, 193f, 614
Phagocytosis, 6, 6f, 17
  inflammatory response, 57–58
Phagolysosome, 6, 6f
Phagosome, 6, 6f, 17
  in inflammation, 57–58
Phalen maneuver, 904
Phantom limb pain, 882
Pharyngeal efferent (PE) neurons, 843
Pharyngeal phase, of swallowing, 685, 688f
Pharyngoesophageal sphincter, 681
Phenotype, 100
Phenylketonuria (PKU), 113–114
Pheochromocytoma, 430
Pheomelanin, 1162
Philadelphia chromosome, 139, 252–253, 252f, 254
Phimosis, 1029
Phosphate buffers, 197
Phospholipids, in cell membrane, 2–3
Phosphorus
  CKD and, 654
  imbalance of, with CKD, 648–649
Photopic vision, 974
Photosensitivity, drug-induced, 1189
Physical maps, in genetics, 103–104
Physiologic dead space, 529
Physiologic reserve, for adaptation, 216
Physiologic shunt, 530
Pia mater, 846, 846f, 852, 852f
PID. *See* Pelvic inflammatory disease
PI genes. *See* Protein inhibitor genes
Pigmentary skin disorders, 1167–1168, 1168f
Pigmented birthmarks, 1199–1200, 1200f
Pilosebaceous unit, 1165
Pink puffers, 581
Pinocytosis, 17
Pinocytotic vesicle, 17
Pitting edema, 166, 166f
Pituitary gland. *See also* Hypothalamic-pituitary axis
  adenomas of, 776
  anterior, control of, 775
  disorders of, 775–782
  hormones of, 769, 770f
  hyperpituitarism, 776
  hypopituitarism, 776
  male reproductive system and, 1013, 1013f
Pityriasis rosea, 1186, 1186f
PKDs. *See* Polycystic kidney diseases
PKU. *See* Phenylketonuria
Planar joints, 1092
Plaque
  atherosclerotic. *See* Atherosclerotic plaque
  fibrous atheromatous, 413, 413f
  lesion, 1167, 1167f
  neuritic, 959, 960f
Plasma, carbon dioxide transport, 194, 194f
Plasma cell dyscrasias, 258–260, 259f
Plasma cells, in inflammation, 54
Plasma-derived mediators, 58–59, 59f
Plasma membrane. *See* Cell membrane
Plasmapheresis, for, 273
Plasminogen, 265
Platelet(s), 263–264, 264f
  disorders of, 271–274, 272f
  impaired function of, 274
  increased function of, 269–270
  in inflammation, 53
Platelet-activating factor (PAF), in inflammation, 61
Platelet plug formation, 265–268, 266f
  disorders of, 271–274, 271b, 272f
Pleiotropism, 324
Pleomorphism, 134
Pleura, 514f, 520
  disorders of, 569–572, 570f–571f
Pleural effusion, 520, 569–570
Pleurisy. *See* Pleuritis
Pleuritis, 569
Plexuses, 846f, 847
Pluripotent stem cells, 78
PMDD. *See* Premenstrual dysphoric disorder
PML. *See* Progressive multifocal leukoencephalopathy

PMNs. *See* Polymorphonuclear neutrophils
PMS. *See* Premenstrual syndrome
Pneumococcal pneumonia, 547–548
Pneumonia, 545–549, 546b
  acute bacterial, 547–549, 548t
  aspiration, 516
  atypical, 546, 546f
  classification of, 546–547, 546f
  community-acquired, 546–547
  hospital-acquired, 547
  in immunocompromised persons, 547
  with influenza, 545
  Legionnaire disease, 548–549
  pneumococcal, 547–548
  primary atypical, 549
  typical, 546, 546f
Pneumonitis, hypersensitivity, 352
Pneumotaxic center, 536–537, 536f
Pneumothorax, 570–572
  clinical features of, 571–572, 571f
  spontaneous, 570–571, 570f
  tension, 571, 571f
  traumatic, 571
PNS. *See* Peripheral nervous system
Podocytes, 604, 605f
Poiseuille law, 524
Polyarthritis, 468
Polycystic kidney diseases (PKDs), 630–632, 631f
  autosomal dominant, 631–632, 631f
  autosomal recessive, 632
Polycystic ovary syndrome (PCOS), 1052–1053
Polycythemia, 293
Polydactyly, 1120
Polydipsia, 170
Polygenic inheritance, 101
Polymerase chain reaction (PCR), 314, 314f
Polymorphisms, 93
Polymorphonuclear neutrophils (PMNs), 345
  in inflammation, 53, 53f
Polymyalgia rheumatica, 1155
Polyneuropathy, 905
Polyps, adenomatous, 724, 724f
Polyribosomes. *See* Polysomes
Polysaccharides, 30
Polysomes, 4, 5f, 96
Polysomy, 119
Pontine micturition center, 661–662, 661f
Portal circulation, 370f, 730–731
Portal hypertension, 746–748, 746b, 747f–748f
Portosystemic shunts, 747f, 748
Port-wine stains, 1200, 1200f
Position sensation, 869
Positron emission tomography (PET), for endocrine function, 772
Postconcussion syndrome, 936
Postherpetic neuralgia, 881, 1179
Post infection glomerulonephritis, 622–623, 622t, 623f
Postrenal failure, 642c, 642f, 644
Posttraumatic stress disorder (PTSD), 219–220
Postural hypotension, 923
Postvoid residual (PVR) urine, 663
Potassium
  balance of, 178–183, 178b
    disorders of, 179–183, 180f
    regulation of, 178–179, 179f
      mechanisms of, 179f
  elimination of, regulation of, 613–614
Potassium/hydrogen exchange, 196–197
Prader-Willi syndrome, 102, 115
Preadipocytes, 225
Precocious puberty, 782
Preeclampsia–eclampsia, 433–434, 433t
Preganglionic neurons, 841, 843
Pregnancy
  HIV in, 373
  hypertension in, 433–434, 433t
Pregnancy-associated plasma protein A (PAPP-A), for prenatal screening and diagnosis, 128
Preload, 394–395, 395f, 487
Premature aging. *See* Progeria
Premature ventricular complex (PVC), 391
Premenstrual dysphoric disorder (PMDD), 1057–1058, 1058c
Premenstrual molimina, 1057–1058
Premenstrual syndrome (PMS), 1057–1058
Prenatal diagnosis, 126–129
  cytogenetic and biochemical assays, 128–129
  invasive testing for, 127f, 128
  maternal serum markers for, 127–128
  methods for, 126–129, 127f
  ultrasonography for, 126–127
Prenatal screening. *See* Prenatal diagnosis
  methods for, 127f
Prerenal failure, 642c, 642–643, 642f
Presbycusis, 999
Presbyopia, 972
Pressure, in circulatory system, 379–382, 379f, 382f
Pressure diuresis, 427
Pressure natriuresis, 427
Pressure overload, in heart failure, 494
Pressure ulcers, 1192–1193, 1192f
Priapism, 1017
Prickle cells, 1161, 1161f
Prickly heat, 1199, 1199f
Primary active transport, 16
Primary intention, in wound healing, 82, 82f
Primary motor cortex, 850, 851f
Principal cells, 609
Prinzmetal angina, 460–461
Prions, 301
Prodromal stage, of infection, 311, 311f
Prodrome, 68, 68f
Proerythroblasts, 281, 282f
Progenitor cells, 74
Progeria, 48–49, 48f
Progesterone, 1038–1039
Programmed cell death. *See* Apoptosis
Programmed theories, of cellular aging, 47
Progressive multifocal leukoencephalopathy (PML), 370
Prohormone, 764
Prolactin, 1036, 1060
Prolapse, mitral valve, 471, 471f
Proliferative phase
  neoplasms and, 132
  in would healing, 82, 84, 84f
Promoter region, 93–95, 96f
Promyelocytes, 247, 247f
Propionibacterium acnes, 1180
Proprioception, 848, 894
Prostaglandins, in circulatory control, 402
Prostate, 1010f, 1013, 1023
  benign hyperplasia, 1024–1026, 1024b, 1024f–1025f
  cancer of, 1024b, 1026–1027
Prostatitis, 1023–1024
Protease inhibitors, 315
  for HIV infection, 372–373

Proteases, in emphysema, 580, 580f
Proteasomes, 6, 34
Proteins. *See also specific proteins*
  buffer activity of, 195
  in cell membrane, 2–3, 3f
  CKD and, 654
  digestion and absorption of, 696–697, 722, 723t
  energy requirements for, 226–228
  renal blood flow and, 613
  synthesis of, 93–97
    liver in, 732t, 733–734, 733f
  for wound healing, 83, 85
Protein-energy malnutrition, 235–236, 236f
Protein inhibitor (PI) genes, 580
Proteinuria, 616, 622t, 625–626, 626f
Proteoglycans, 30
Proteome, 90
Proteomics, 90
Protoplasm, 2
Proud flesh, 83
Proximal convoluted tubule, 603f, 605
  urine formation in, 607–608, 607f–608f
PRRs. *See* Pattern recognition receptors
Pruritus, 1168–1169
  with cholestasis, 736
Pseudogout, 1155
Pseudomembranous exudates, 62
Pseudostratified epithelium, 22–23, 24f
Psoriasis, 1184–1186, 1185f
Psoriatic arthritis, 1147
Psychosocial dwarfism, 779
Psychosocial factors, in adaptation, 217–218
PTH. *See* Parathyroid hormone
PTO. *See* Thyroid peroxidase
PTSD. *See* Posttraumatic stress disorder
Puberty, precocious, 782
Pudendal nerve, 660–661
Pulmonary angiography, for pulmonary embolism, 591
Pulmonary arterial hypertension (PAH), 592–593, 592f
Pulmonary circulation, 377–378, 378b, 378f, 518f, 519–520
  in congenital heart defects, 475–476
  disorders of, 589–593, 589b
    cor pulmonale, 593
    pulmonary embolism, 589–591, 590f
    pulmonary hypertension, 591–593, 592f
Pulmonary edema, acute, 496
Pulmonary embolism, 589–591, 590f
Pulmonary function studies, 526–527, 527t
Pulmonary hypertension, 591–593, 592f
Pulmonary stenosis, 477f, 479–480
Pulmonary ventilation, 528
Pulmonic valves, 387–388, 387f–388f
Pulse oximeter, 567–568
Pulse pressure, 422, 422f
Pulsus paradoxus, 449
Punnett square, 102, 102f
Pupillary reflexes, 939–940, 940f
Purine bases, in DNA, 90
Purkinje system, 389, 389f
Purulent exudates, 62
Pustular disorders, 1179–1181
Pustules, 1167, 1167f
PVC. *See* Premature ventricular complex
PVR. *See* Peripheral vascular resistance
PVR urine. *See* Postvoid residual urine
Pyelonephritis, 628–629, 628f–629f
Pyloric region, 681, 681f
Pyloric sphincter, 681, 681f
Pyogenic, 62
Pyogenic osteomyelitis, 1109–1110
Pyrimidine bases, in DNA, 90
Pyrogens, fever and, 67
Pyruvic acid, in energy metabolism, 10b, 12

Q

Q fever, 305–306
Quadrantanopia, 984
Quadriplegia, 898, 898f
Quick-relief medications, for asthma, 577

R

RA. *See* Rheumatoid arthritis
RAAS. *See* Renin-angiotensin-aldosterone system
Radiation. *See also* Ultraviolet radiation
  cancer and, 145
  cellular injury from, 39–40
  in heat loss, 66–67, 66t
  as teratogenic agent, 124
Radiation therapy, for cancer, 151
Ragged red fibers, 116
Rapid filling period, in cardiac cycle, 393
Rapidly progressive glomerulonephritis, 622t, 623, 624f
RAS. *See* Reticular activating system
Rashes, 1166–1167
Rathke pouch, 775
Raynaud phenomenon, 419, 419f
RBC. *See* Red blood cell count
RDA. *See* Recommended Dietary Allowance
RDS. *See* Respiratory distress syndrome
Reactive arthritis, 1146–1147, 1147f
Reactive oxygen species (ROS)
  cellular injury and, 43
  in wound healing, 85
Receptor-mediated endocytosis, 17
Receptors, 310
  adrenergic, 860f, 861
  of cell membrane, 13–14, 13f
  cholinergic, 860–861, 860f
  for hormones, 765–768, 768c
    cell surface, 766–768, 766f
    nuclear, 767–768, 767f
  neurotransmitters, 835–836, 836f
  pain, 871–873
Recessive trait, 102
Recombinant DNA technology, 104–106
Recommended Dietary Allowance (RDA), 226
Rectocele, 1050, 1051f
Rectum, cancer of, 724–725, 724f
Recurrent fever, 68, 69f
Recycling vesicles, 5, 6f
Red blood cell(s), 279–284, 280f, 281b
  age-related changes in, 293–296
    in elderly, 295–296
    in neonates, 293–295, 294t
  laboratory tests for, 283–284, 283t, 284f
  life span and destruction of, 282–283, 283f
  membrane of, inherited disorders of, 286–288
  production of, 281–282, 283f
Red blood cell count (RBC), 283, 283t
Redundancy, 324
Reed-Sternberg cells, 257, 257f
Referred pain, 875–876, 876f
Reflexes
  deep tendon, 894–895

knee-jerk, 897, 897f
pupillary, 939–940, 940f
spinal, 848, 893–894, 896, 896f, 898–899
with spinal cord injury, 921
stretch, 894–896, 896f
Refraction disorders, 971–972, 972f
Refractory periods, in cardiac conduction system, 390–391, 391f
Regenerative medicine, 78
Regulatory T cells, 341
Regurgitation
of aortic valve, 470f, 472–473
mitral valve, 470–471, 470f
Rejection
patterns of, 353–354
solid organ, 353
Relapsing fever, 68, 69f, 304–305
Relative refractory periods, 391, 391f, 834
Relaxation, for stress, 220–221, 220b
Remittent fever, 68, 69f
Remodeling phase, in would healing, 83, 83f, 85, 85f
Renal calculi, 634–637, 635b, 635t, 636f
Renal cell carcinoma, 638, 638f
Renal clearance, 613
Renal colic, 636–637
Renal corpuscle, 604, 605f
Renal cysts, 632
Renal failure
acute. *See* Acute renal failure
chronic. *See* Chronic kidney disease
Renal osteodystrophy, 185
Renal rickets, 1134–1135
Renin-angiotensin-aldosterone system (RAAS), 426
in blood pressure, 615
in heart failure, 492–493
stress response of, 214
Replicative senescence, 47
Repolarization, 834, 834f
Residual bodies, 6, 6f
Residual volume (RV), 526
in asthma, 576
Resistance, in circulatory system, 380–382, 382f
Resistance stage, in GAS, 211
Resistance vessels, 423
Resistin, 232
Resolution stage, of infection, 311–312, 311f
Respiratory acidosis, 203–204, 203b, 204t
Respiratory airways, 514b, 518–520, 518f
Respiratory alkalosis, 203b, 204–205, 204t
Respiratory center, 536–537, 536f
Respiratory distress syndrome (RDS)
acute, 507, 593–595, 594c, 594f
adult, 524
infant, 524, 559–560, 559f
Respiratory failure, 595c, 595–597
clinical features of, 596
hypercapnic/hypoxemic, 596
hypoxemic, 595c, 595–596
impending, signs of, 563, 563c
Respiratory muscles, 522–523, 522f–523f
with spinal cord injury, 921
Respiratory neurons, 536–537, 536f
Respiratory system
in acid-base balance, 195
in heart failure, 495
structural organization of, 513–520, 514b, 514f
thermal injury and, 1191
Respiratory tissues, 513, 514f
Respiratory tract infections, 540–554. *See also specific infections*
in children, 557–563
with HIV, 369–370, 369f
in neonates, 559–560, 559f, 561t, 563c
Resting membrane potential (RMP), 19b, 20, 179–180, 180f, 833, 834f
Restrictive cardiomyopathies, 463–464
Retching, 697–698, 698f
Reticular activating system (RAS), 844, 938–939, 939f
Reticular connective tissue, 25
Reticular dermis, 1163
Reticular fibers, 25, 30, 31b
Reticular formation, 844
Reticulate body, 305
Reticulocytes, 281–282, 282f
laboratory tests for, 283, 283t
Reticuloendothelial cells. *See* Kupffer cells
Retina, 973–974, 974f
blood supply to, 974–976, 975f
disorders of, 975b, 976–978, 976f–977f
Retinal detachment, 978–979, 978f
Retinoblastoma, 139–140, 140f
Retinopathies, 976–978, 977f
Reuptake, 835
Reverse transcriptase, 302
Reverse transcriptase inhibitors, for HIV infection, 372
RF. *See* Rheumatic fever; Rheumatoid factor
Rhabdomyolysis, 644
RHD. *See* Rheumatic heart disease
Rhegmatogenous detachment, of retina, 978–979, 978f
Rheumatic carditis, 467–468
Rheumatic disorders, 1138–1156, 1138b
in children, 1153–1154
crystal-induced arthropathies, 1151–1152, 1152f
in elderly, 1154–1156
osteoarthritis, 1147–1151, 1148b, 1148f–1149f, 1150t
seronegative spondyloarthropathies, 1145–1147, 1145b, 1146f–1147f
systemic autoimmune, 1138–1145, 1138b
Rheumatic fever (RF), 467–468
Rheumatic heart disease (RHD), 467–468
Rheumatoid arthritis (RA), 1138–1142, 1139f–1140f, 1141c, 1154
Rheumatoid factor (RF), 1138
Rhinitis, 541
Rhinophyma, 1181, 1181f
Rhinosinusitis, 541–543, 542f
Rhinovirus, 542
Rhythmic movements, of gastrointestinal system, 684
Ribonucleic acid. *See* RNA
Ribosomal RNA (rRNA), 4
structure and function of, 93
Ribosomes, 4, 5f, 9b
Rickets, 1135–1136, 1136f
Rickettsiaceae, 305–306
Right ventricular heart failure, 489–490, 490f
Ring formation, in chromosome, 118, 118f
RMP. *See* Resting membrane potential
RNA
in protein synthesis, 92
structure and function of, 93
synthesis of, 4
transcription, 93–95, 94f, 96f
translation, 95–97
RNAi. *See* RNA interference
RNA interference (RNAi), 106–107
RNA polymerases, 93–95, 96f
RNA sequencing, for infection diagnosis, 313–314, 314f

Robertsonian translocation, in chromosome, 118, 118f
Romberg test, 1004
ROS. *See* Reactive oxygen species
Rosacea, 1181, 1181f
Roseola infantum, 1200
Rotational testing, 1004
Rotator cuff, injuries to, 1099–1100, 1099f
Rotavirus, 714
Rough ER, 5, 5f
rRNA. *See* Ribosomal RNA
Rubella, 1200–1201, 1200f
Rubeola, 1201, 1201f
Rubor, in inflammation, 55
Ruffini corpuscles, 1163
Ruffini end-organs, 868
RV. *See* Residual volume

S

Salivary secretions, 691, 691t
Saltatory conduction, 831
San Joaquin fever, 553
SA node. *See* Sinoatrial node
Saprophytes, 300
Sarcoidosis, 588–589
Sarcoma, 132–133, 133t
Sarcomeres, 26, 26f, 385
Sarcoplasm, 25
Sarcoplasmic reticulum, 26, 26f
SARS. *See* Severe acute respiratory syndrome
Satellite cells, 29
Satiety, 228–229, 229f
Scar formation, 80–82
Scavenger receptors, 328
Schistosoma haematobium, 675
Schwann cells, 29
SCI. *See* Spinal cord injury
Sciatic, 907
SCID. *See* Severe combined immunodeficiency
SCLCs. *See* Small cell lung cancers
Scleroderma, 1144–1145
Sclerosing adenosis, 1061
Sclerotherapy, for varicose veins, 441
Scoliosis, 1125–1127, 1126f
Scotopic vision, 974
Scrotum, 1018–1019, 1018f–1019f
  cancer of, 1022
  disorders of, 1019–1023, 1019f–1020f
Sebaceous glands, 1164–1165
Seborrheic keratosis, 1202, 1202f
Secondary active transport, 16–17, 606, 607f
Secondary intention, in wound healing, 82, 82f
Second-degree burn, 1189–1190
Secretin, 690, 690t
Secretions, of gastrointestinal system, 691–693, 691t, 692f
Secretory diarrhea, 718
Secretory granules, 23
Segmental demyelination, 903
Segmentation waves, in small intestine, 688, 689f
Seizures, 955–959, 955b
  classification of, 956c, 956–958
  diagnosis of, 958
  provoked, 956
  treatment for, 958
  unprovoked, 956
Selectins, 30, 31b
  in inflammation, 54
Self-renewal, 75
Semen, production of, 1011–1013, 1011f–1012f
Semilunar valves, 386–388, 387f–388f
Seminal vesicles, 1012–1013
Seminiferous tubules, 1011–1012, 1011f
Senile purpura, 275
Sensation
  position, 869
  thermal, 869
Sensorineural hearing loss, 997c, 997–998
Sensory homunculus, 867, 867f
Sensory systems, 864–868, 864f
Sensory unit, 864
Sentinel node, 137
Sepsis, 500c, 501f, 505–506, 506f
  thermal injury and, 1191
Septal defects
  atrial, 477f–478f, 478
  ventricular, 477f, 478–479
Septic shock, 500c, 501f, 505–506, 506f
Septum primum, 478
Septum secundum, 478
Serology, for infection diagnosis, 312–313
Seronegative spondyloarthropathies, 1145–1147, 1145b, 1146f–1147f
Serosal layer, in gastrointestinal system, 682, 682f
Serotonin. *See* 5-Hydroxytryptamine
Serous exudates, 62
Sertoli cells, 1011–1012, 1011f
Serum bilirubin, 736
Serum biomarkers, in acute coronary syndromes, 454–456
Serum creatinine, 617–618, 617f, 617t
Serum sickness, 350–351
Severe acute respiratory syndrome (SARS), 316
Severe combined immunodeficiency (SCID), 363
Severe hypertension, 432
Sex chromosomes, 97, 98f. *See also* X-linked disorders
  numeric disorders of, 120–122
Sexual function
  CKD and, 651
  disruption in, with spinal cord injury, 923
Sexually transmitted infections (STIs), 1067–1080, 1068b
  of external genitalia, 1068–1071, 1069f–1070f
  vaginal, 1072–1074, 1072f–1073f
  vaginal-urogenital-systemic, 1074–1078, 1075f–1077f
Shingles. *See* Postherpetic neuralgia
Shivering, for heat production, 65–66
Shock, 499–508, 499b
  anaphylactic, 500c, 501f, 505
  cardiogenic, 500c, 500–502, 501f–502f
  compensatory mechanisms of, 500
  complications of, 507–508
  distributive, 500c, 501f, 504–506
  hypovolemic, 500c, 501f, 502–504, 503f
  neurogenic, 500c, 501f, 505
  obstructive, 500c, 501f, 504
  pathophysiology of, 499–500
  septic, 500c, 501f, 505–506, 506f
  types of, 500c, 500–506
Short stature
  in children, 778c, 778–779
  idiopathic, 779
Shoulder, injuries to, 1099–1100, 1099f
Shunts
  in congenital heart disease, 475
  in lungs, 530
  portosystemic, 747f, 748
Shy-Drager syndrome, 438

SIADH. *See* Syndrome of inappropriate antidiuretic hormone
Sickle cell disease, 286–288, 286f, 287f
Silent myocardial infarction, 460
Simple diffusion, 15, 20b
Simple epithelium, 21–22, 24f
Single-breath test, 531
Single-gene disorders, 110–116, 111t
  with atypical patterns of inheritance, 114–116
  autosomal dominant, 110–113, 110f, 111t
  autosomal recessive, 113–114, 113f
  X-linked, 114, 115f
Single-gene trait, 100–101
Single-nucleotide polymorphisms (SNPs), 104
Single-ventricle anatomy, 481, 481f
Sinoatrial (SA) node, 388–389, 389f
Sinusitis, 541
Skeletal muscle, 25–27, 26f, 31b
  contraction of, 26–27, 27f
  disorders of, 900–901, 900f
Skeletal system. *See also* Bone(s); Cartilage
  disorders of
    in children, 1116–1127
    hereditary and congenital, 1120–1123
    infections, 1109–1112
    metabolic, 1130–1137, 1131b
    neoplasms, 1113–1116
    rheumatic, 1138–1156, 1138b
    traumatic, 1096–1109. *See also* Fracture(s)
  structures of, 1081–1091, 1082b
Skin
  appendages, 1164–1166, 1165f–1166f
  basement membrane zone, 1164, 1164f–1165f
  cancer of, 1195–1198, 1195b. *See also specific type*
  dermis, 1160f, 1162–1164
  disorders of, 1166–1170
    age-related, 1198–1203
    allergic and hypersensitive, 1181–1184, 1182f–1184f
    of dark skin, 1169–1170, 1170t
    dry, 1168–1169
    infectious, 1172–1179, 1173b
    lesions, 1166–1167, 1167f
    nevi, 1194–1195, 1194f–1195f
    papulosquamous dermatoses, 1184–1187, 1185f–1187f
    pigmentary, 1167–1168, 1168f
    pressure ulcers, 1192–1193, 1192f
    primary, 1172–1187
    pruritus, 1168–1169
    pustular, 1179–1181
    rashes, 1166–1167
    thermal, 1189–1192, 1190t
    ultraviolet radiation, 1188–1189, 1188b
  epidermis, 1160–1162, 1160f–1162f
  structure and function of, 1159–1166, 1160b, 1160f
  turgor of, 174
Skin eruptions, drug-induced, 1183–1184, 1184f
Skinfold thickness, 230
Skin integrity
  with CKD, 651
  with spinal cord injury, 924
Skin tags, 1202
Skip lesions, 712
SLE. *See* Systemic lupus erythematosus
Sleep disorders, in cancer, 147
Sleep-wake cycles, adaptation and, 217
Slime, 310
Slipped capital femoral epiphysis, 1125
Slipped disk, 906–907, 906f–907f
Slow response, cardiac action potential, 390, 390f
Slow waves, in gastrointestinal motility, 684, 687, 687f
Small cell lung cancers (SCLCs), 555
Small intestine
  disorders of, 710–725
  motility in, 686–689, 686f–687f, 689f
    disorders of, 717–721, 717b, 718c, 720f–721f
Smoking
  CKD and, 652
  emphysema and, 580, 580f
  IPF and, 588
Smooth ER, 5, 5f
Smooth muscle, 25, 27–28, 28f, 31b
  contraction of, 28
  intestinal, 687, 687f
  vascular, 396–397, 406–407
SNPs. *See* Single-nucleotide polymorphisms
Sodium
  balance of
    disorders of, 172–177, 172f, 173b
    regulation of, 168–169
  elimination of, regulation of, 613–614
Soft tissue injuries, 1097
Solar lentigines, 1203
Somatosensory function
  central processing of, 867–868, 867f
  dermatomes in, 864–865, 865f
  modalities of, 868–869, 868f
  organization and control of, 863–869, 864b
  sensory systems in, 864–868, 864f
  sensory unit in, 864
  spinal circuitry in, 865–867, 866f
  with spinal cord injury, 920–921
Somatotropin. *See* Growth hormone
Spasmodic croup, 561f, 561t, 562
Spastic bladder, 661f, 665–666, 665t, 666f
Spasticity, 898
Special somatic afferent (SSA) fibers, 841, 863
Special visceral afferent (SVA) neurons, 841
Specific gravity, of urine, 617
Specific immunity. *See* Adaptive immunity
Specificity theory, of pain, 870
Spectrin, 279, 280f
Spermatocele, 1020
Spermatogenesis, 1011–1013, 1011f–1012f
Spermatogenic cells
  ductile transport of, 1012, 1012f
  production of, 1011–1012, 1011f
S phase, of cell cycle, 74, 76, 76f
Sphenoidal sinuses, 541, 542f
Spherocytosis, 286
Sphincter of Oddi, 731
Spider fingers, 112, 112f
Spinal cord, 845–848, 846f–847f
  ascending neural pathways and, 873–874, 873f
  in bladder control, injury and, 666
  in motor function, 892
Spinal cord injury (SCI), 916–924
  acute, 917–918
  autonomic nervous system disruption with, 921–923, 922f
  classification of, 918c, 918–920, 919f–920f
  functional abilities with, 920, 920t
  motor and somatosensory function with, 920–921
  repair of, 924
  vertebral column, 916–917, 917f
Spinal cord shock, 917

Spinal nerves, 846f–847f, 847
root disorders, 905–908
Spinal reflexes, 848, 893–894, 896, 896f, 898–899
Spinal shock, 505
Spinal tap, 847
Spiral fracture, 1103, 1103f
Spirochetes, 304–305, 305f
Spirometer, 526
Spleen, 322f, 323–324
Splenomegaly, 747–748, 747f
Split-thickness skin graft, for thermal injury, 1192
Spondyloarthropathies
juvenile, 1154
seronegative, 1145–1147, 1145b, 1146f–1147f
Spontaneous bacterial peritonitis, 747
Spontaneous pneumothorax, 570–571, 570f
Sporangiospores, 306
Sports-related injuries, 1097
Sprain, 1098, 1098f
Spurs, 1149, 1149f
Squamous cell carcinoma, 132–133, 133t, 1197–1198, 1198f
lungs, 555
Squamous cell hyperplasia, 1041
Squamous epithelial tissue, 21, 24f
SSA fibers. *See* Special somatic afferent fibers
Stable angina, 460, 460f
Stable tissues, 75
Staghorn stones. *See* Magnesium ammonium phosphate stones
Stapes, 989f, 990
Staphylococcal infections
infective endocarditis, 466
rhinosinusitis, 542
Starvation. *See* Malnutrition
Statum corneum, 1161, 1161f
Statum germinativum, 1161, 1161f
Statum granulosum, 1161, 1161f
Statum lucidum, 1161, 1161f
Statum spinosum, 1161, 1161f
Status epilepticus, 958–959
Steatorrhea, 696
ST elevation myocardial infarction (STEMI), 455f, 458f, 459f. *See* Myocardial infarction
Stem cells, 75, 75f, 78
STEMI. *See* Myocardial infarction
Stenosis
of aortic valve, 470f, 472
mitral valve, 470, 470f
Stereognosis, 866
Stevens-Johnson syndrome, 1184
Stimulation tests, for endocrine function, 771–772
STIs. *See* Sexually transmitted infections
Stomach, 680f–681f, 681
cancer of, 709
disorders of, 705–709, 705b, 706f–707f
motility in, 685, 688
Stop codes, 92, 92t
Strabismus, 985–987, 986f
Strain, 1097–1098
Stratified epithelium, 22–23, 24f
Strawberry hemangiomas. *See* Hemangiomas of infancy
Strawberry spots, 1073
Stress
acute, effects of, 218–219
adaptation to, 215–218, 215b, 216f
cellular response to, 33–38, 34b, 34f–35f, 37f
chronic, effects of, 219
PTSD, 219–220
response to, 210–215, 212t, 213f
disorders in, 218–221
treatment for, 220–221
Stress fractures, 1102
Stress incontinence, 668–669, 668b, 668t
Stressors, 211
Stress ulcers, 709
Stretch receptors, 537
Stretch reflex, 894–896, 896f
Striatum, 909, 909f
Stridor, 559
Stroke, 943–948, 943t, 944b
deficits from, 947–948
diagnosis of, 946–947, 946t
hemorrhagic, 945–946
ischemic, 944–945, 944f
treatment of, 947
Stroke volume, in cardiac cycle, 394
Stromal tissues, 73
Struvite stones. *See* Magnesium ammonium phosphate stones
Stunned myocardium, 457
Subarachnoid hemorrhage, aneurysmal, 948–950, 949f
Subcortical brain centers, in bladder control, 661f, 662
Subdural hematomas, 937, 937f
Subluxation, 1098
Submucosal layer, in gastrointestinal system, 682, 682f
Submucosal plexus, 684, 686, 686f
Substantia nigra, 909, 909f
Subthalamic nucleus, 909, 909f
Sudden cardiac death, 495
Sunburn, 1189
Superantigens, 358
Superficial basal cell carcinoma, 1197
Superficial mycoses, 307
Superficial spreading melanoma, 1196
Superior vena cava syndrome, 556
Supernormal excitatory period, 391
Supplementary motor cortex, 850, 851f
Support stockings
for deep venous thrombosis, 443
for pulmonary embolism, 591
for varicose veins, 441
Suppression tests, for endocrine function, 771–772
Suppurative exudates, 62
Supratentorial herniation, of brain, 931, 931f, 933, 934f
Surface tension, in lung compliance, 523–524, 524f
Surfactant, 518–519, 519f, 523–524, 524f
RDS and, 559–560, 559f
Surgery
for cancer, 151
for infections, 315
for pain, 879
Sustained fever, 68, 69f
SVA neurons. *See* Special visceral afferent neurons
Swallowing, 685, 688f
disorders of, 701
Swallowing center, 685, 688f
Sweat glands, 1164
Sweat test, for cystic fibrosis, 585
Sympathetic nervous system, 856–857, 857t, 858f–859f
in bladder control, 661f, 662
in gastrointestinal system, 684–686, 685f–686f
heart failure and, 491–492
neurotransmission in, 859–861, 860f
Symporters, 15, 15f

Symptomatology, 310–311
Synapses, 28
  transmission at, 834–837, 836f–837f
Synaptic vesicles, 835
Synarthroses, 1092
Syncytium, 386
Syndrome of inappropriate antidiuretic hormone (SIADH), 171–172
Syngeneic graft, 353
Synovial fluid, 1092
Synovial joints, 1092–1094, 1093f–1094f
Syphilis, 305, 1077–1078, 1077f
Systemic autoimmune rheumatic disease, 1138–1145, 1138b
Systemic circulation, 377–378, 378b, 378f, 396–402, 397b
Systemic immune complex disorders, 350–351
Systemic inflammatory response syndrome, 65
Systemic lupus erythematosus (SLE), 1142–1144, 1143f
  glomerulonephritis with, 626
Systemic sclerosis, 1144–1145
Systemic vascular resistance. *See* Peripheral vascular resistance
Systole, 392–393, 393f
Systolic heart failure, 488
Systolic pressure, 424, 424f

T

Takotsubo cardiomyopathy, 464–465
Tall stature, 780
Tamm-Horsfall mucoprotein, 616
Target organ damage, 431, 431c
Tattoos, 37
Tay-Sachs disease, 6, 36, 114
Tazarotene, for psoriasis, 1186
TB. *See* Tuberculosis
TBW. *See* Total body water
T-cell receptor (TCR), 335, 336f–337f, 339, 340f
TCR. *See* T-cell receptor
Telangiectases, 1203
Telogen follicles, 1166
Telomerase, 47
Telomeres, 47, 99
Temperature
  cellular injury from, 38–39
  regulation of, 65–67, 65f, 66f, 66t
Temperature regulation, disruption of, with spinal cord injury, 923–924
Temporal lobe, 851, 851f
Temporomandibular joint pain, 886
Tendons, 1092–1093, 1097
Teniae coli, 716
Tension pneumothorax, 571, 571f
Tension-type headache, 885
Tentorium cerebelli, 852, 853f
Teratogenic agents, 123–126, 124c, 124b
Terminal cisternae, 26, 26f
Terry nails, 651
Testes, 1010, 1010f, 1018–1019, 1018f–1019f
  cancer of, 1022–1023
  disorders of, 1019–1023, 1019f–1020f
  torsion of, 1020–1021, 1020f
  tunica disorders, 1019–1020, 1019f
  undescended, 1029–1030, 1029f
Testosterone, 1011, 1011c, 1030
Tethering, inflammatory response, 57–58
Tetralogy of Fallot, 477f, 480
Tetraplegia, 898, 898f
Thalassemias, 288–290
α-Thalassemias, 289
β-Thalassemias, 288–289
Theophylline, for asthma, 578
Thermal injury, 1189–1192, 1190t
  classification of, 1189–1190, 1190t
  systemic complications of, 1190–1191
  treatment of, 1191–1192
Thermal sensation, 869
Thermoregulatory center, 65
Thermostatic set point, 65
Third-degree burn, 1190
Third-space accumulation, 167
Thirst, 177
  disorders of, 169–170, 170f
Thoracic aneurysm, 420
Threshold potential, 833, 834f
Thromboangiitis obliterans, 418
Thrombocytes. *See* Platelet(s)
Thrombocytopathia, 274
Thrombocytopenia, 271–273, 272f, 749
Thrombocytosis, 270
Thrombophlebitis, 757
Thrombopoietin, 263
Thrombotic microangiopathies, 273
Thrombotic stroke, 945
Thrombotic thrombocytopenic purpura (TTP), 273
Thymic hypoplasia, 362, 362f
Thymic selection, 323
Thymine, in DNA, 90
Thyrocalcitonin, 1090
Thyroglobulin, 783
Thyroid gland
  control of, 782–785, 783f–784f, 784b
  disorders of, 785–789, 786t
    hyperthyroidism, 786t, 788, 789f
    hypothyroidism, 786–788, 786f, 786t, 788f
  function tests for, 785
  hormones of, 784–785, 784b
Thyroid peroxidase (PTO), 783
Thyroid storm, 788
Tibial torsion, 1118f, 1119
Tibia vara, 1120, 1120f
Tic douloureux. *See* Trigeminal neuralgia
TIIV. *See* Trivalent inactivated influenza vaccine
Tinea capitis, 1174, 1174f
Tinea corporis, 1174, 1174f
Tinea faciale, 1174
Tinea manis, 1175
Tinea pedis, 1174–1175, 1175f
Tinea unguium, 1175, 1175f
Tinel sign, 904
Tinnitus, 995–996
Tissue, 1, 20–31, 31b
  connective. *See* Connective tissue
  embryonic origin of, 21, 21b, 22t, 23f
  epithelial, 22t. *See* Epithelial tissue
  extracellular components of, 29–31
  muscle. *See* Muscle tissue
  nervous. *See* Nervous tissue
  oxygen dissociation in, 533, 533f
  proliferative capacity of, 75
  turgor of, 174
Tissue regeneration, 80–87, 80b, 81f
  cutaneous, 82–85, 82f–83f
  factors affecting, 83–87
  phases of, 80–82, 81f
TLC. *See* Total lung capacity

TLRs, 329t. *See* Toll-like receptors
T lymphocytes, 246, 246f
  in adaptive immunity, 334, 334f–335f
  cell-mediated immunity and, 339–341, 340f
  differentiation of, 244, 244f
  immunodeficiency disorders of, 361–363
  in innate immunity, 320f, 321–323
  tolerance to, 356–358, 356f
TNF-α. *See* Tumor necrosis factor-α
Toenails, 1166, 1166f
Tolerable Upper Intake level, 226
Tolerance, in immunity, 342
Toll-like receptors (TLRs), 328–329, 329t
Tonic-clonic seizures, 957–958
Tonicity, 162, 162f
Tonic movements, of gastrointestinal system, 684
Tophi, 1151, 1152f
Torsional deformities, of limbs, 1117–1119, 1118f–1119f
Total body water (TBW), 167–168, 168f
Total lung capacity (TLC), 526, 527t
  in emphysema, 579–580
Totipotent stem cells, 78
Toxic epidermal necrolysis, 1184
Toxins, 309–310, 309t
  neuromuscular junction disorder, 901–903, 901f
Toxoplasmosis, 370
Trabeculae, 664
Trachea, 516–517, 517f
Tracheobronchial tree, 516–518, 516f–517f
Transcription, RNA in, 93–95, 94f, 96f
Transcription factors, 97
Transferrin, 281, 281f
Transfer RNA (tRNA), 4
  structure and function of, 93
Transient left ventricular apical ballooning. *See* Takotsubo cardiomyopathy
Transitional epithelium, 23, 24f
Translation, RNA in, 95–97
Translocation, in chromosome, 118, 118f
Transmembrane proteins, 3, 3f
Transmigration, 31
  inflammatory response, 57–58
Transmissible neurodegenerative diseases, 301
Transplantation
  heart, 498–499
  of hematopoietic cells, 354
  immunopathology of, 353–355
  kidney, for CKD, 654
  liver
    for hepatitis, 741
    for liver failure, 750
  lung, 593
Transport maximum, 607
Transport mechanism, of cell membrane, 14–17, 14f–15f
Transpulmonary pressure, 525, 526f
Transtentorial herniation, of brain, 931, 931f, 933, 934f
Transverse fracture, 1103, 1103f
Trauma
  brain injury, 935–938
  corneal, 969
  malnutrition in, 236–237
Traumatic pneumothorax, 571
Tremor, 899
Treponema pallidum, 1077–1078
Tricarboxylic acid cycle. *See* Citric acid cycle
Trichomonas vaginalis, 1072–1073, 1072f
Trichomoniasis, vaginal, 1072–1073, 1072f
Trigeminal neuralgia, 881
Triglycerides, in energy storage, 225
Trigone, 659, 660f
Triplet repeat mutations, 115
Trisomy 21. *See* Down syndrome
Trivalent inactivated influenza vaccine (TIIV), 545
tRNA. *See* Transfer RNA
Tropomyosin, 27, 27f
Troponin, 27, 27f
Troponin assays, 455–456
Trousseau sign, 188, 188f
Truncal ataxia, 908
TTP. *See* Thrombotic thrombocytopenic purpura
T tubules, 26, 26f
Tuberculosis (TB), 549–553, 550b
  diagnosis of, 552
  etiology of, 549–550, 549f
  with HIV, 369–370
  pathogenesis of, 550, 551f
  primary, 550–551, 551f
  secondary, 551–552, 551f
  treatment of, 552–553
Tuberculosis osteomyelitis, 1111
Tubulin, 7, 8f
Tubulointerstitial disease, 627–630, 628f–629f. *See also specific disease*
Tumor(s)
  benign
    biology of, 133, 134t
    characteristics of, 131–139, 132b
  cell characteristics of, 134–136, 135f
  cell transformation to, 142, 142f
  growth of, 135–137, 136f
  in inflammation, 55
  of kidneys, 637–639
  malignant
    biology of, 133–134, 134t
    characteristics of, 131–139, 132b
  staging and grading of, 150–151
  terminology of, 132–133, 133t
Tumor antigens, 143
Tumor markers, 149–150, 149t
Tumor necrosis factor-α (TNF-α)
  in acute inflammation, 61, 61f
  in chronic inflammation, 63
Tumor-suppressor genes, 139–140, 140f
Tunicae, 396, 396f, 405, 406f
Tunnel vision, 984
Turbulent airflow, 525
Turbulent blood flow, 380–381, 383, 383f
Turner syndrome, 120–121, 121f
Tympanic membrane, 989, 989f
Typical pneumonia, 546–549, 546f, 548t
Tyrosinase, 1161

U

UA. *See* Unstable angina
Ubiquitin, 34
Ubiquitination, 6
Ulcers
  Curling, 709
  Cushing, 709
  peptic, disease, 707–709, 707f
  pressure, 1192–1193, 1192f
  stress, 709
Ulceration, 62
Ulcerative colitis, 711f, 711t, 713–714, 713f

Ultrasonography
for liver function, 736
for prenatal screening, 126–127, 127f
Ultraviolet (UV) radiation
cellular injury from, 40
skin damage with, 1188–1189, 1188b
Umbilical cord blood sampling, percutaneous, 128
UMNs. *See* Upper motor neurons
Undernutrition. *See* Malnutrition
Uninhibited bladder, 666
Uniparental disomy, 102
Uniporters, 14–15, 15f
Unstable angina (UA), 456
Upper motor neurons (UMNs), 843, 893
disorders of, 913–924
Up-regulation, 765
Uracil, 92
Urea. *See also* Blood urea nitrogen
elimination of, 614–615
synthesis of, 732t, 733–734, 733f
Urease, kidney stones and, 636
Uremia, 650–651
Uremic encephalopathy, 651
Urethrovesical reflux, 672
Urge incontinence, 668
Uric acid, elimination of, 614
Uric acid stones, 635–636, 635t
Urinary incontinence, 667–670, 668b
diagnosis and treatment of, 669–670
in elderly, 670
overflow, 668b, 668t, 669
stress, 668, 668t
Urinary tract infection (UTI), 671–675, 671b
catheter-induced infection, 672
in children, 674
clinical features of, 672–673
diagnosis and treatment of, 673
in elderly, 674–675
etiologic factors in, 671–672
obstruction and reflux in, 672
in women, 673–674
Urinary tract obstruction, 633–637, 633f, 633t, 664–665
compensatory and decompensatory changes, 664–665, 664f, 665c
renal damage with, 633–634, 634f
Urine
concentration of, 609
elimination of, control of, 659–663, 660b, 660f–661f, 662t
formation of, 605–611, 606f–611f
osmolality of, 617
specific gravity of, 617
Urine retention, 664–665, 665c
Urine tests, 616–617, 616t, 673
for endocrine function, 771
Urobilinogen, 734
Urticaria, 1183, 1183f
Uterine leiomyomas, 1049–1050, 1050f
Uterus, 1035, 1035f
adenomyosis, 1048
cancer of, 1044b, 1048–1050
disorders of, 1046–1051
infectious, 1046–1047, 1046f
endometriosis, 1047–1048, 1047f–1048f
prolapse, 1050–1051, 1051f
support disorders of, 1050–1051
UTI. *See* Urinary tract infection
UV radiation. *See* Ultraviolet radiation

V

VAD. *See* Ventricular assist devices
Vagina, 1035, 1035f
cancer of, 1043
candidiasis, 1072, 1072f
disorders of, 1042–1043
infections of, 1072–1074, 1072f–1073f
trichomoniasis, 1072–1073, 1072f
Vaginal intraepithelial neoplasia (VAIN), 1043
Vaginitis, 1042–1043
Vaginosis, bacterial, 1073
VAIN. *See* Vaginal intraepithelial neoplasia
Valley fever, 553
Valvular heart disease, 468–473, 469b
aortic valve disorders, 470f, 471–473
diagnosis and treatment of, 473
hemodynamic derangements, 469, 469f, 470f
mitral valve disorders, 469–471, 470f–471f
Variant angina, 460–461
Varicella, 1201–1202, 1201f
Varicella Zoster keratitis, 971
Varicocele, 1019f, 1020
Varicose veins, 440–441, 440f
Vasa recta, 604, 609–610, 610f
Vasa vasorum, 405
Vascular birthmarks, 1199
Vascular dementia, 961–962
Vascular disorders, bleeding with, 275
Vascular function, autonomic regulation of, 403
Vascular lesions, 1203
Vasculitides, 414–415, 415f, 415t
Vasculitis, 414–415, 415f, 415t
Vasoactive medications, 504
Vasoconstriction, hypoxia-induced, 530
Vasodilation, 55–56
Vasodilator agents, for heart failure, 498
Vasogenic edema, 929–930
Vasomotor center, 402
Vasopressin. *See* Antidiuretic hormone
Vasospastic angina, 460–461
Vasovagal response, 922
VC. *See* Vital capacity
Veins, varicose, 440–441, 440f
Velocity, of blood flow, 380–382, 382f
Venous insufficiency, chronic, 441–442, 442f
Venous lakes, 1203
Venous system, 398, 398f
disorders of, 439–443, 439b
in lower extremities, 439–440, 440f
Ventilation, 521–525, 521f, 528–529
alveolar, 528, 566–567
chest cage and, 522–523, 522f–523f
dead air space, 529
disorders of, 203–204, 203b
distribution of, 528–529
lung compliance, 523–524, 524f
in neonate, 557–558, 558f
perfusion matching with, 530, 530b, 530f, 595–596
pulmonary, 528
in respiration, 566–567
respiratory pressures and, 521–522, 521f
Ventilation-perfusion scan, for pulmonary embolism, 591
Ventricular assist devices (VAD), for heart failure, 498
Ventricular septal defects, 477f, 478–479

Ventricular system, 852–854, 853f
Ventricular volume overload, in heart failure, 494
Verrucae, 1177–1178
Vertebral column, injury to, 916–917, 917f
Vertical transmission, of infectious agents, 308
Vertigo, 1002
  benign paroxysmal positional, 1001f, 1002–1003
Very–low-density lipoprotein (VLDL), 407–408, 408f
Vesicoureteral reflux, 672
Vesicular transport, 6f, 17, 20b
Vessel spasm, in hemostasis, 265–266, 266f
Vestibular folds, 515f, 516
Vestibular system, 1000–1002, 1001f–1002f
  disorders of, 1002–1003
    treatment of, 1004
  tests of, 1004
Vestibule, 1034, 1034f
Villus, 694–695, 694f
Viral conjunctivitis, 969
Viral croup, 561–562, 561f, 561t
Viral hepatitis, 737–741
  chronic, 740–741
Viral infections
  in intestines, 714–715
  of skin, 1177–1179, 1178f–1179f
Viral meningitis, 952
Virulence of infections, 309–310, 309t
Viruses, 301–302, 301f–302f
  cancer and, 145–146
Visceral epithelial cells, 604, 605f
Visceral layer, 569
Visceral pain, 875
Visceral pericardium, 447
Visceral peritoneum, 682
Viscosity, 380
Visual field defects, 983f, 984
Vital capacity (VC), 526
Vitamins, 762–763
  absorption of, 722, 723t
  requirements of, 228
  for wound healing, 85
Vitamin B_{12}-deficiency anemia, 291, 291f
Vitamin C, deficiency of, 275
Vitamin D
  activation of, 615
  in bone formation and metabolism, 1090–1091, 1090t, 1091f
  osteomalacia and, 1134–1135
Vitamin K, deficiency of, 275
Vitiligo, 1168, 1168f
VLDL. *See* Very–low-density lipoprotein
Vocal folds, 515f, 516
Volume, in circulatory system, 379, 379f
Volvulus, 720, 720f
Vomiting, 697–698, 698f
Vomitus, 697
Von Gierke disease, 36
Von Recklinghausen disease. *See* Neurofibromatosis
Von Willebrand disease, 274
Vulva, 1033–1035, 1034f–1035f
  disorders of, 1041–1042
  neoplasms of, 1041–1042, 1044b
Vulvodynia, 1042

W

Washout phenomenon, 671
Wasting syndrome, 371–372
Water, absorption of, 722, 723t
Water balance
  disorders of, 172–177, 172f, 173b
  regulation of, 167–168, 168f
    mechanism of, 169
Water intoxication, 176
Weakness, with heart failure, 495
Wear-and-tear arthritis. *See* Osteoarthritis
Wear-and-tear pigment. *See* Lipofuscin
Weight
  loss of, 233
  measurement of, 229–230, 230t
Weil syndrome, 304
Werner syndrome, 49
Wernicke-Korsakoff syndrome, 962
Western blot assay, for HIV, 372
West Nile virus (WNV), 316
Wheal, 1167, 1167f
White blood cells. *See* Leukocytes
White fat, 225–226
Whiteheads, 1179–1180
White matter, 831
  longitudinal tracts of, 843–845, 843f–844f, 844t
Wilms tumor, 637–638, 638f
Windpipe. *See* Trachea
Wiskott-Aldrich syndrome, 363
WNV. *See* West Nile virus
Women, urinary tract infections in, 673–674
Wound healing, 80–87, 80b, 81f
  cutaneous, 82–85, 83f–85f
  in elderly, 86–87
  factors affecting, 83–87
  phases of, 80–82, 81f
Wound separation, 86
Woven bone, 1084–1085

X

Xanthomas, 410, 410f
X chromosome, 97–98, 98f
Xerosis, 1169
X-linked agammaglobulinemia, 360–361
X-linked disorders, 114, 115f

Y

Y chromosome, 97–98, 98f
Yeasts, 306, 306f

Z

Z line, 26, 26f
Zollinger-Ellison syndrome, 708–709
Zygote, 89